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The Impact of Early Life Stress on Longtime Heart Rate Variability and Neurocognitive Impairment in Infants with Critical Illness–A Comparison of Infants after Preterm Birth and Congenital Heart Disease

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Abstract

Current literature about the programming effect of early life stress on neurocognition and cardiovascular risk focused on psychosocial risk factors and intrauterine growth retardation. Some data report on the programming effect of pediatric intensive care medicine most of all with respect to the protective effect of analgetics and sedatives on neurologic outcome.

Introduction

Evans DJ et al. [1] showed in 2001 that elevated norepinephrine levels are associated with adverse outcome in preterm infants [1]. However only a few paper report about early life stress due to severe disease in infancy in a daily life setting. 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 [2]. 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 [3]. Further 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 [4].

We recently publish 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 in children with congenital heart disease by pharmacotherapy and a careful handling of invasive procedures [5]. We introduce the term autonomic imprinting to understand the lifelong consequences of early life stress on the autonomic nervous system [6]. 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 [7]. We now compare these 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.

Norepinephrine Plasma Levels in Infants after Preterm Birth and Congenital Heart Disease

Figure 1 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 life (estimated from the figure 1011 ± 300 ng/l). Evans DJ et al. [1] proposed a norepinephrine cut off plasma level of 1530 ng/l to estimate a worse outcome in preterm infants [1]. Norepinephrine levels of preterm infants with a favorable outcome are in the high normal level (629 ± 80 ng/l) of 126 neonates who need mechanical ventilation (425 ± 250 ng/l) [8] and our published data from infants with congenital heart disease without heart failure (560 ± 247 ng/l)(4). 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 after cardiac surgery (estimated from the figure 1200 ± 700 ng/l) as published by Gruber et al. [9]. A retrospective analysis from 86 of our infants with congenital heart disease treated 20 years ago at the university

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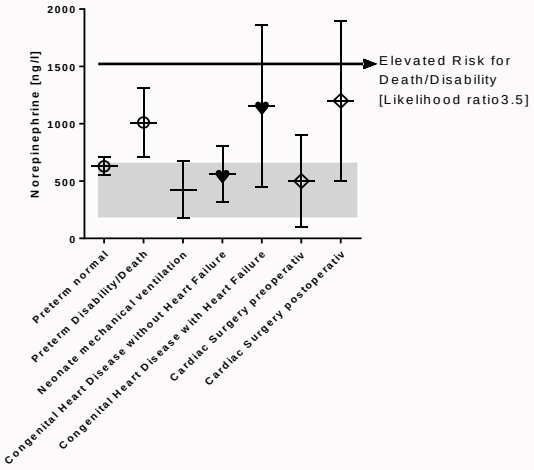

Figure 1: Norepinephrine Levels of Preterm Infants Stratified.

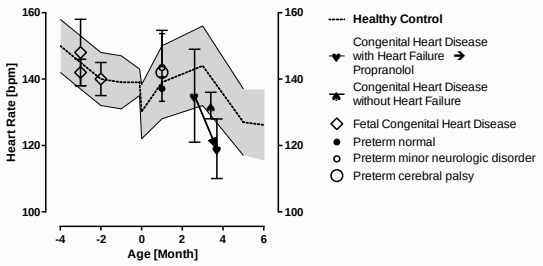

Figure 2: Only Infants who Received Propranolol of Cause Severe Heart Failure.

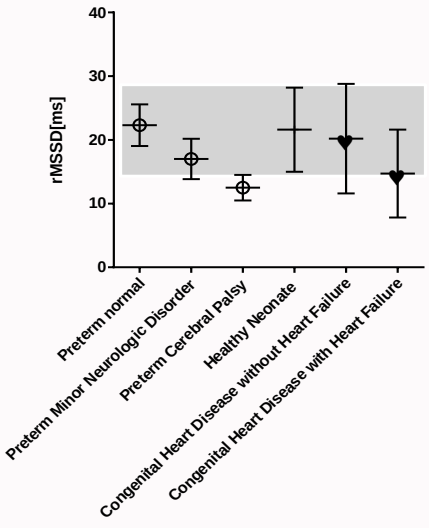

Figure 3: HRV in Preterm Infants Predict.

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 of 1530 ng/l to estimate a worse outcome in preterm infants. Today …..(wird gerad eausgewertet).

24 Hour Heart Rate Variability in Infants after Preterm Birth and Congenital Heart Disease

Obviously it is impossible to estimate early life stress by heart

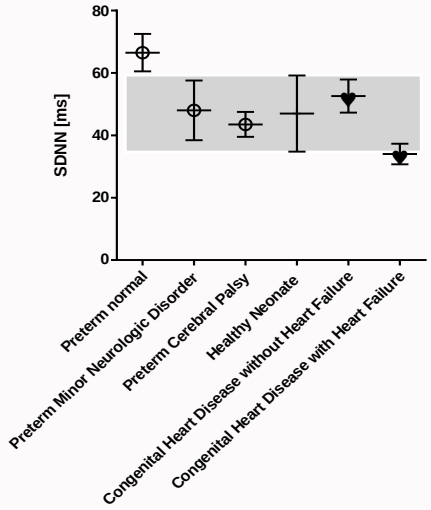

Figure 4: However Rmssd is Only Significantly Reduced.

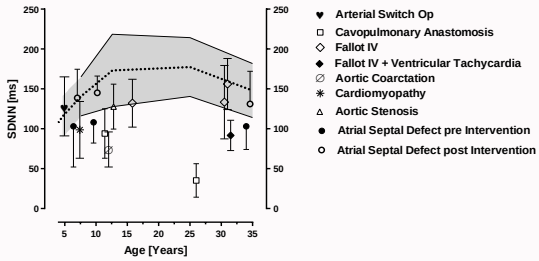

Figure 5: HRV Remains Reduced in Most Children and Young Adults After Cardiac Surgery.

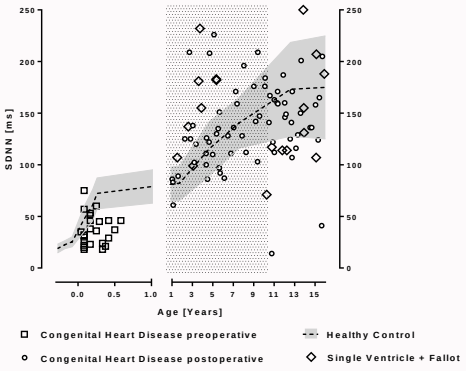

Figure 6: HRV Data of the Entire Group of Children.

rate in infants if the mean heart rate is mostly normal in – and ex utero despite prematurity or significant heart defects (Figure 2). Only infants who received propranolol of cause severe heart failure had significantly reduced mean heart rates [4]. In contrast SDNN and rMSSD differentiate between preterm infants with favorable outcome and those who develop minor neurologic disorder or cerebral palsy but SDNN seems to be enhanced in healthy preterms treated in the pediatric intensive care unit [10] (Figure 3 and 4). However rMSSD is only significantly reduced in infants who develop cerebral palsy. In summary elevated norepinephrine levels as well as reduced HRV in preterm infants predict the neurodevelopmental outcome. These data are in accordance with the correlation of HRV and 2 year neurodevelopmental outcome in hypoxic ischemic encephalopathy

Table 1: Comparison of Children with Congenital Heart Defects with Healthy Controls.

	1 - 10 Years (CurrentConcept)			11 - 16 Years (Historical Control)		
Parameter	**HealthyControl**	**Heart Defects**	**p-value**	**HealthyControl**	**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 powerHF: 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

as published by RM Goulding [11]. 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 [4]. The follow up data show that HRV remains reduced in most children and young adults after cardiac surgery (Figure 5) but remains normal in patients who are operated as neonates with the arterial switch operation or after interventional closure of an atrial septal defects [12]. 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. [13].

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 [14]. Unfortunately nobody correlate the HRV data registered in thousands of routine Holter ECG's from infants with congenital heart disease with their neurodevelopmental outcomes.

However, Figure 6 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 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 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 beta blockers and a carefully use of diuretics that stimulate the neurohormonal systems in a prospective randomized trial [3].

Magnet Resonance Imaging to Understand Neurocognitive Impairment

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 [15]. 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 ADHD and 0.99 vs.0.2/1000 person-years for ASD) [16]. 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: $p < 0.01$) [17]. 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 [18] and after ECMO therapy [19]. 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 [20]. These changes persist in later life and show significant correlation with the neurodevelopmental outcome [21]. However reduced brain volumes of the hippocampus, caudate, putamen, thalamus, insula and prefrontal cortex are also shown in adults with heart failure [22,23].

Table 2: MRI Scans Using Voxel-Based Cortical Thickness and Morphometry.

	Congenital Heart Disease	Adult Heart Failure	SGA	Preterms	ADHD	HRV
Caudate	+	+	+	+	+	+
Putamen	+	+	+	+	+	+
GlobPallidum		+		+	+	
Thalamus	+	+	+	+	+	
Hippocampus	+	+				*
Amygdala						+
Cortex						
Cingula		+		+	+	+
Insula	+	+		+		+
Prefrontal	+	+	+	+		+
Occipital	+			+		
Parietal		+	+	+		
Temporal	+		+	+		+
Para hippocampal	+	+				+
Post central	+					
Precentral	+					

Furthermore such brain "injuries" were also shown in children with attention deficit hyperactivity disorder [24] and children with low birth weight due to small for gestational age syndrome [25]. Most of these brain structures are parts of the so called central autonomic network and limbic system. Wei L et al. [26] found associations of the putamen, caudate, insula, and hippocampus with heart rate variability [26] (Table 2).

Clinical Implication

Follow up studies of children with congenital heart disease [12], premature birth [27], small for gestational age syndrome [6] and attention deficit hyperactivity disorder [7] 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 [6]. Elevated norepinephrine levels, reduced HRV and MRI imaging indicate brain injury very early in newborns and we have to look for the underlying patho-mechanism 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 [6].

This model 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 [28]. 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 autonomic regulation 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. This is even more important for children if the urgently needed prospective studies (for example pharmacotherapy of pediatric heart failure) were not done [29].

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