

## Heart Failure in Infants with Congenital Heart Defects – The Concept of Autonomic Imprinting

Buchhorn R<sup>1\*</sup>, Motz R<sup>2</sup> and Kambiz Norozi<sup>3</sup>

<sup>1</sup>Caritas Krankenhaus Bad Mergentheim, Department of Pediatrics, Germany

<sup>2</sup>Pediatric Cardiology Practice, Oldenburg, Germany

<sup>3</sup>Department of Paediatrics, Western University, London, Canada

\*Corresponding Author: 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: reiner.buchhorn@ckbm.de

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### Abstract

Heart failure is the main cause of death in children with congenital heart disease (CHD) with long term consequences, such as impaired linear growth and worse neurodevelopmental outcomes. According to our recently published "Early Life Stress" model we prove if medical therapy of heart failure modulates the autonomic nervous system(ANS) as the common target of these CHD related disease.

**Methods:** Stress in terms of an autonomic dysregulation was measured by Holter ECG, norepinephrine and brain natriuretic peptide (NT-BNP). We examined 40 infants with CHD and severe heart failure treated with Propranolol ± Digoxin and diuretics, 13 infants with CHD and mild heart failure without medication compared to healthy control patients.

**Results:** Withdrawal of vagal activity seems to be the first negative impact to the ANS in infants with CHD. The second hit to the ANS is sympathetic activation by heart failure but the fetal and neonatal ANS seems to be able to prevent the deleterious effect of increased heart rates despite highly elevated norepinephrine levels. In this situation, beta blockers reduce heart rate to sub physiological values and improve heart rate variability. Digoxin seems to further improve vagus activity. Immune activation seems to be the third final and often fatal hit to the autonomic nervous system if vagus activity further decreases to values below a high frequency power of 20ms.

**Conclusion:** Modulation of "early life stress" with beta blockers and digoxin improve ANS dysfunction in infants with CHD and may probably improve longtime consequences, such as impaired linear growth and worse neurodevelopmental outcomes.

**Abbreviations:** ECG: Electrocardiogram; HRV: Heart Rate Variability; ANS: Autonomic Nervous System; NN: Normal RR intervals; SDNN: Standard Deviation of all NN intervals; rMSSD: Square root of the mean of the sum of the squares of differences between adjacent NN intervals; HF: High Frequency Index (Frequency domain measure); LF: Low Frequency Index (Frequency domain measure); HR: Heart Rate.

## Introduction

Heart failure is the main cause of death in children with congenital heart disease (CHD). Three quarters of heart failure related death in childhood occur in infancy due to CHD [1]. Unfortunately, veiled by the success of surgeries in patients with CHD, this global problem of heart failure in infancy eludes the attention of many healthcare professionals. Children and most of all infants, who are at highest risk of death, cannot participate on the progress of pharmacotherapy of heart failure as shown in adults with a 31% reduction of heart failure related mortality by the use of beta blockers [2]. CHD accounts for more years lost than leukemia and asthma combined; however only 284 of 5035 pediatric trials focus on cardiovascular disease and they do not seem to be representative of the public health burden [3].

Only four prospective randomized trials were undertaken in the high risk group of infants with heart failure due to CHD [4-8]. The US trial focused on the use of enalapril, which is recommended by the national guidelines, but the results showed no survival benefit and a significant impairment of growth [5]. A trial from Turkey showed no clinical benefit for digoxin [6] in contrast to a univariate analysis of pharmacotherapy on interstage mortality in children with single ventricle from the National Cardiology Quality Improvement Collaborative registry [9]. Buchhorn et al. introduced propranolol for treatment of infants with severe heart failure due to CHD 20 years ago [10] and showed a clear clinical and neurohormonal benefit in a prospective randomized trial [4]. Further development of propranolol treatment took place in three Pediatric Departments in Germany and at the All India Institute of Medical Science, where more than 50% of children with single ventricles were treated with beta blockers preoperatively [11].

More recently, long term consequences of heart failure in infancy, such as impaired linear growth [12-14] and worse neurodevelopmental outcomes [15], have been demonstrated

in literature. Lower trajectory of weight, height, and head circumference z-scores have been shown to be associated with impaired neurodevelopmental outcomes. Enalapril, frequently used in infants with heart failure, significantly impaired head circumference growth velocity during the critical development period of infancy [5, 16] and may have lifelong effects on neurodevelopment. Propranolol therapy may increase weight gain in infants with severe heart failure [17].

Recently, we published our concept of autonomic imprinting by early life stress and the longtime consequences on growth and cognition [18, 32]. Heart failure in early infancy is one of the most prominent stressful life events that is best shown by highly elevated norepinephrine levels and reduced heart rate variability (HRV) in 24 hour ECG monitoring. We conducted a retrospective study using HRV data from infants with severe heart failure who were treated with propranolol at three Pediatric Cardiology Departments in Germany within the last 20 years.

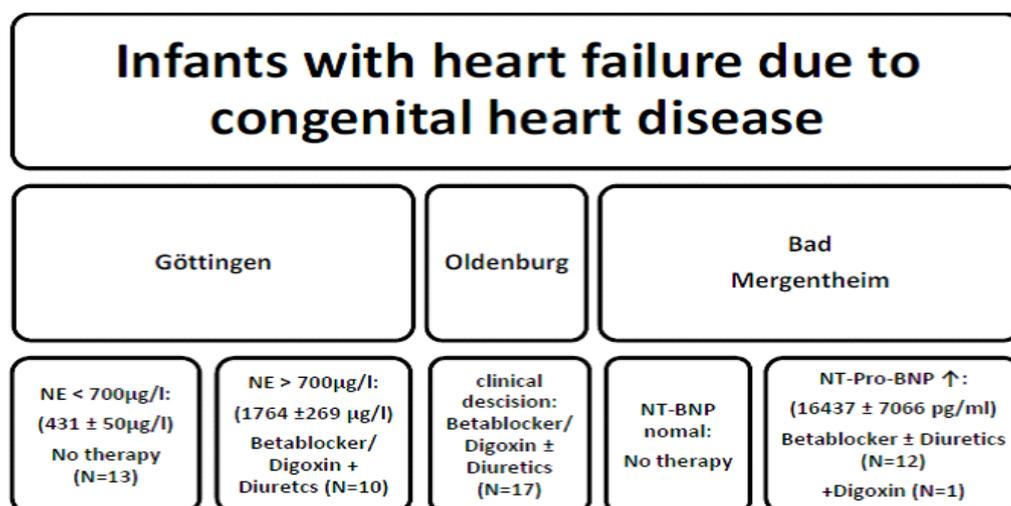
## Methods

### Subjects

This is a retrospective study analyzing patients' data from three Pediatric Cardiology Departments in Germany between the years 1995 and 2005 (Figure 1).

After the introduction of beta blocker treatment for heart failure in infants with CHD in 1995 in the Department of Pediatric Cardiology at the University of Göttingen, Germany, this therapy concept was followed up to 2002. In Göttingen we evaluated neurohormonal activation in heart failure by measuring plasma norepinephrine and 24 hour-Holter-ECG-monitoring (MARS 5000® Holter analysis system, Marquette Hellige Medical systems, Milwaukee, WI, USA). 10 of 12 infants with highly elevated norepinephrine levels ( $1764 \pm 269 \mu\text{g/l}$ ) were treated with propranolol in addition to the so called standard therapy with digoxin and diuretics.

**Figure 1:** Subjects and therapeutical management



The same concept was applied to 17 infants with CHD and congestive heart failure in the Department of Pediatric Cardiology in Oldenburg using Pathfinder™ (Reynolds, Germany, software version 7,520) for analyzing of 24-hour-Holter monitoring. The third patients' collective, including 13 infants with CHD and congestive heart failure, were treated in the Department of Pediatrics in Bad Mergentheim. The treatment was started based on clinical symptoms as well as increased serum NT-Pro-BNP as a result of enhanced neurohormonal activation. Their medication included beta blocker and only one patient became on top of that digoxin. The 24-hour-Holter ECG was analyzed using Reynolds Pathfinder II (Spacelabs, Germany; 1,000 scans/sec).

As a reference we used the normal values of HRV for 24-hour-Holter monitoring published by Massin et al. for healthy infants [19].

### Processing and Analysis of 24-hour-Holter Recordings

Autonomic control of autonomic function was assessed by time domain analysis of 24-hour ambulatory digital recordings of the electrocardiogram. Two-channel Holterrecorders were used while the children followed their normal daily routines. All Holter recordings were reviewed by an experienced cardiologist and were edited to validate the system's QRS labeling in order to exclude artifacts. Measures of HRV were calculated employing only normal to normal intervals. The Holter ECG's were analyzed as average values from the entire 24 hours of analyzable data.

### Time Domain Measures

Measurement and physiological interpretation of HRV parameters were performed according to the standards of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [20]. Mean RR interval, resulting heart rate and the following HRV parameters were calculated as 24-hour average values: square root of the mean of the sum of squares of differences between adjacent NN-intervals (rMSSD), the standard deviation of NN intervals (SDNN) and number of pairs of adjacent NN intervals differing more than 50 ms divided by the total number of all NN intervals (pNN50). rMSSD, pNN50, and heart rate predominantly reflect a response to changes in vagal tone. SDNN is dually influenced by cholinergic and adrenergic activity, as well as other physiological inputs.

### Frequency Domain Measures

Beat-to-beat fluctuations were transformed to the frequency domain using Fast Fourier Transformation. Spectral power was determined over three frequency regions of interest: very low frequency power (VLF, 0.004 - 0.04 Hz), low frequency power (LF, 0.04 - 0.15 Hz) and high frequency ipower (HF, 0.15 - 0.4 Hz) with derived LF/HF ratio. High frequency power reflects mostly vagal tone.

### Statistical Analysis

All results are reported as mean  $\pm$  standard deviation. Because most clinical variables were normally distributed, parametric techniques were used. Differences between the patients groups and controls were tested with an unpaired t-test. For all parameters, a p-value of  $p < 0.05$  was considered statistically significant. The data analyses were performed using Prism™ Version 6.00 (GraphPad software Inc., USA).

### Ethics

After publication of the compassionate use trial with 6 infants [10], the 10 infants in Göttingen were treated in the prospective randomized trial: CHF-PRO- INFANT[4]. The German Federal Institute for Drugs and Medical Devices (BfArM) and the local ethics committee approved the protocol, which was conducted in accordance with the Declaration of Helsinki II and the Note for Guidance on Clinical Investigation of Medicinal Products in children (CPMP 1997). The parent's written consent was obtained.

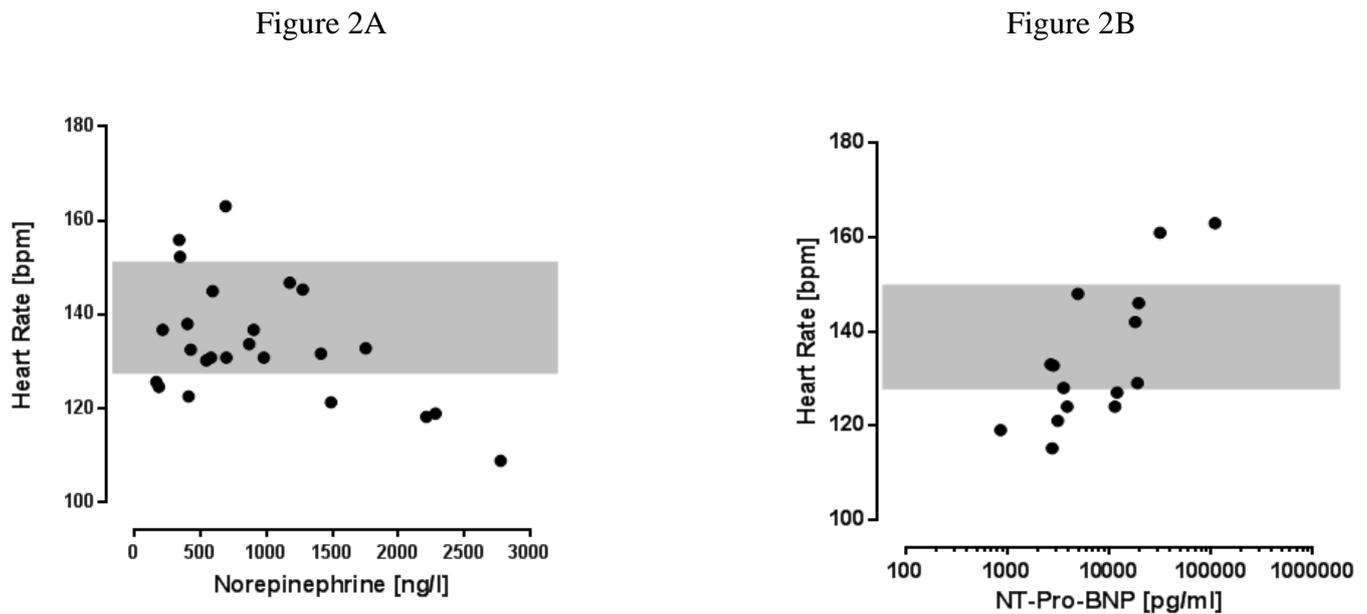
After this trial, propranolol treatment for heart failure in infants with congenital heart disease became part of the German guidelines published by the German society of pediatric cardiology. According to this guideline propranolol is a part of the local clinical routine in Oldenburg and Bad Mergentheim.

### Results

The infants with CHD and norepinephrine levels below 700 $\mu$ g/l had normal global HRV measured by SDNN; however, the vagus activity, measured by rMSSD was reduced.

Infants with CHD and elevated norepinephrine levels due to heart failure who received a standard therapy with diuretics  $\pm$  digoxin showed normal mean heart rates on average. In contrast to adults with decompensated heart failure [21], we could not find a correlation between average 24-hour heart rate and norepinephrine levels. To our surprise average heart rates were reduced in infants with the highest norepinephrine levels (Figure 2A). However we found a significant correlation between the mean 24-hour heart rates and NT-Pro-BNP levels ( $r=0.706$ ;  $p=0.0033$ ; Figure 2B). Autonomic dysfunction in all infants with elevated norepinephrine levels were indicated by low HRV with significantly reduced SDNN values and vagus activities measured by rMSSD (Table 1). We found a significant improvement of HRV after the reduction of the mean heart rate to sub physiological values with 2mg/kg/day propranolol. However, vagus activities remained reduced despite this improvement of HRV. The 28 infants who additionally received digoxin had significantly higher rMSSD values compared to the 12 infants who received no digoxin.

**Figure 2:** 24 hour heart rate according to neurohormonal activation



24 hour average heart rates in infants with congenital heart defects did not correlate with norepinephrine level(A) but we found a significant correlation between the mean 24hour heart rates and NT-Pro-BNP levels (B,  $r=0.706$ ;  $p=0.0033$ )

**Table 1:** 24 hour heart rate variability in infants with heart failure due to congenital heart disease

	Healthy Control	No Therapy NE < 700 µg/l	Digoxin/Diuretics NE > 700 µg/l	Propranolol	- Digoxin	+ Digoxin
N	44	13	12	40	12	28
Age [Month]	3.5 ± 3.2	3.4 ± 0.6	2.6 ± 0.6	3.6 ± 2.8	2.4 ± 2.6	4.3 ± 2.8
Heart Rate [bpm]	139 ± 13	132 ± 13	137 ± 13	<b>119 ± 9****</b>	119 ± 8	119 ± 11
SDNN [ms]	60.9 ± 21.8	52.6 ± 19.3	<b>37.3 ± 14.6****</b>	<b>45.0 ± 18.7*</b>	47 ± 14	44 ± 15
rMSSD [ms]	22.4 ± 10.1	<b>16.5 ± 7.6*</b>	<b>15.2 ± 7.2 **</b>	<b>16.5 ± 9.7*</b>	11.8 ± 5.5	<b>19.8 ± 9.9*</b>

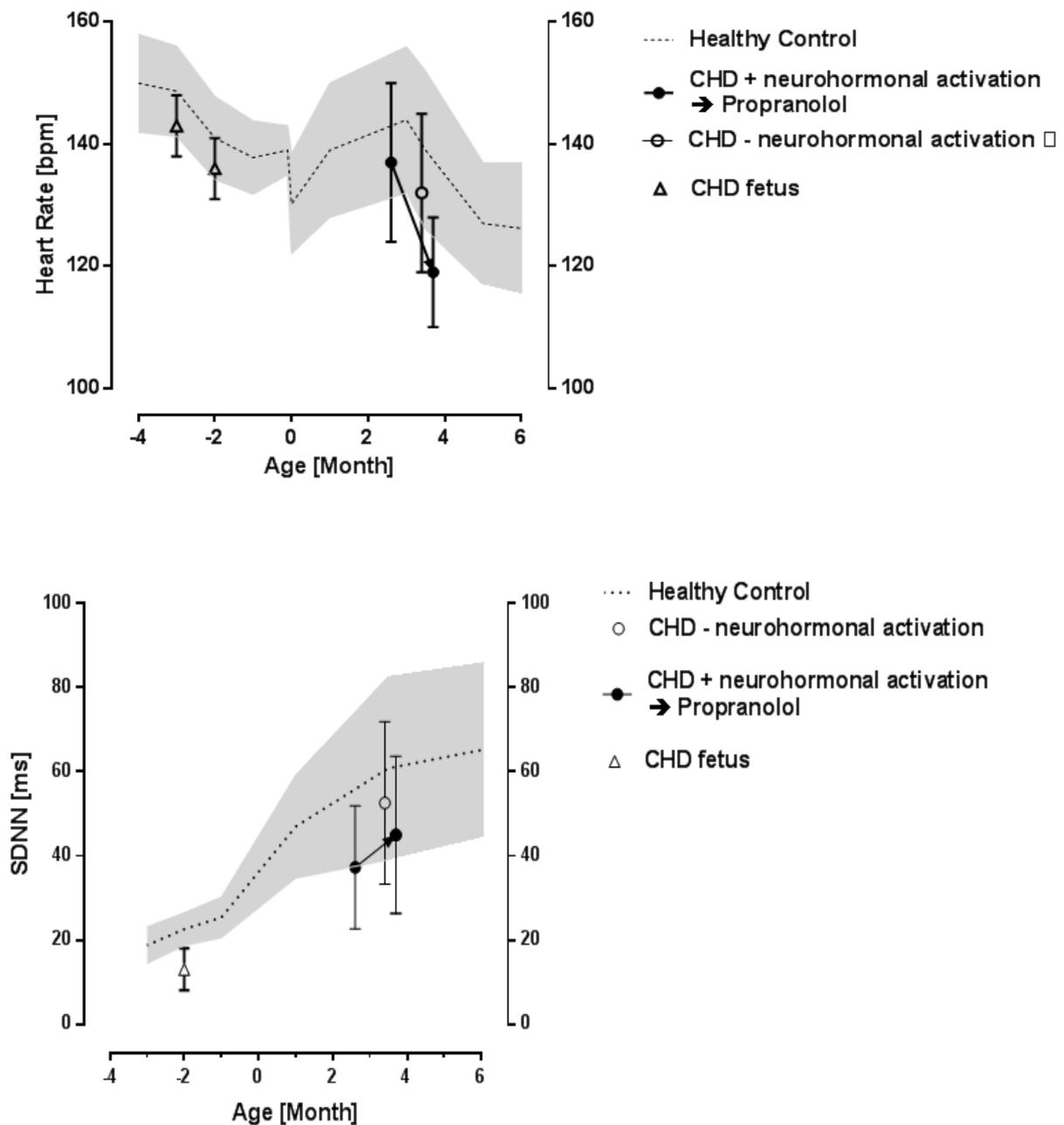
Values are given in mean ± SD. Probability of difference using student t-test; significant values are in bold: \* P-value < 0.005; \*\* P-value < 0.001; \*\*\*\*P-value < 0.0001

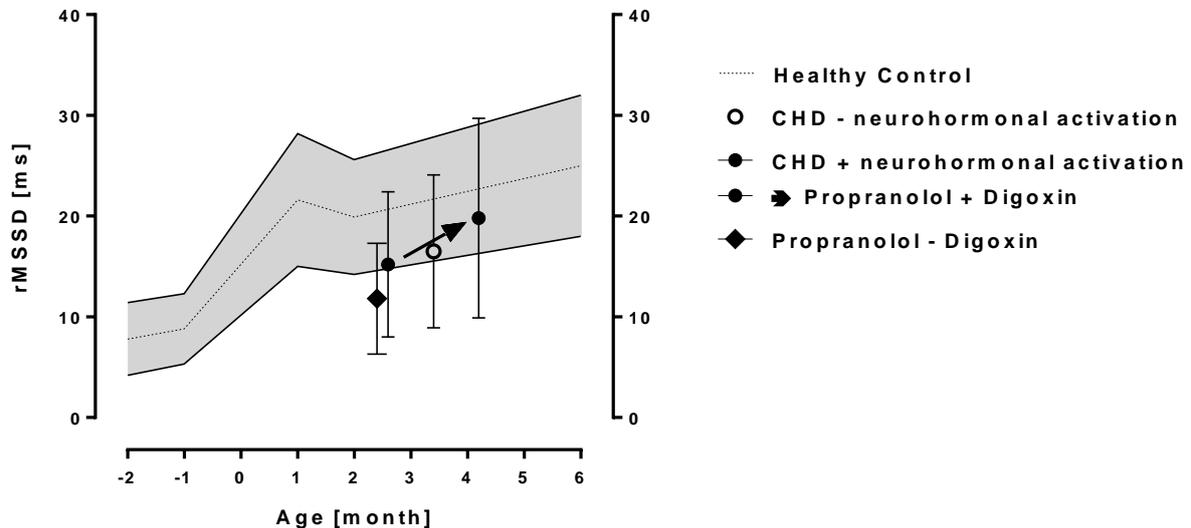
SDNN: Standard deviation of all NN intervals; rMSSD: The square root of the mean of the sum of the squares of differences between adjacent NN intervals

To evaluate our concept of autonomic imprinting we compare our HRV data with data from the literature [22, 23]. Autonomic regulation in fetuses with CHD, including hypoplastic left heart syndrome, transposition of the great arteries and Tetralogy of Fallot, had significantly reduced heart rates and HRV (Figure 3). These heart rates remained in the low normal range in all infants but global HRV is only

reduced in infants with elevated norepinephrine levels due to heart failure. As shown in utero, infants with most severe congenital heart defects (e.g. hypoplastic left heart syndrome) have low heart rates and the lowest HRV. Vagus maturation indicated by an increase of rMSSD in and ex utero (Figure 3) seems to be reduced in nearly all infants with significant congenital heart disease.

**Figure 3:** Fetal and neonatal heart rate variability in patients with congenital heart disease compared to healthy controls (fetal data from literature [22])





Maturation of the autonomic nervous system in and ex utero illustrated by normal values from the literature [19, 22, 23].

## Discussion

Although mortality due to childhood heart failure is dominantly seen in infants with congenital heart disease, research in this high risk group is very limited. Despite our promising results of beta blockers in infants with severe heart failure due to CHD, these patients were excluded from the US carvedilol trial [24]. The US enalapril trial focused on infants with single ventricle but again as shown by the relatively low BNP values (80; 44–155 pg/ml in the so called high risk group [16] infants with severe heart failure dropped out. Thus, to include this high-risk group, our study population consists of infants with heart failure due to congenital heart defects from three separate Pediatric Departments in Germany (n =40).

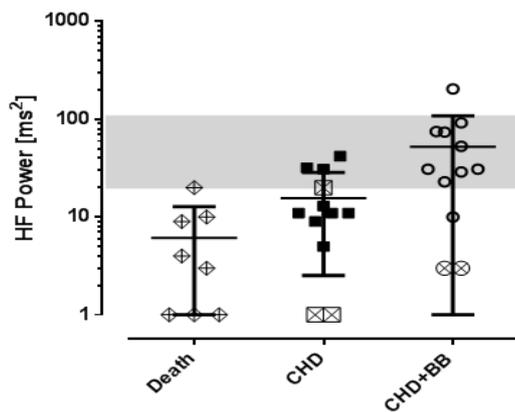
The treatment of these high risk infants demands close monitoring. Methods for monitoring heart failure in infants have evolved from plasma rennin and norepinephrine measurements to NT-Pro-BNP measurements. In 2000 we implemented heart rate variability (HRV) by Holter ECG's and we were able to publish the results in 2001[4] and 2004[18]. We further improved this method and for this study, we were capable of HRV online-Monitoring from routine ECG monitors on our intensive care unit at the Caritas Hospital in Bad Mergentheim (Dräger Infinity™ to Pathfinder™, Reynolds, Germany).

The clinical benefit of propranolol in infants with severe heart failure is documented in two prospective randomized trials [4,8]. This paper focuses on the effect of propranolol with or without digoxin on the autonomic nervous system. As previously shown in adults [26] and children [18], we found a significant improvement of global HRV indicated

by higher SDNN values in patients who received beta blockers for heart failure treatment. However, vagus activity, indicated by rMSSD, increased after introduction of propranolol but remained significantly reduced in infants with the lowest rMSSD values and in infants who didn't received additional digoxin. Infants with CHD, norepinephrine levels below 700µg/l, and normal global HRV measured by SDNN seemed to need no medical therapy for heart failure although all the congenital heart defects of these infants had to be operated due to hemodynamic reasons.

The beneficial effect of digoxin on vagus activity has been shown in adults with heart failure [27]. Differences between treatment groups with or without digoxin were also seen in this study's pediatric population. Of note are two infants with Down's syndrome and single ventricle who were treated for the first time with propranolol late at the age of 6 and 10 month after pretreatment with only diuretics in other hospitals. In contrast to the other infants, vagus activity measured by rMSSD or high frequency power in these two infants remained extremely low (Figure 4). Both infants died before the next operative step. The first infant died from an intractable inflammatory disease called hemophagocytic lymphohistiocytosis published in 2010 [7]. The second infant died after the preoperative heart catheter at the university hospital. Interestingly, all infants in our institution who died within the last 4 years of cause cardiac and non-cardiac disease had such low vagus activities measured by online HRV monitoring on our intensive care unit (Figure 4). In accordance with a prospective trial of HRV risk stratification in premature infants with necrotizing enterocolitis, we measure this very low HF-Power more than 1 week before the infants died [28].

**Figure 4:** 24 hour HRV online monitoring from the intensive care unit

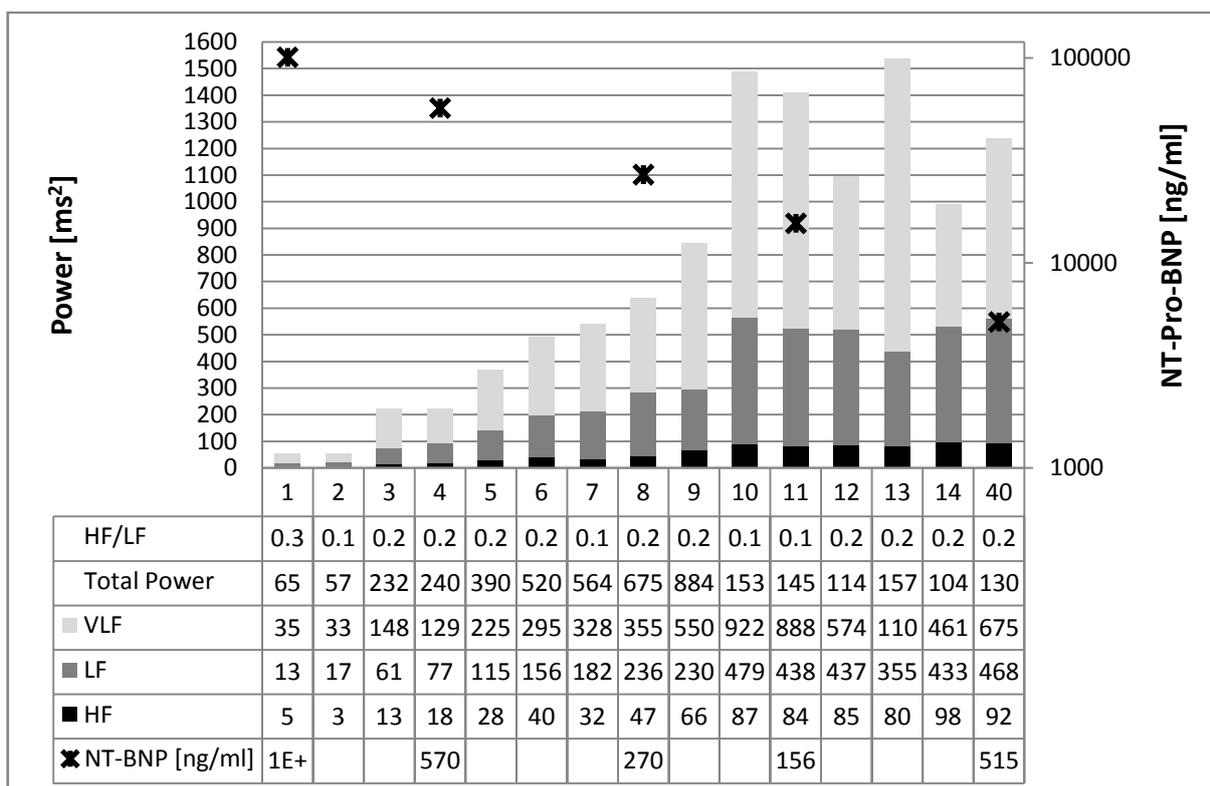


24 hour HRV analysis by online HRV monitoring from the intensive care unit Bad Mergentheim. Prior to beta blockers (group CHD) the infants have reduced vagus activity measured with the frequency domain parameter HF Power. HF Power improves during beta blocker treatment (group CHD+BB) but remained low in the two children with very low HF Power who died some month later. One infant with trisomy 18 and single ventricle received no medical therapy and died in a palliative setting. All infants who died on this intensive care unit from cardiac and non-cardiac reasons (group Death) had such low HF power below 20 ms<sup>2</sup> more than 1 week before death.

Based upon these observations and the possibility for online HRV monitoring, we started carvedilol in a neonate with Down's syndrome and VSD with a very high NT-Pro BNP value of 101000 pg/ml who was treated with dobutamine due to left ventricular dysfunction. As shown in figure 5, we could stop dobutamine after 24 hours while HRV increase to normal values within one week and NT-Pro BNP decrease

rapidly. The baby could be quickly weaned from ventilator and complete breastfeeding was established at the time of admission after 2 weeks. Up to the successful operation, treated with 0.7 mg/kg carvedilol, he was free of clinical heart failure with normal weight gain. The baby was successfully operated at the age of six month.

**Figure 5:** Effect of the switch from dobutamine to carvedilol therapy at day 2 on online- HRV and NT-Pro-BN Pin a neonate with severe heart failure due to VSD



In conclusion, we have to modify our current pathophysiological model of infants with heart failure [29]: Today, we realize that infants with mild heart failure due to congenital heart disease have reduced vagus activities on average indicated by significantly reduced rMSSD. Withdrawal of vagal activity seems to be the first negative impact to the autonomic nervous system in patients with congenital heart disease in and ex utero and may be translated into differences in growth and neurodevelopment outcome. There are no data if or how to treat isolated withdrawal of vagal activity in infants without clinical heart failure. The second hit to the autonomic nervous system is sympathetic activation by heart failure but in contrast to adults with heart failure[30] the fetal and neonatal ANS seems to be able to prevent the deleterious effect of increased heart rates perhaps by down-regulation of the adrenergic receptors. In this situation, beta blockers reduce heart rate to sub physiological values and improve HRV. Perhaps digoxin is able to further improve vagus activity. Immune activation seems to be the third and final hit to the autonomic nervous system if vagus activity further decreases [31] to values below high frequency power of 20ms. In this life-threatening situation, especially in infants with a long history of untreated neurohormonal activation, vagus activity does not seem to improve after beta blockers. Future research should investigate whether specific immune therapy will improve prognosis in these infants with the highest risk to die.

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## Limitations

Methodological limitations of our study include high dropout rates and small sample populations, as in other trials with ACE inhibitors [5] or beta blockers [24]. These limitations may be attributed to high mortality rates of infants with heart failure. According to Inuzuka R, et al.[25], the mortality rate was 60% in infants at the first stage towards Fontan circulation with BNP > 100 pg/ml. We can clearly demonstrate the severity of heart failure of our infants with very high norepinephrine levels and NT-Pro-BNP values of infants with severe heart failure [32]. However we need 20 years to collect 40 well documented cases with such a high neurohormonal activation.

## Disclosures

Authors have nothing to disclose and have no conflict of interest.

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