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Medical Treatment of Heart Failure in Infancy has Long Term Effects on the Autonomic Nervous System – The Concept of Autonomic Imprinting

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Abstract

Heart failure is the main cause of death in children with congenital heart disease (CHD) and has unfortunate long term consequences, such as impaired linear growth and worse neurodevelopmental outcomes. According to our recently published "Early Life Stress" model we attempt to prove whether medical therapy of heart failure in infancy can indeed modulate the autonomic nervous system (ANS) in the long-term follow up of these children.

Methods: Stress in terms of autonomic dysfunction was measured by Holter ECG. We examined a complete cohort of 49 children with operated CHD who were treated preoperatively with digoxin and diuretics if indicated (historical control group), in comparison to a complete cohort of 48 children who were treated with propranolol if brain natriuretic peptide levels were elevated (current concept group). If the historical control group had to be significantly older at the time of our analysis, we compared each group with an age matched healthy local control group.

Results: As shown in many publications, our historical control group shows significantly reduced HRV at the long-term follow up after surgery of CHD. Compared to an age matched healthy control group, the children of our current concept group have significantly lower 24 hour heart rates and higher HRV indicated by time domain and frequency domain analysis.

Conclusion: Our concept to modulate “early life stress” due heart failure from CHD with beta blockers, early surgery and careful use of diuretics improve heart rate variability in long-term follow up and may have long-term consequences on growth, neurodevelopmental outcomes and cardiovascular risk.

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 in infancy is the main cause of death in congenital heart defects (CHD) and has long term consequences, such as impaired linear growth [1] and faulty neurodevelopmental outcomes [2]. These patients, even those diagnosed with simple CHD have substantially increased long-term mortality and cardiac morbidity compared with the general population, most of all due to an increased risk of sudden cardiac death [3].

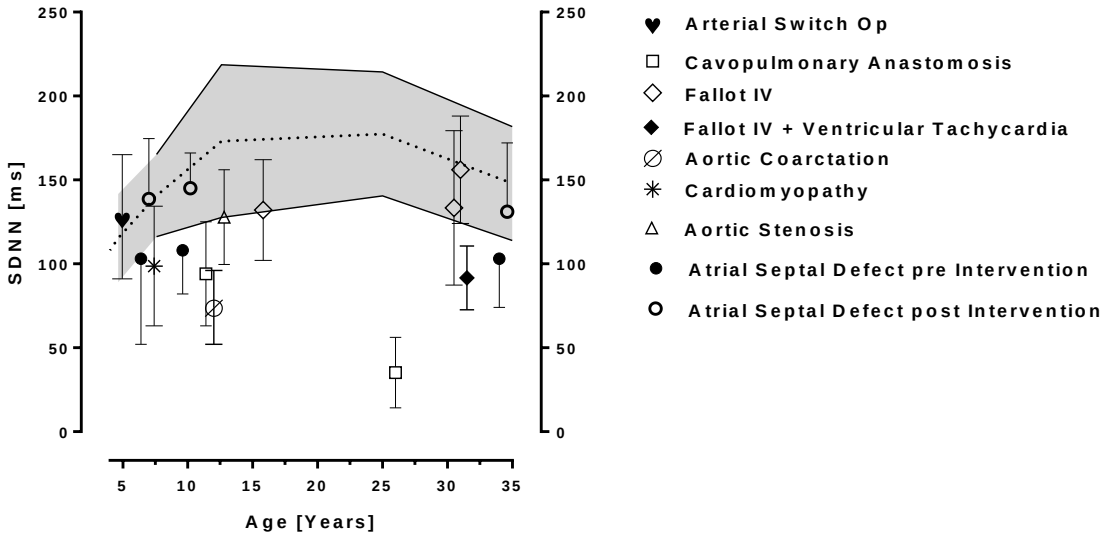
Buchhorn et al. [4] introduced propranolol for treatment of infants with severe heart failure due to congenital heart defects 20 years ago [4] and showed a clear clinical and neurohormonal benefit in a prospective randomized trial [5]. Heart failure in early infancy is one of the most prominent stressful life events that is best shown by highly elevated norepinephrine levels and reduced heart rate variability (HRV) in 24 hour ECG monitoring [6]. Recently, we published our concept of autonomic imprinting by early life stress in children with short stature [7] and in infants with heart failure due to congenital heart defects.

Heart rate variability - an indicator of the autonomic nervous system - is reduced in the long-term follow up after heart surgery of children with congenital heart defects, except in children with transposition of the great arteries after arterial switch operation in early infancy [8] or after interventional closure of atrial septal defects in early childhood [9, 10] (Figure 1). Reduced HRV is most pronounced in long term follow up of children with a single ventricle [11, 12] and Tetralogy of Fallot [13] and may be related to ventricular arrhythmias and sudden death [14].

We conducted a retrospective study using HRV data from a complete cohort of children with congenital heart defects from a single department of pediatrics and compared two conceptual concepts of treating heart failure in infancy within the last 16 years: Up to 2004 children with significant heart defects were routinely treated with digoxin and diuretics preoperatively (=Historical Control Group). After 2005 infants who had developed heart failure indicated by elevated NT-BNP blood levels were treated with propranolol preoperatively (=Current Concept Group). This treatment protocol and the immediate effects on HRV were published in detail recently.

We present our current concept of autonomic imprinting by analyzing the effect of pharmacological blockade of early life stress due to heart failure on long-term HRV after surgery of congenital heart defects.

Figure 1: Global HRV indicated as SDNN in Patients with Congenital Heart Defects from literature



Methods

Subjects

Patient characteristics and type of surgery are illustrated in table 1. The complexity of the cardiac surgery indicated by the Aristoteles Score is not significantly different between the groups and relatively high with only 3 or 4 catheter interventions per group. The most important differences between the two groups are:

a) Significantly lower age at cardiac surgery and
b) Higher preoperative use of beta blockers in infants with heart failure in the current concept group.

If the historical group had to be significantly older in comparison to the current concept group at the time of our analysis we compare each group with an age matched healthy local control group recently published in the International Journal of Cardiology (table 2).

Table 1: Comparison of Congenital Heart Defects and Cardiac Surgery

	1 - 10 Years Current Concept	11 - 16 Years Historical Control
Simple Septal Defects	29	24
Fallot like Defects	4	11
Aortic Coarctation	7	3
Valvular Defects	2	5
Single Ventricle	4	3
Transposition of Great Arteries	3	2
Surgery versus Intervention	45 versus 3	45 versus 4
Aristoteles Score	6.9 ± 2.9	7.5 ± 3.6
Age at Operation [years]	1.4 ± 1.8	3.4 ± 3.4**
Preoperative Beta Blockers	10	0
NT-BNP [pg/ml]	225 ± 358	165 ± 250

NT-BNP: Brain Natriuretic Peptide; ** P-value < 0.001 of the T-test

Table 2: Comparison of Children with Congenital Heart Defects with Healthy Controls in two time periods

	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
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
TP	3547 ± 2141	5772 ± 4112****	0.0004	6551 ± 3096	4675 ± 3332**	0.0036
VLF	1854 ± 1263	3543 ± 3057***	0.0001	3949 ± 2549	2608 ± 1808**	0.003
LF	978 ± 629	1371 ± 853**	0.0067	1676 ± 616	1155 ± 783***	0.0002
HF	618 ± 336	730 ± 745	ns	857 ± 331	821 ± 1310	ns
HF/LF	0.68 ± 0.23	0.56 ± 0.26*	0.011	0.53 ± 0.17	0.63 ± 0.39	ns

BMI: Body Mass Index; 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:

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

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 Holter recorders 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 [15]. 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 power (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 ± standard deviation. Because most clinical variables were normally distributed, parametric techniques were used. Differences between the patient 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 [4], we performed the prospective randomized trial: CHF-PRO – INFANT [5]. 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 Bad Mergentheim.

Results

Compared to the age matched healthy control group the children of our current concept group had significantly lower 24 hour heart rates and higher HRV indicated by time domain and frequency domain analysis (table 2). Arrhythmias indicated by the number of premature ventricular contractions in 24 hours were not significantly different in comparison to the healthy control group.

As shown in many publications from other groups, our historical control group shows significantly reduced HRV as well as a significant increase in premature ventricular contractions in 24 hours after cardiac surgery of CHD. This difference is illustrated for global HRV in Figure 2 and vagus activity indicated by rMSSD values in Figure 3. Preoperative data from our former publications are illustrated in these figures.

The height percentile of the current concept group with 26.2 is significantly lower than the control group (45 percentile), whereas the percentile of body weight does not show any statistical difference between those groups (table 2). In the current concept group 7 out of 48 (15%) have a height/age z-score < (-2). Mean height/age z-score of -0.94 ± 1.04 in the current concept group is not significantly different from the historical control group (-0.67 ± 1.6). However the historical control group shows normal height (41.5 percentile) and normal body mass index (51.3 percentile) and does not differ from the control group.

Figure 2: Global heart rate variability indicated as SDNN in children with congenital heart defects

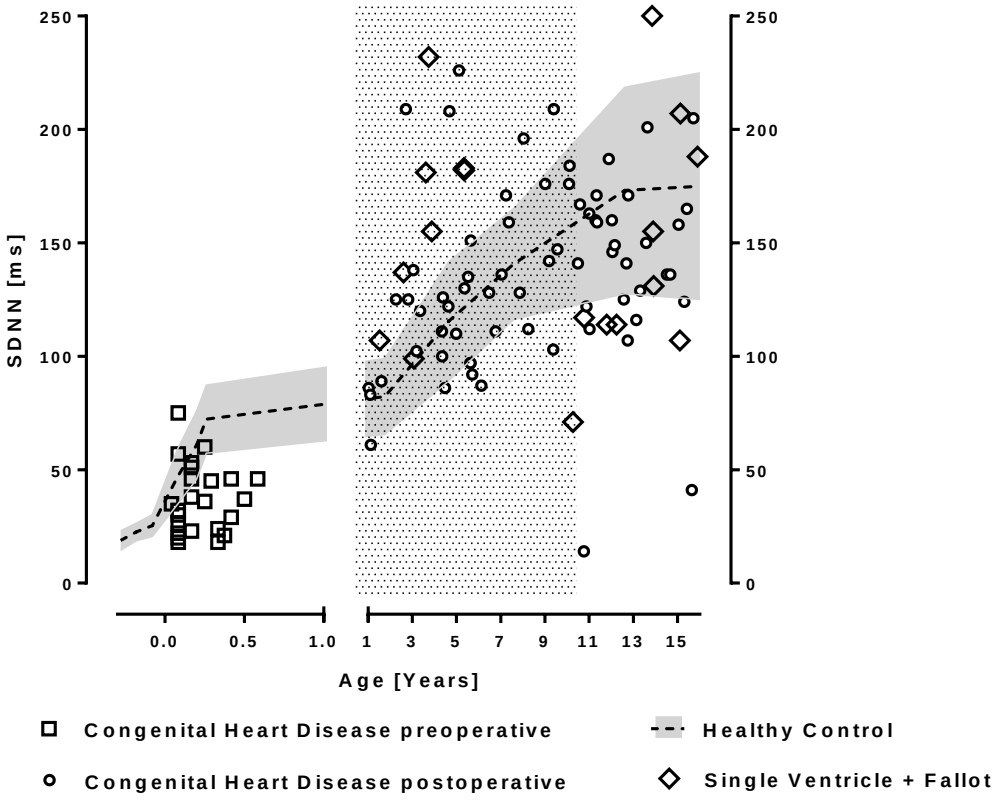
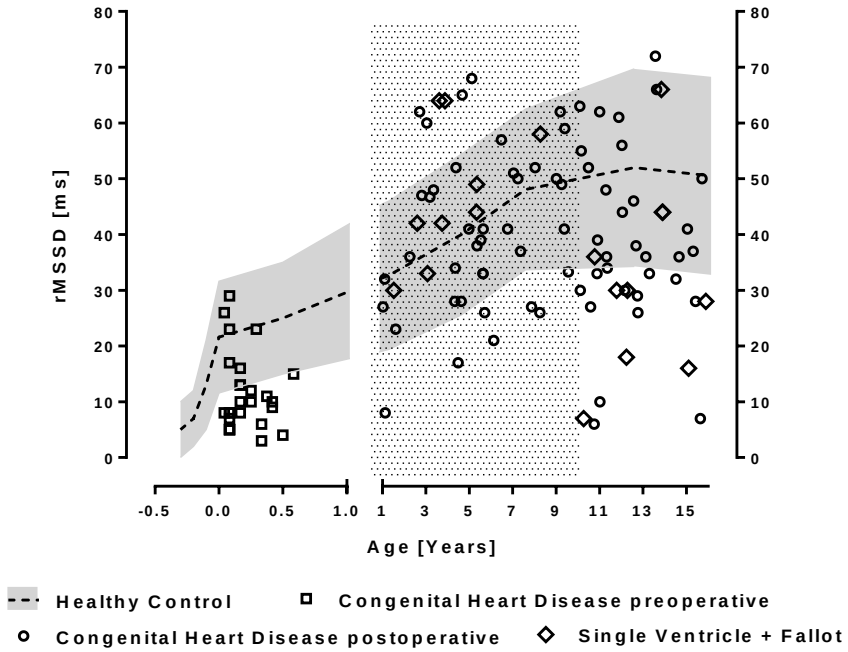


Figure 3: Vagus activity indicated as rMSSD in children with congenital heart defects



Discussion

Our current concept of treating heart failure due to congenital heart disease in infancy, is based upon our prospective randomized trial [5] and a well-defined pathophysiological concept as recently published: Withdrawal of vagal activity seems to be the first negative impact on the autonomic nervous system in patients with congenital heart disease post-natal and may be translated into differences in growth and neurodevelopmental outcome. There are no data to suggest, if or how to treat isolated withdrawal of vagal activity in infants without clinical heart failure. The second effect on the autonomic nervous system is sympathetic activation by heart failure; but in contrast to adults with heart failure, the fetal and neonatal autonomic nervous systems (ANS) seem 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. The third and final end result which effects the autonomic nervous system seems to be the immune activation, in the case that vagal activity further decreases to values below high frequency power of 20ms [16]. In this life-threatening situation, especially in infants with a long history of untreated neurohormonal activation, vagal activity does not seem to improve after beta blockers - two of our infants died in this situation in our institution as recently published [17].

All other infants survived with a good long-term outcome and we have now come to realize that these children do not show the damage of the autonomic nervous system as frequently shown in long-term follow up, most of all in children with complex heart defects with ongoing heart failure or cyanosis in infancy due to a single ventricle or Tetralogy of Fallot. Traditionally heart failure in these infants is treated with digoxin and diuretics, such as in our historical control group as well as in many other institutions. Our current concept of treating heart failure in infancy is comprisedof much more than only treating heart failure with beta blockers which was only necessary in 10 infants: We further did not use unproven drugs like ACE-inhibitors and we had only used diuretics on some infants with clear clinical congestion. We were in favor of performing cardiac surgery as early as possible with a mean age of 1.4 years on average: Those infants with heart failure due to left-to-right shunts and Tetralogy of Fallot were operated at six month and a target body weight of six kilograms. During the entire study period all our children were operated at the same university hospitals and in most cases by the same surgeons in Southern Germany.

Our data refute a hypothesis from H. Ohuchi et al. [18] published in several papers in *Circulation*, who speculates that cardiac surgery per se, along with surgery-related damage, impairs cardiac autonomic nervous activity, and “no further improvement in cardiac autonomic nervous activity may be expected in the future”. He discussed three possible explanations for the severely impaired cardiac autonomic nervous activity in Fontan patients: (1) surgery-related direct and/or subclinical damage, such as ischemia and/or denervation…; (2) heart failure, as demonstrated in adult cardiac patients; and (3) preoperative pathology, such as hypoxia. Data before and after the arterial switch operation [8] clearly indicate that this damage of the autonomic nervous system is not an inevitable consequence of cardiac surgery but rather an avoidable consequence of early life stress due to heart failure. The time has come that pediatric cardiologists must assume the responsibility of the fatal long-term consequences of an unproven and failed heart failure therapy in infants with CHD [19].

In our concept growth is an indicator of early life stress as recently published [7]. Many groups had shown impaired growth in children with CHD most of all related to heart failure in infancy. Our current concept group with an average age of 5.3 years is significantly shorter compared to the control (height percentile 26.2 vs 45.4, Table 2). One explanation could be due to constitutional growth delay as published in 2009 [20]. However only 7 children (15%) have a height/age z-score < (-2): 3 of them had Down's syndrome, one a microdeletion 22q11and one a proven growth hormone deficiency. The remaining two children were operated on coarctation of aorta at 4 weeks of age and a 10mm atrial septal defect at the age of 4 years respectively. None of the children with severe CHD in our current concept group shows dwarfism! The history of dwarfism in children with congenital heart defects is intriguing: In 1962/27% [21], in 1995/37% [22] and 2015/21% [23] children with CHD showed a height below two standard deviations. These comparisons indicate that despite earlier diagnosis and major advances in medical and surgical management, growth restriction remains an ongoing problem. Dwarfism in our current concept is nearly completely related to congenital syndromes and the mean height/age z-score of -0.94 ± 1.04 is higher than -1.06 ± 1.47 recently published by CL Costello [23]. In later life patients with CHD show an incomplete catch-up growth that is more pronounced in women with normal target heights [24] as shown in our historical control group.

Moreover, with respect to impaired neurodevelopmental outcomes after surgery of CHD [25-27], attention deficit disorder with and without hyperactivity occur in many children after surgery of CHD [28] most of all after surgery in the first year of life [29]. We could show that attention deficit disorder is related to reduced HRV, most of all reduced vagal activity indicated by the parameter rMSSD [30]. Compared to the age matched healthy control group rMSSD is enhanced in our current concept group and significantly reduced in the historical control group.We urgently need psychological test data if this difference truly is related to a better neurodevelopmental outcome. The impact of early life stress on cognitive and emotional disease in later life is well known [31]. If early life stress is not preventable due to intractable disease like heart failure (or prematurity,…..) it would be very useful to improve long-term outcome by pharmacological blockade much like shown in our current concept group.

Sudden cardiac death seems to be the most important cause of late mortality in patients with CHD, as recently shown even in those patients with simple heart defects [3]. Sudden death is related to disturbances of the autonomic nervous system indicated by low HRV [32]. Nearly all data from adults indicate that high HRV – as demonstrated in our current concept group – is the best "life insurance" against sudden cardiac death.

Conclusion

In conclusion, our concept to modulate "early life stress" due heart failure from CHD with beta blockers, early surgery and careful use of diuretics improve heart rate variability in long term follow up and may have long-term consequences on growth, neurodevelopmental outcomes and cardiovascular risk (Figure 4).

Figure 4: Our concept according the big unsolved problems in pediatric cardiology:

1. Heart Failure (in infancy)
2. (Lifethreatening) Arrrhythmias
3. Impaired Neurodevelopment
4. Growth Failure (as a surrogate parameter)

- Is there a common target?
- Yes – Autonomic Nervous System
- Is there a common cause?
- Yes – Autonomic Imprinting by Early Life Stress

Limitations

This retrospective study shows preliminary data to prove a concept called: autonomic imprinting by early life stress. There are many limitations according to unproved differences in the treatment of congenital heart defects in different time periods, such as operative technique, anesthesia and postoperative care. However nobody has shown that this therapeutically progress improves HRV, neurodevelopmental outcome [33], cardiovascular risk or final height [23] in long term follow up. In 2005 R. Buchhorn left university to further develop his concept of autonomic imprinting in a small department of pediatrics in the rural part of Germany, if this concept was not supported by local, national and international "stakeholders" [34]. At that time period it would not have been possible to acquire any financial support for a prospective study to proof this concept with a follow up of more than 10 years.

Disclosures:

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

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