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Case Report

Improving Pharmacotherapy for Heart Failure in Infants with Monitoring of Heart Rate Variability

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ABSTRACT

Heart failure is one of the main causes of death in infants with and without congenital heart disease and has long term consequences in surviving infants, such as impaired linear growth, worse neurodevelopmental outcomes and an enhanced cardiovascular mortality. Current pharmacotherapy is not proven by prospective randomized trials. We use online monitoring of heart rate variability (HRV) to measure the effect of pharmacotherapy on the autonomic nervous system.

Methods: The infants are routinely monitored with Dräger Infinity Monitors™ (Dräger; Germany) on our pediatric intensive care unit. For analysis of heart rate variability, we export the monitor data to the Pathfinder™ ECG Software using a network connection. 7 clinical cases are discussed.

Results: Infants with a high frequency power in the spectral analysis of heart rate variability below 20ms had a high risk to die from heart failure ± inflammation. Propranolol but not metoprolol improves HRV, NT-Pro BNP and troponin T values. We anticipate a further improvement of HRV in 2 cases with an additional digoxin treatment.

Conclusion: Reduced HRV seems to be an important risk factor for life threatening complications in infants with severe heart failure and should be monitored in infants with severe heart failure. Propranolol but not metoprolol improves HRV. Additional digoxin further improves HRV in two cases treated with propranolol. These preliminary results have to be proven by prospective trials using HRV analysis for risk stratification.

Introduction

Heart failure is the main cause of death in children with congenital heart disease. Three quarters of heart failure related death in childhood with congenital heart disease occur in infancy [1]. A simplified picture from different sources about the global burden of pediatric heart failure will help to identify the specific problems in childhood heart failure:

- Two thirds of children who die from heart failure are infants
- The main cause of childhood heart failure in Europe and the US are congenital heart defects (80% overall, 40% left-to-right shunts and 20% complex heart defects)
- The main causes of childhood heart failure in the developing world are acquired heart failure due to anemia and infections
- Heart failure is one of the main causes of infant mortality worldwide.

Moreover, heart failure in infancy has longtime consequences: In 2015, we published a model called “autonomic imprinting” based on heart rate variability measurements that offers an explanation on how early life stress impairs growth, cognition, and increases cardiovascular risk in later life [2]. Heart failure is only one of the different causes of early life stress, which include intrauterine growth retardation, prematurity and maternal stress.

Late mortality is the main problem after cardiac surgery in infancy not only in infants with severe congenital heart defects but also in infants with less severe congenital heart defects like atrial- and ventricular septal defects. One quarter of mortality after congenital heart surgery is related to simple left to right shunts in United States and Finland [3, 4]. Based upon the current hemodynamic models of postoperative heart failure after congenital heart surgery of these simple defects do not explain this

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late mortality. Today, we are able to demonstrate that our concept to prevent and treat early life stress in children with congenital heart defects has longtime beneficial effects on the autonomic nervous system as measured by 24 hour heart rate variability [5].

I Clinical trials in pediatric heart failure

Unfortunately, despite the fact that most of the children who died from heart failure in Europe and the US are infants with congenital heart defects, the main focus of heart failure research in pediatric cardiology has been in older children with ventricular dysfunction. There are only 4 prospective randomized trials in infants with heart failure due to congenital heart defects, three of these studies are investigator-initiated trials from Germany, Turkey and India [6-9]. In contrast to enalapril and digoxin, beta blockers improve clinical signs of heart failure and neurohormonal activation. The effect on mortality remains unclear in these small trials but is similar to the 13% in the enalapril and placebo group of the US trial. For this trial 230 from the 533 infants of the Single Ventricle Reconstruction Trial who were eligible were recruited, and 31 died. The overall one-year mortality of 555 infants with a single right ventricle was even higher (30%) [10].

II The current treatment of pediatric heart failure

It is unclear what the current practice in childhood heart failure is. Beta blockers are introduced in the German guidelines in 2006 and in the Canadian guidelines in 2013. It is certain that preoperative beta blocker treatment in infants with congenital heart disease remains highly controversial, but more and more pediatric cardiologists routinely use beta blockers (metoprolol or carvedilol) despite criticism from the opinion leaders. However, published data from the US show that infants with a single ventricle are treated with diuretics (90%), ACE inhibitors (38%) and Digoxin (28%) [11].

III The Digoxin Discussion

The discussion of pediatric cardiologists has been focused for nearly 100 years on the question whether digitalis should be used or not. The first reports on the effects of digitalis in children are published 1921 [12]. AS Nadas et al published the use of digitalis in 41 infants and children 1953 in the New England Journal of Medicine and conclude: "obviously the groups responding best were the patients with myocardial disease, paroxysmal tachycardia and rheumatic disease" and "…the patients with congenital heart disease, among whom therapeutic failures were numerous" [13]. With respect to the anticipated effect of digitalis on contractility in infants with a large ventricular defect, TR Kimball et al. concluded "when digoxin was added to diuretics, contractility index was significantly greater than in control subjects" without a significant improvement of clinical symptoms [14]. There is no prospective randomized trial within these 100 years that show any improvement after digitalis in infants with heart failure. In 1997 the Digitalis Investigation Group proof the effect of digoxin in adults with reduced ejection fraction and show that "digoxin did not reduce overall mortality, but it reduced rate of hospitalization both overall and worsening heart failure" [15].
With respect to these facts, we are surprised to the results from the Pediatric Heart Network Single Ventricle Reconstruction Trial published in 2016 that " Digoxin use in infants with single ventricle heart disease is associated with significantly reduced interstage mortality" [16]. However, two years later – using the same public dataset – DT Truong et al conclude: "Digoxin was not associated with improved survival during the interstage or at 14 months in a mixed single ventricle cohort," [17].

IV The Propranolol Way

Deeply impressed by Finn Waagstein's report about beta blocker treatment for heart failure published in 1975 and the neurohormonal heart failure model published by Milton Packer in 1993, I introduce beta blocker therapy in infants heart failure in 1996 in a compassionate use clinical trial with 6 infants who had severe heart failure due to congenital heart disease [18-20]. I shared a similar experience to Finn Waagstein with my disappointment treating infants with severe heart failure, because standard therapy with ACE inhibitors and loop diuretics was ineffective and the mortality remained unacceptably high as published in 2000 [21]. At this time, Propranolol was the most used beta blocker in pediatric cardiology most of all for the treatment of hypoxic spells in Tetralogy of Fallot and arrhythmias. However, there was a lack of acceptance by many of our peers and without any funding we performed the prospective randomized trial CHF-Pro-Infant published in 2001 [8]. It was the first prospective randomized trial who really showed a clinical improvement in this patient group. However, we cannot convince the international pediatric cardiologists to introduce propranolol in the treatment of infant heart failure. Recently we publish our results of 40 infants with severe heart failure treated in 3 different institutions with propranolol ± digoxin [22]. There is a significant improvement of clinical symptoms, neurohormonal activation and heart rate variability in propranolol treated infants. However, 28 infants who were treated with additional digoxin had significantly higher vagus activity indicated by the HRV parameter RMSSD (19.8 ± 9.9ms) compared to 12 infants who are only treated with propranolol (11.8 ± 5.5). These data have led to a reassessment of the use of digoxin in our clinic.

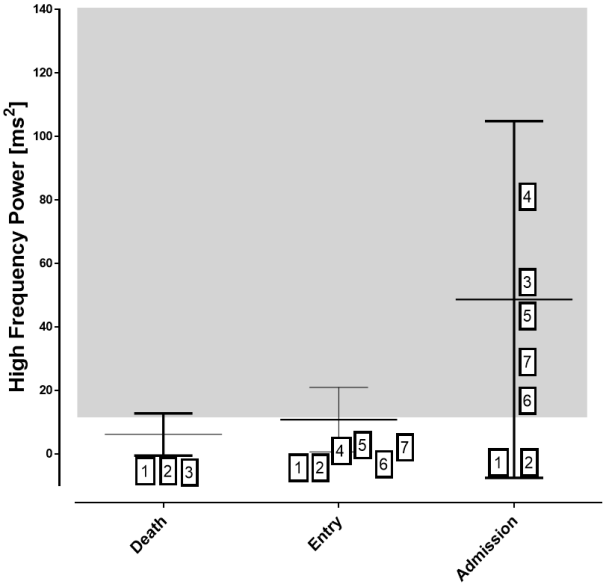

Figure 1: The HRV parameter high frequency power measured on PICU by HRV monitoring in 20 selected infants with severe disease. Eight infants die. The data of 7 infants – discussed in this case collection – are given at entry and admission. Normal values (5-95%) of healthy neonates are illustrated as grey box.

V Monitoring

We are aware that pharmacotherapy in these high risk infants with severe heart failure demands for a good monitoring. Starting with blood tests for renin and norepinephrine levels up to 2005 we currently use NT-Pro-BNP measurements. Beginning in 1998 we additionally used heart rate variability (HRV) monitoring with Holter ECG's in these infants. Currently we use online HRV monitoring in these infants on our pediatric intensive care unit (PICU), using a network connection between our Infinity Monitors™ (Dräger; Germany) with the Pathfinder ™ Holter ECG Software (Spacelab; Germany). We have HRV data from 20 infants with severe disease who were treated on our PICU as shown in (Figure 1). For this publication we select 7 cases, who demonstrate the effect of pharmacotherapy on the autonomic nervous system.

Methods

I Subjects

Within the last eight years, 8 infants died on our PICU. Three of these infants had a singular ventricle, two with a Down syndrome and one with trisomy 18. The two infants with Down syndrome had a palliation (pulmonary banding and resection of coarctation) and are treated with a beta blocker for severe heart failure prior to the next operative step (case 1 + 2). The infant with trisomy 18 had a palliative care and no operation. One infant who died, had a hypertrophic cardiomyopathy due to a mitochondriopathy. One further infant who died suffer from heart failure due to neonatal-onset multisystem inflammatory disease (NOMID). Further three infants, who died had no heart failure.

All other infants who received a beta blocker had successful cardiac surgery: Case 4 had 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 and was switched to carvedilol. Case 5 and 6 had severe heart failure despite treatment with metoprolol and are switched to propranolol. Case 6 and 7 received additional digoxin to improve ongoing heart failure despite propranolol.

II Processing and analysis of 24-hour-Holter recordings

The infants are routinely monitored with our Dräger Infinity Monitors™ (Dräger; Germany). For analysis of heart rate variability we daily export the monitor data to the Pathfinde ™ ECG Software using a network connection. 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. For this publication, we only use frequency domain measures if the time domain measures have very low values in neonates and cannot differentiate the changes of the autonomic nervous system.

III Frequency 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 [23]. 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). High frequency power reflects mostly vagal tone.

IV Ethics

After publication of the compassionate use trial with propranolol in 6 infants with severe heart failure, 10 infants were treated in the prospective randomized trial CHF-PRO- INFANT [8]. 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) [20]. The parent's written consent was obtained. Today, beta blocker treatment of pediatric heart failure is in accordance with our national guidelines. Carvedilol (for children > 1year) and propranolol (for infants) are proven in prospective randomized heart failure trials without any advices for severe adverse events in children with congenital heart disease. In the current cases, the technical implementation of heart surgery and cardiac catheterization as well as therapy planning took place in the cardio thoracic university centers. The conversion of the therapy was discussed extensively with the parents and an oral consent was obtained.

Results

Case 1

The boy who was born with Down syndrome and an unbalanced, left dominant atrioventricular septal defect with aortic coarctation. Despite coarctation repair and pulmonary artery banding, he suffers from intractable heart failure and fever of unknown origin. If he remained in heart failure despite multiple therapeutic and diagnostic efforts over 5 month intensive care to stabilize his cardiopulmonary status he received a low dose propranolol which resulted in dramatic immunomodulatory effects. Immunoactivation was indicated by high procalcitonin release and normoblastosis and leads to a hepatic compromise as indicated by high lactate dehydrogenase and alanine aminotransferase levels probably caused by macrophage activation. A therapeutic switch to β1 receptor blocker metoprolol appeared to be instrumental in hemodynamic improvement and allowed the discharge from hospital despite very low heart rate variability. However, the infant died of cause inflammatory reactivation and intractable pulmonary obstructive disease. The autopsy results revealed hemophagocytic lymphohistiocytosis. The interactions between the adrenergic system and the cytokine network in this highly activated inflammatory state are discussed in our publication [24].

Case 2

The girl who was born with Down syndrome, an unbalanced, left dominant atrioventricular septal defect and aortic coarctation. She had coarctation repair and pulmonary artery banding with uneventfully operative course with little signs of heart failure treated with low dose diuretics. The cardio thoracic center decides for a single ventricle repair and a bidirectional cavopulmonary anastomosis at the age of 9 month. However, she had a take-down at the second postoperative day and needs extracorporeal membrane oxygenation for 11 days. After successful

weaning she had severe heart failure with 4 mm aorto-pulmonary shunt. Online HRV monitoring shows the "collapse" of the autonomic nervous system with nearly no heart rate variability (Figure 2). Despite the clinical improvement with 2mg/kg propranolol the HRV remained extremely low. The girl died suddenly one day after the preoperative diagnostic heart catheter in the cardio thoracic center at the age of 14 months.

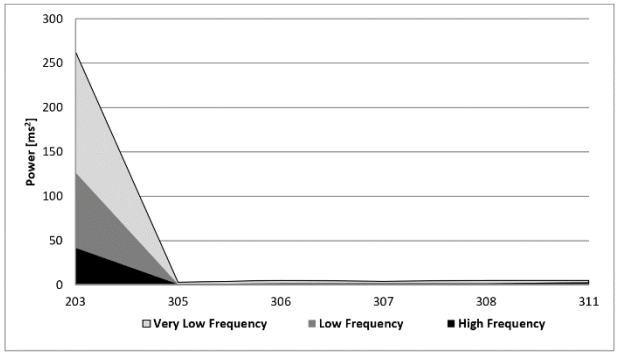

Figure 2: The girl who was born with Down syndrome, an unbalanced, left dominant atrioventricular septal defect and aortic coarctation. She had a take-down after a bidirectional cavopulmonary anastomosis at the age of 9 month and needs extracorporal membrane oxygenation. After weaning online HRV monitoring shows the "collapse" of the autonomic nervous system with nearly no heart rate variability. Despite the clinical improvement with 2mg/kg propranolol the HRV remained extremely low. The girl died suddenly one day after the preoperative diagnostic heart catheter in the cardio thoracic center at the age of 14 months.

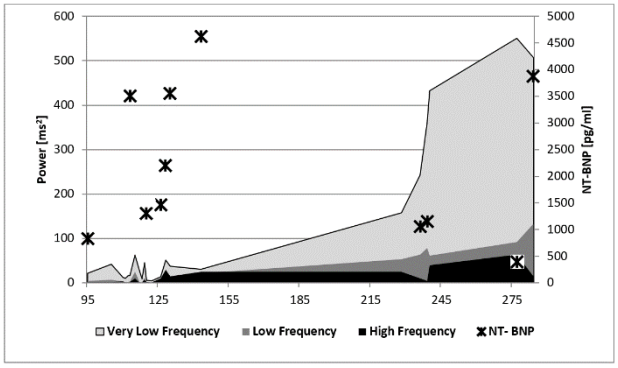

Figure 3: The girl was born small for gestational age with a birth weight of 1025g and after 31 gestational weeks. The clinical course was complicated by an inflammatory disease called neonatal-onset multisystem inflammatory disease (NOMID). She suffered from severe heart failure due to inflammation indicated by high NT-BNP levels and low HRV. If prednisolone cannot prevent these complications the baby received the interleukin -1 antagonist anakinra at day 230. There was an impressive clinical improvement, decrease of NT-BNP levels and increase of HRV.

Case 3

The girl was born small for gestational age with a birth weight of 1025g and after 31 gestational weeks. The clinical course was complicated by an inflammatory disease called neonatal-onset multisystem inflammatory disease (NOMID). It is the most severe form of CAPS (Cryopyrin-Associated Autoinflammatory Syndromes) and characterized by continuous often low grade fever, aseptic meningitis, cutaneous rash, and arthropathy, starting in the first weeks of life. Within the first year of life she suffered from multiple courses of systemic inflammatory response syndrome with pneumonia treated with antibiotics and mechanical ventilation. If prednisolone cannot prevent these complications the baby received the interleukin -1 antagonist anakinra at day 230. There was an impressive clinical improvement but unfortunately the baby died during the next pneumonia at day 290. Very high NT-BNP values indicate heart failure without congenital heart disease and normal ejection fraction. There was no clear clinical improvement with carvedilol therapy but after anakinra we observed a significant increase of HRV and decrease of NT-BNP values.

Case 4

We started carvedilol in this 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 4), 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.

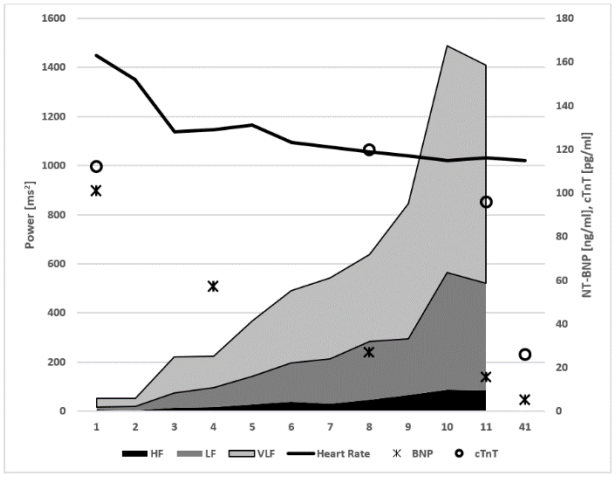

Figure 4: Carvedilol was started at the third day of life in this neonate with Down's syndrome and VSD with a very high NT-Pro BNP value of 101000 pg/ml, who was treated with dobutamine of cause left ventricular dysfunction. Dobutamine was stopped after 24 hours while HRV increase to normal values within one week and NT-Pro BNP decrease rapidly. Cardiac troponin T normalizes at day 41.

Case 5

This girl had biventricular repair of pulmonary atresia at the age of 6 month. She suffers from severe heart failure of cause the hypoplastic pulmonary arteries despite metoprolol, sildenafil, frusemide, hydrochlorothiazide and oxygen therapy. After 4 month of this unsatisfactory therapy we decide to change the cardio selective beta blocker metoprolol (24mg) to 15mg propranolol. HRV online monitoring on our PICU showed an impressive decrease of heart rate and increase of HRV (Figure 5). The clinical improvement gives us the

opportunity to stop therapy with sildenafil, diuretics and oxygen. NT-Pro-BNP drop down from 6476 to 837 pg/ml. This case demonstrate that propranolol has extraordinary effects on heart rate and HRV in infants with heart failure compared to metoprolol.

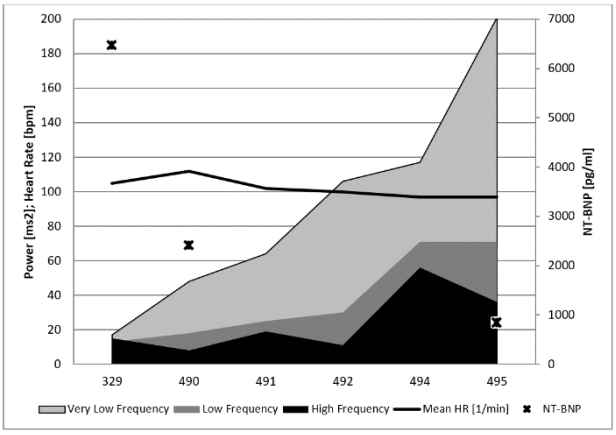

Figure 5: This girl had biventricular repair of pulmonary atresia at the age of 6 month. She suffers from severe heart failure of cause the hypoplastic pulmonary arteries despite metoprolol, sildenafil, frusemide, hydrochlorothiazide and oxygen therapy. After 4 month of this unsatisfactory therapy, we decide to change the cardio selective beta blocker metoprolol (24mg) to 15mg propranolol. HRV online monitoring on our PICU showed a decrease of heart rate and increase of HRV. The clinical improvement gives us the opportunity to stop therapy with sildenafil, diuretics and oxygen. NT-Pro-BNP drop down from 6476 to 837 pg/ml.

Case 6

This girl suffers from severe heart failure due to pulmonary overcirculation of cause a truncus arteriosus communis despite a pharmacotherapy with metoprolol, spironolactone and hydrochlorothiazide. Cardiac surgeons refused immediate operation because of low birth weight of 2400g but despite nasogastric tube there was no weight gain. We decide to change the cardio selective beta blocker metoprolol (0.5mg/kg) to 2mg/kg propranolol. The heart rate dropped down from 154 bpm to 134 bpm HRV but online monitoring on our PICU show only little improvement. After introducing digoxin we observe an improvement of HRV while the digoxin level increase and a further decrease of average heart rate to the target of 125 bpm. Based on a normal weight gain the baby was successfully operated with an age of 6 weeks and a bodyweight of 3,5 kg.

However, she had severe postoperative heart failure, treated with sildenafil, frusemide, hydrochlorothiazide, spironolactone and digoxin. She suffers from metabolic alkalosis due to high dose diuretic treatment and need complete nasogastric tube feeding. We introduce 2mg/kg propranolol and could terminate sildenafil, frusemide, hydrochlorothiazide, spironolactone and digoxin step by step. Again, heart rate variability improved, and nasogastric tube feeding could be terminated (Figure 7). Due to a residual septal defect, we are able to a close noninvasive monitoring of the pulmonalis pressure as shown in (Figure 7). The increase of heart rate variability is related to a decrease of the pulmonary pressure despite termination of sildenafil. However, the most impressive effect of propranolol is the improvement of right ventricular function measured by the myocardial performance index.

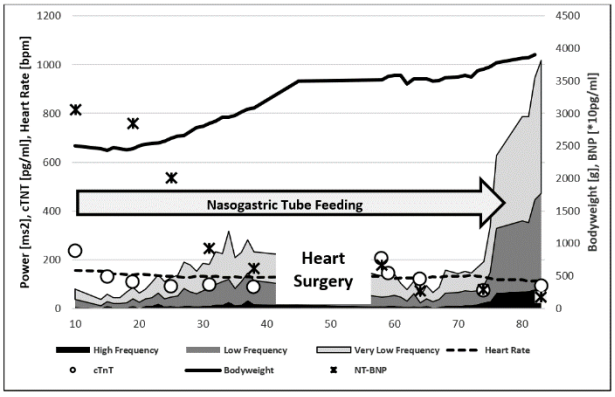

Figure 6: This girl suffered from severe heart failure due to pulmonary overcirculation of cause a truncus arteriosus communis despite a pharmacotherapy with metoprolol, spironolactone and hydrochlorothiazide. Cardiac surgeons refused immediate operation because of low birth weight of 2400g but despite nasogastric tube there was no weight gain. We decide to change the cardio selective beta blocker metoprolol (0.5mg/kg) to 2mg/kg propranolol. The heart rate dropped down from 154 bpm to 134 bpm HRV but online monitoring on our PICU show only little improvement. After introducing digoxin we observe a further improvement of HRV while the digoxin level increases and a further decrease of average heart rate to the target of 125 bpm. Due to improved weight gain she had successful cardiac surgery with 3.5kg bodyweight. Highly elevated NT-BNP and cardiac troponin T drop down after changing from metoprolol to propranolol. After corrective surgery she suffers from severe heart failure treated with sildenafil, frusemide, hydrochlorothiazide, spironolactone and digoxin. We terminate this therapy and switched to propranolol step by step. Again NT-BNP and cardiac troponin T decrease and HRV increase.

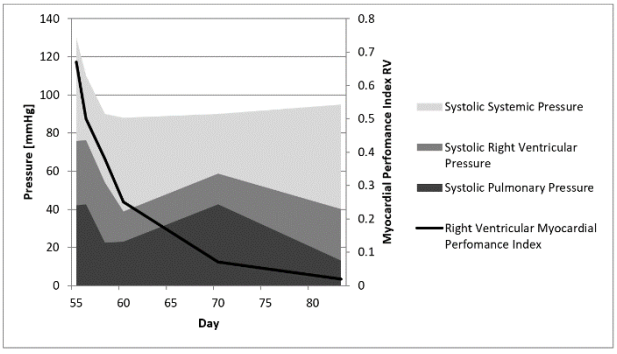

Figure 7: Noninvasive monitoring of pulmonary hemodynamics via Doppler echocardiography of the residual ventricular septal defect and RV-PA conduit in a girl after truncus arteriosus communis corrective surgery (case6). While switching from 2.3mg/kg sildenafil at day 55 to 2.9mg/kg propranolol at day 70 step by step the systemic and pulmonary pressure decrease to normal values and the right ventricular myocardial performance index improves (normal value < 0.4).

Case 7

The girl who was born with Down syndrome and an atrioventricular septal defect combined with a Tetralogy of Fallot. After hypoxic spells despite propranolol she had a modified Ballock Taussig Anastomosis at the age of 3 month. She suffered from severe heart failure due to

pulmonary overcirculation and enhanced pulmonary pressure treated with frusemide, hydrochlorothiazide and spironolactone. Treatment with 2mg/kg propranolol leads to more pulmonary overcirculation, higher NT-BNP values and edema. We change to a lower propranolol dose of 0.5mg/kg together with digoxin to reduce the flow in right ventricular outflow tract. (Figure 7) shows improvement of HRV, lower heart rate, lower NT-BNP and lower pulmonary pressure in this case. She was successfully operated with an age of 7 months and a bodyweight of 6.5 kg.

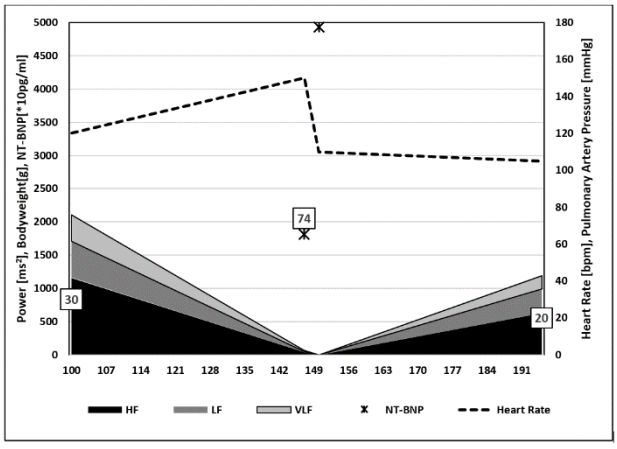

Figure 8: The girl who was born with Down syndrome and an atrioventricular septal defect combined with a Tetralogy of Fallot. After hypoxic spells despite propranolol she had a modified Ballock Taussig Anastomosis at the age of 3 month. She suffered from severe heart failure due to pulmonary overcirculation and enhanced pulmonary pressure treated with frusemide, hydrochlorothiazide and spironolactone. Treatment with 2mg/kg propranolol leads to more pulmonary overcirculation, higher NT-BNP values and edema. We change to a lower propranolol dose of 0.5mg/kg together with digoxin to reduce the flow in the right ventricular outflow tract. HRV increased, heart rate and NT-BNP decrease. Systolic pulmonary artery pressure dropped down from 74mmHg to 20mmHg measured by Doppler echocardiography.

Discussion

5 from 8 infants who died on our PICU of a rural Department of Pediatrics within the last 8 years suffer from heart failure. 4 infants had a single ventricle, one had an inflammatory disease. In accordance with a prospective trial of HRV risk stratification in premature infants with necrotizing enterocolitis, we measure very low high frequency power in spectral analysis of heart rate variability in these infants who died [25] (Figure 1).

Unfortunately, there are no convincing studies that can help pediatricians how to treat these babies. This is the reason why we decide to improve our monitoring using online HRV monitoring with a "self-made" network connection to measure the effect of pharmacotherapy on the autonomic nervous system. On the first view, we are able to visualize our therapeutic efforts to improve the very low heart rate variabilities in case 3 to 7 – our surrogate parameter for the therapeutic success. Indeed, we do not know if our decisions are the best – 3 infants, who received maximal heart failure therapy, died. However, based upon the CHF-Pro-Infant trial, we are able again to show the immediate improvement of heart rate variability using propranolol and digoxin. This improvement of heart rate variability was accompanied by the decrease of highly elevated NT-Pro-BNP and troponin T values in case 4,5 and 6. All these surrogate parameters have an important impact on prognosis [26-28]. As shown in case 4, the unselective beta blocker carvedilol also improves heart rate variability, decrease very high NT-BNP values and decrease elevated troponin T levels. Furthermore, as shown in case 5 and 6 the cardio selective beta blocker metoprolol failed to improve these values. However in the same infants with severe heart failure the switch from the cardio selective beta blocker metoprolol to propranolol clearly improve heart rate variability, decrease very high NT-BNP values and cardiac Troponin T. Case 6 and 7 additionally received digoxin: In case 7 there are hemodynamic reasons for digoxin, if 2mg/kg propranolol leads to more pulmonary over circulation, higher NT-BNP values and edema in the infant after an aorto-pulmonary shunt in Tetralogy of Fallot together with an atrioventricular septal defect. A lower propranolol dose of 0.5mg/kg together with digoxin leads to higher HRV, lower heart rate, lower NT-BNP and lower pulmonary pressure. However, in case 6 there are no hemodynamic or myocardial explanation for the improvement after additional digoxin. We anticipate a specific effect on the autonomic nervous. The beneficial effect of digoxin on vagus activity has been shown in adults with heart failure [29-30]. Our own retrospective analyses had shown significantly higher RMSSD values in infants with additional digoxin compared to infants who only received propranolol. All these babies with HRV improvement had an impressive clinical improvement and a very good weight gain with successful elective cardiac surgery some month later. The two babies with Down's syndrome who failed to improve HRV with propranolol died before cardiac surgery. One published case developed hemophagocytic lymphohistiocytosis and the other died after diagnostic heart catheter. At this time, we didn't use digoxin. In our own assessment, these case histories are helpful to have a look in the current "black box" of heart failure therapy in infants with congenital heart disease:

1) The unselective β blockers propranolol and carvedilol may improve reduced heart rate variability in infants with severe heart failure. The cardio selective β_1-receptor blocker metoprolol seems not to improve HRV in these infants with severe heart failure due to congenital heart disease. This must be clarified in a prospective trial.
2) Carvedilol (case 4) and Propranolol (case 6) seem to protect against subclinical myocardial injury in infants with severe heart failure, indicated by elevated cardiac troponin T (cTnT). CTnT is a specific marker of myocardial injury that is elevated in patients with heart failure and congenital heart disease, even in newborns [26]. However, healthy neonates have higher cTnT values up to 100pg/ml compared to healthy adults (<14pg/ml) [31]. CTnT has been investigated as a prognostic marker and is a strong and independent predictor of all-cause and cardiovascular mortality, and of hospitalization for cardiovascular causes in patients with chronic heart failure [32]. Two recently published studies confirm the prognostic value of elevated cTnT level in children with congenital heart disease [33, 34]. Beta blockers have protective effects against myocardial injury in adults with congestive heart failure and protect these patients against elevated cTnT [35, 36].
3) In cases with additional inflammation beta blockers probably cannot improve prognosis (case 1). The IL-1 receptor blocker anakinra may improve heart failure but immune suppression

enhances the risk for life threatening infections (case 3).

4) Probably digoxin improve prognosis in infants with congenital heart defects due to a specific effect on the autonomic nervous system and not by improving ventricular function that is hyper normal in nearly all infants with pulmonary over circulation [30].
5) In selected cases resolution of heart failure with propranolol improves pulmonary hypertension (case 6+7).
6) After an over 20 years' experience with propranolol in infants with severe heart failure the 7 cases show our own learning curve: Our treatment goal is no longer only the improvement of clinical heart failure symptoms, but much more a significant improvement in HRV with a target high frequency power over $20ms^2$. Infants with a lower high frequency power may be clinically stable but have an extremely high risk of life-threatening inflammation (case 1) and didn't tolerate usually harmless medical interventions like a diagnostic heart catheter (case 2). After the reimplementation of digoxin in such cases we observe a further improvement of HRV (case 6). Infants with pulmonary over circulation and a dynamic right ventricular outflow tract stenosis may worsen with propranolol and must be treated with additional digoxin of cause hemodynamic reasons (case 7).

It is not appropriate to make recommendations based upon 7 cases of whom 3 died. However, perhaps I can convince some colleagues to use HRV monitoring to improve their pharmacotherapy in infants with severe heart failure. As long as there is no effort in pediatric cardiology to confirm or refute the impressive clinical benefits of propranolol in infants with severe heart failure due to congenital heart disease, this seems to be a reasonable treatment strategy for this potentially fatal disease. Until adequate clinical trials are not performed, therapy in infants with heart failure should be evaluated using valid surrogate parameters. In contrast to biochemical parameters, the HRV analysis is based on existing routine data. HRV analysis is cheap and immediately available. Recently, it has been shown that HRV monitoring is associated improved prognosis in very low birthweight patients [37]. We recently change our therapeutic standard as shown in (Figure 9) and re-introduce digoxin in selected cases with low HRV despite propranolol. In contrast, most guidelines do not change within the last 20 years despite negative results for ACE inhibitors in a large prospective, randomized trial [6].

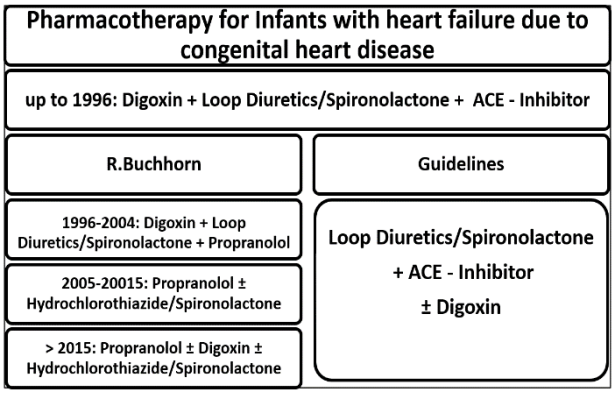

Figure 9:

Disclosures

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

Abbreviations

ACE:	Angiotensin converting enzyme
ECG:	Electrocardiogram
HF:	High Frequency Index (Frequency domain measure)
HR:	Heart rate
HRV:	Heart rate variability
LF:	Low Frequency Index (Frequency domain measure)
NN:	Normal RR intervals
PICU:	Pediatric Intensive Care Unit
VLF:	Very Low Frequency Index (Frequency domain measure)

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