

# Analyzing Heart Rate Variability in Infants Using Non-Linear Poincaré Techniques

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## Abstract

*Congenital heart defects, such as Hypoplastic Left Heart Syndrome, are the most prevalent type of birth defect. Palliative reconstructive procedures may interrupt autonomic cardiac function and increase infant mortality rate. Autonomic cardiac tone is classically assessed using linear, Fourier-based techniques. A non-linear Poincaré technique is proposed to more completely characterize heart rate variability in terms of short-term (SD1) and long-term (SD2) variability and randomness (SD1/SD2). 24-hour ECG data was collected for 27 normal infants (Group I) and 26 infants with congenital heart defects (Group II) and analyzed in five-minute segments. At birth, Group II showed reduced SD1 and SD2 and increased SD1/SD2 ( $p < 0.001$ ). Post-procedure, greater SD1 and SD2 ( $p < 0.001$ ) was seen in Group II. Poincaré analysis captures congenital differences in autonomic cardiac function and improvements over time.*

## 1. Introduction

Congenital heart disease is defined as gross structural abnormality of the heart or great vessels that may be functionally relevant [1]. Congenital heart defects are the most prevalent type of birth defect affecting 1 in every 100 to 200 infants [2]. Hypoplastic Left Heart Syndrome (HLHS) is a congenital heart defect characterized by an underdeveloped left ventricle, aorta and aortic valve. Normal fetal development, with the exception of the hypoplastic left heart, is possible because the ductus arteriosus and foramen ovale allow fetal circulation to bypass the pulmonary circuit and the right ventricle pumps blood throughout the body. These vessels close when respiration begins in the neonate and the right ventricle no longer supplies systemic blood flow. The underdeveloped left ventricle of HLHS infants is unable to support systemic circulation and intervention is necessary [3,4].

HLHS infants typically undergo a 3-stage reconstructive procedure to pump systemic blood through the right ventricle. The first stage, known as the Norwood procedure, is performed in the first days of the neonate's life. The Norwood procedure requires removal of the atrial septum, creation of a neo-aorta, and connection of the pulmonary and brachiocephalic arteries, which is also known as a Blalock-Taussig (BT) shunt [3,5]. Unfortunately the Norwood procedure has been associated with a high risk of death.

Either the Glenn or hemi-Fontan procedure is performed 3-9 months after Norwood, and this is followed by the final stage Fontan procedure typically at 2-3 years of age. Infants born with other congenital heart defects undergo only the BT shunt procedure or aortic arch reconstruction. Understanding the affects of congenital heart defects and reconstructive procedures on autonomic cardiac function is of clinical interest to improve palliation of infants.

Heart rate variability (HRV) is often used to assess cardiac autonomic tone and reduced HRV has been correlated to increased risk of cardiovascular mortality in adults. HRV uses the ECG to derive the intervals between the R waves. HRV has traditionally been assessed using either time-domain measures (for example the mean normal-to-normal interval, or its standard deviation) or frequency domain measures [6]. Analysis of the variations in the adult heart rate has been categorized as high frequency (0.15 – 0.4 Hz), low frequency (0.04 – 0.15 Hz), and very low frequency (0.0001 – 0.04 Hz). In adults, high frequency is believed to be a marker of the parasympathetic tone and the low frequency of primarily the sympathetic tone, though parasympathetic tone may contribute. Currently, a significant amount of data obtained from adults demonstrate that decreased HRV is a risk factor for sudden death in both cardiac and non-cardiac conditions. This correlation was first noted as an increased risk of sudden death for patients post myocardial infarction [7], and alteration in HRV is associated with conditions such as congestive heart

failure [8], sudden infant death syndrome [9] and multiple organ failure [10].

Unfortunately, little data is available about the risk of sudden death associated with alterations in HRV in the pediatric population or after cardiac surgery. Only one study to date has evaluated the HRV in the population which had previously undergone the Norwood procedure. Davos et al. showed a marked derangement in HRV in patients late after the Fontan procedure [11]. Additionally, studies have shown alterations in HRV in patients with both repaired and unrepaired congenital heart disease [12], though the impact of these alterations have yet to be determined. There is some evidence that the classical methods require modification of physiologically based frequency bands for application in infant HRV analysis [13-15].

Frequency domain measures assume that the R-R interval time series is stationary, or that the variations are harmonic or sinusoidal. In reality, HR fluctuations can be both periodic (e.g., due to respiration) and non-periodic (e.g., due to abrupt changes in the environment or state of the child). Thus HRV may be due to complex, dynamic interactions of biological signals and non-linear techniques may strengthen analyses of physiological conditions. S maps have revealed complex, non-linear heart patterns in the developing infant [16] and power law slope and Poincaré plots have demonstrated increased risk and adversity in cardiovascular disease patients [17].

Poincaré plots, also known as return maps, are scatter plots in which the current RR interval is plotted against a following RR interval. These maps provide a very effective graphical method for representing the underlying structure of the RR interval time series. The maps look like a cloud of points dispersed along the line of identity (as shown in **Figure 1**). Generally an ellipse is fitted around the Poincaré points with SD1 as the short axis, and SD2 as the long axis of the ellipse. SD1 is the breadth of the return map perpendicular to the line of identity; it represents the short term variability over a single beat. SD2 is the length of the return map along the line of the identity, and it represents the long term variability over a single beat. SD1 has been correlated with high frequency power while SD2 has been correlated with both low and high frequency powers. The ratio SD1/SD2 is associated with the randomness of the HRV signal. It has been suggested that the ratio SD1/SD2, which is a measure of the randomness in HRV time series, has the strongest association with mortality in adults [17].

We postulate that the patients undergoing arch reconstruction, as seen in the Norwood population, may have alterations or interruptions in the cardiac autonomic innervation coursing over the aortic arch. To evaluate the

influence of possible confounding variables, such as hypoxemia and congestive heart failure from volume overload, we compare HRV of patients who are undergoing the Norwood procedure, a Blalock-Taussig shunt, or aortic arch reconstruction with two ventricle anatomy, to infants without cardiovascular disease. Our hypothesis is a difference in cardiac autonomic tone exists between normal infants and infants born with congenital heart disease before and after reconstructive surgery. The specific aim of this work is to utilize a non-linear Poincaré analysis to quantify cardiac function in normal infants and infants born with congenital heart disorders before and after reconstructive procedures. The long-term objective is to explain the mortality following Norwood's procedure.

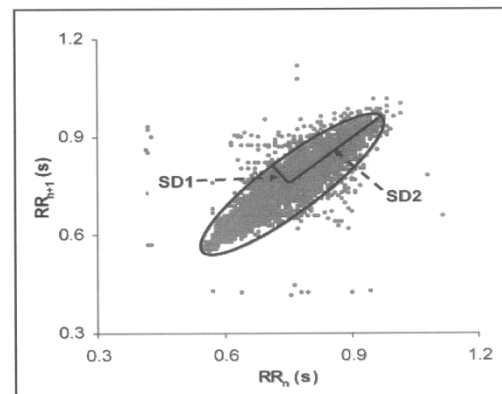


Figure 1. Example of a return map (Poincaré plot) with an interval ( $RR_n$ ) plotted against the next interval ( $RR_{n+1}$ ). Also illustrated are the short axis (SD1) and long axis (SD2) of the enclosing ellipse.

## 2. Methods

Infants were enrolled at The University of Iowa and at the University of Michigan. The infants were enrolled and data were collected only after obtaining IRB approval at each institution, and only after obtaining written consent of each infant's parents or guardians.

Thirty-six infants were enrolled at Iowa and 17 infants were enrolled at Michigan. Of these 53 infants, 27 had no cardiac defect and were enrolled as Group I (NN) infants. The remaining 26 infants with congenital heart defects were enrolled as Group II infants. Group II included 15 HLHS infants, 5 AA infants and 6 BT infants.

Twenty-four-hour ECG data were collected and analyzed in five-minute segments. Those segments containing artifact were removed from the study. Mean data from each five-minute segment were averaged throughout the 24-hour period. Data were collected for Group II infants at pre-Norwood procedure (pre-procedure), 3-4 weeks post-Norwood procedure (post-procedure1), and at a follow-up time just before the

Glenn or hemi-Fontan procedure (post-procedure2). ECG data were obtained for Group I infants at age-matched times. All of the Group II infants were given clinically appropriate medication (such as prostaglandin) as medically indicated. Five of the Group II infants died some time after the Norwood procedure was performed. Not all of the remaining infants participated in all studies.

MATLAB code was written to extract the RR intervals from 24-hour ECG recordings, and to plot one RR interval ( $RR_n$ ) against the next interval ( $RR_{n+1}$ ). The code then calculated SD1 and SD2 after rotating the plot axes by  $\theta=\pi/4$  radians. SD1 was calculated as the standard deviation of points around the rotated x-axis. SD2 was calculated as the standard deviation of points along the rotated x-axis. (See **Figure 1**).

Statistical analyses were performed using paired t-tests with significance being defined at the  $\alpha=0.05$  level.

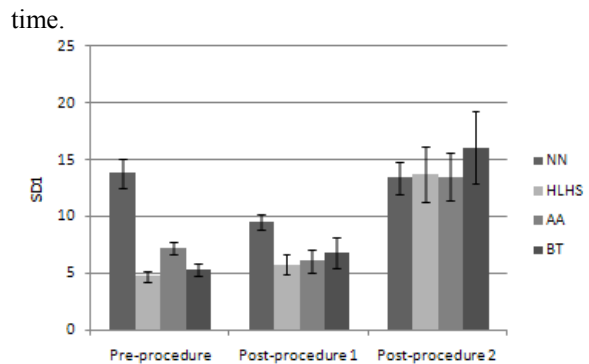
### 3. Results

Table 1 shows the average heart rate for all infants in the study. The pre-procedure HR for normal infants was lower than HLHS, AA and BT infants ( $p<0.05$ ). The HR for HLHS infants was higher than the HR for AA and BT infants.

Table 1- Average heart rate for NN, HLHS, AA and BT infants for pre-procedure, post-procedure1, and post-procedure2 times. \* indicates difference between average HR for Group I and Group II infants. \*\* indicate difference between HLHS infants, and AA and BT infants at pre-procedure time.

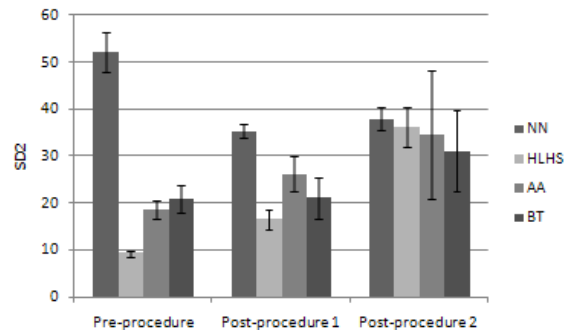
Group	Procedure	n	Mean $\pm$ SEM
NN	Pre-procedure	27	123.9 $\pm$ 1.6*
	Post-procedure1	19	141.4 $\pm$ 2.2
	Post-procedure2	15	130.0 $\pm$ 2.9
HLHS	Pre-procedure	13	161.9 $\pm$ 2.3**
	Post-procedure1	9	142.9 $\pm$ 2.6
	Post-procedure2	6	120.2 $\pm$ 5.2
AA	Pre-procedure	5	155.0 $\pm$ 4.2
	Post-procedure1	4	144.5 $\pm$ 3.2
	Post-procedure2	2	136.1 $\pm$ 8.7
BT	Pre-procedure	6	146.4 $\pm$ 2.2
	Post-procedure1	6	142.6 $\pm$ 4.3
	Post-procedure2	5	114.0 $\pm$ 8.3

**Figure 2** shows the results of SD1 values for Group I and Group II infants. There was a significant difference between the Group I (NN) SD1 values and the Group II (HLHS, AA, and BT) values for the pre-procedure and post-procedure1 times, but not for the post-procedure2



**Figure 2** – SD1 for all infants at three data collection times. There is a significant difference between Group I infants and Group II infants at the pre-procedure and post-procedure1 times.

**Figure 3** shows the results of SD2 values for Group I and Group II infants. There was a significant difference between the Group I SD2 values and the Group II values for the pre-procedure and post-procedure1 time, but not for the post-procedure2 time. Note that SD2 for the HLHS infants at post-procedure1 time was smaller than the values for AA and BT infants, though this difference was not statistically significant.



**Figure 3** – SD2 for all infants at three data collection times. There is a significant difference between Group I infants and Group II infants at the pre-procedure and post-procedure1 times.

**Figure 4** shows the results of SD1/SD2 values for Group I and Group II infants. There was a significant difference between NN and HLHS and AA infants, but not for the BT infants. Note also that the SD1/SD2 ratio increased with time for the AA and BT infants, but not the NN and HLHS infants.

There was no difference at the pre-procedure time in SD1, SD2 or SD1/SD2 between the infants who died after a procedure, and the infants in Group II who survived.

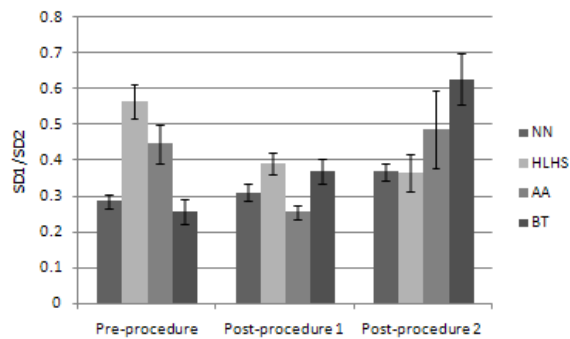


Figure 4 – SD1/SD2 for all infants at three data collection times. There is a significant difference between NN and HLHS and AA infants pre-procedure. There is an increase in SD1/SD2 for AA and BT infants with time.

#### 4. Discussion and conclusions

We found that differences in SD1 and SD2 between normal and Group II infants, which were most likely due to reduced parasympathetic and enhanced sympathetic cardiac tone, disappeared as the infants aged. This result implies that the surgery did not interrupt adrenergic and cholinergic pathways to the heart and these pathways develop normally with age. However, the increased SD1/SD2 values over time in AA and BT infants suggest a higher level of randomness is present in HR.

We found no difference in SD1, SD2 and SD1/SD2 at any time in HLHS infants who died post-Norwood and HLHS infants who survived. We found this result in spite of the fact that the infants died due to their cardiac diseases. The study did not identify them as high-risk. Perhaps our techniques were not sensitive enough to predict death in these infants. We used a lag of one heart beat, i.e., each RR interval is plotted against the next. Other studies have been performed where longer lags have been used to evaluate HRV with the assumption that one heart cycle affects not only the next cycle, but also cycles 6-10 beats later. We did not evaluate the effects of altering the lag, but such an evaluation might be fruitful.

The standard way of studying HRV is with Fourier analysis. It would be useful to compare and contrast the results of a Fourier analysis with the results of a Poincaré analysis.

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