Published in final edited form as:

Comput Biol Med. 2013 December ; 43(12): 2001–2006. doi:10.1016/j.combiomed.2013.09.019.

MITIGATING THE EFFECT OF NON-STATIONARITY IN SPECTRAL ANALYSIS – AN APPLICATION TO NEONATE HEART RATE ANALYSIS

Rathinaswamy B. Govindan¹, An N. Massaro², Nickie Niforatos², and Adré du Plessis¹

¹Division of Fetal and Transitional Medicine, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010

²Division of Neonatology, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010

Abstract

In order to mitigate the effect of non-stationarity in frequency domain analysis of data, we propose a modification to the power spectral estimation, a widely used technique to characterize physiological signals. Spectral analysis requires partitioning data into smaller epochs determined by the desired frequency resolution. The modified approach proposed here involves dividing the data within each epoch by the standard deviation of the data for that epoch. We applied this modified approach to cardiac beat-to-beat interval data recorded from a newborn infant undergoing hypothermia treatment for birth asphyxia. The critically ill infant had episodes of tachyarrhythmia, distributed sporadically throughout the study, which affected the stationarity of the heart rate. Over the period of continuous heart rate recording, the infant's clinical course deteriorated progressively culminating in death. Coinciding with this clinical deterioration, the heart rate signal showed striking changes in both low-frequency and high-frequency power indicating significant impairment of the autonomic nervous system. The standard spectral approach failed to capture these phenomena because of the non-stationarity of the signal. Conversely, the modified approach proposed here captured the deteriorating physiology of the infant clearly.

Keywords

power spectral analysis; non-stationarity; neonatal heart rate; autonomic nervous system; birth asphyxia

Address for correspondence: Dr. R. B. Govindan, Staff Scientist III, Division of Fetal and Transitional Medicine, Children's National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010, USA, rgovinda@childrensnational.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of Interest

None to declare.

1. Introduction

Physiological signals exhibit features that have a characteristic time scale. For example, the cardiac beat-to-beat interval (RRi) exhibits: 1) slow changes that are related to both sympathetic and parasympathetic components of the autonomic nervous system (ANS) [1], (e.g. baroreflex activity) and 2) fast changes that are related primarily to the parasympathetic (vagal) component of the ANS, (e.g. respiratory sinus arrhythmia) [1]. Investigation of RRi using appropriate signal processing tools can thus provide clinician opportunity to access the function and integrity of the ANS. Several methods exist to evaluate RRi. Time-domain methods include characterization of a) low-frequency component (standard deviation of normal to normal [SDNN] intervals), b) short-term variability or the high-frequency component of the RRi (the root mean square of successive differences [RMSSD]), and c) the probability that the current normal-to-normal RRi is less than x-millisecond from the previous normal-to-normal RRi [pNNx] [2]. Additional methods based on statistical physics such as detrended fluctuation analysis [3] and multifractal analysis [4], have also been used to characterize the low- and high-frequency fluctuations in the RRis. Likewise, novel methods such as phase-rectified signal averaging [5] and phase-plane analysis [6] also have been used to characterize the heart rate in time-domain. In the frequency domain RRis are analyzed using the power spectral approach [2, 7-9]. Unlike the time-domain approaches, the spectral approach allows direct assessment of sympathetic and parasympathetic components of the ANS. Power spectral analysis of cardiac inter-beat intervals can be used to characterize the components occurring at different time scales [8-12]. The influence of respiration on the cardiac beat-to-beat interval (respiratory sinus arrhythmia) can also be readily characterized by spectral analysis [13, 14]. These features make the power spectral approach superior to the time-domain approach in studies such as heart rate variability analysis. However, an implicit assumption in spectral analysis is that the data must be stationary [2]. Given the non-stationary nature of the physiologic data in clinical practice, this is a potentially significant limitation of spectral analysis in physiologic studies, especially in cases of clinical instability.

The non-stationarity can be caused by extrinsic factors (e.g. such as movement of the subject) or by intrinsic factors (e.g. transient changes within the physiology of the system). While the non-stationarity due to extrinsic factors can be minimized by excluding affected data from the analysis, the non-stationarity caused by the intrinsic factors compromises spectral analysis in a more troublesome manner, and leads to incomplete characterization of the data.

In critical care units, a mass of continuous physiological data is acquired by monitors at the bedside. However, there is an enormous redundancy in that a small minority of these data is currently explored for their potential clinically relevant content. There is an urgent need for enhanced anticipation of clinical deterioration since prevention of catastrophic collapse is needed to decrease the acute and long-term complication rates. Real-time integration and processing of the multiple physiological signals monitored may provide valuable early biomarkers of imminent deterioration. However, the methods employed to explore these biomarkers need to perform robustly in the frequent periods of non-stationarity inherent in critical care. This has continued to be a limitation of standard spectral power analyses. In

this report we propose a modification to the spectral power analysis (henceforth call the modified approach) that mitigates the effect of non-stationarity in physiologic signals, and compare its performance against standard technique (henceforth call the standard technique).

2. Materials

2.1 Study Subject

A newborn female infant with perinatal asphyxia due to nuchal cord and meconium aspiration was treated with a whole body hypothermia protocol proposed by the National Institute of Child Health and Human Development [15]. The infant presented with a cord blood pH of 6.9 and clinical encephalopathy. She was placed on a servo-controlled cooling blanket set to maintain an esophageal temperature of 33.5°C. The infant underwent continuous physiological monitoring, (i.e., including electrocardiogram [ECG], blood pressure, pulse oximetry, cerebral oximetry) as part of an ongoing prospective observational study. The study was approved by the Children's National Medical Center Institutional Review Board, and informed consent was obtained.

2.2 Data Collection

ECG was retrieved from the analog port of the bedside monitor (Philips MP70, Philips, MA, USA) using custom software developed in LabView2010 Professional development system (National Instruments Corporation, TX, USA). The data were sampled at 1KHz over a continuous period of 23.5 hours. All processing was performed using MATLAB (Mathworks, Inc., MA, USA).

3. Methods

3.1 Signal Pre-processing

ECG was bandpass filtered between 0.5-70Hz using Butterworth filter with zero-phase distortion. The R-wave was identified using adaptive Hilbert transform approach and beat-to-beat interval (RRi) was computed as successive difference of R-wave occurrence expressed in seconds. The RRi was converted into evenly sampled data using cubic-spline interpolation at a sample rate of 4 Hz. The RRi was divided into 10 minute windows with a sliding overlap of two minutes.

3.2 Standard Approach

In each 10 minute window, the power spectrum was estimated in the standard approach as follows [16]: Step 1) The RRis were partitioned into disjointed (no overlap) 60 second windows (also called Fast Fourier Transform [FFT] length), and the mean was subtracted from them; this is same as convolving the RRis with a rectangular window of 60 second duration. Step 2) in each 60 second window, the periodogram (i.e. the square of the modulus of the FFT of the RRis) was computed; and Step 3) the periodogram was averaged over all the windows to obtain the estimate of the power spectrum. To express this mathematically:

$P(\omega) = \frac{1}{M} \sum_{k=1}^M Per_k(\omega)$, where $Per_k(\omega)$ is the periodogram in the k -th 60 second window and M is the number of 60 second windows, which is 10 in this study. The choice of 60

seconds was used to capture reliably the low-frequency changes down to 0.05Hz. However, we would like to mention that the results reported here did not change significantly for the choice of 30 second window. $P(\omega)$ computed as shown above will have a unit of second^2 . In the presence of non-stationarity, the periodogram from the non-stationary 60 second region will have significantly different characteristics both in amplitude (usually very high) and frequency. The spurious amplitude from the non-stationary region will dominate the average involved in the calculation of $P(\omega)$ resulting in an incorrect characterization of the data.

3.3 Modified Approach

In spectral analysis, the total variance of a signal is decomposed into different frequency components. In other words, the power spectrum is a frequency-domain description of the variance of the RRi. Based on this fact, in a stationary dataset the sum of the powers over all frequency bands is equal to the total variance of the RRis. Thus, for the periodogram from k – th 60 second window, we have the following relation: $\int_{-\infty}^{\infty} \text{Per}_k(\omega) d\omega = \text{var}(x^{(k)})$, where $d\omega$ is the frequency resolution of the spectral estimate, $x^{(k)}$ represents the RRis in the k^{th} 60-second window and $\text{var}(\cdot)$ indicates the variance function. In practice, this integration is performed in the frequency bands from negative half of the sample frequency to positive half of the sample frequency, where the power is calculated.

The proposed modification involves dividing the data after Step 1 (Section 3.2) by its standard deviation. Thus, in the modified approach the periodogram is divided by the variance (recall that the calculation of the spectrum involves squaring of the standard deviation which converts the latter into variance) of the data and the above integral will yield a value of one.

For a stationary dataset the total variance is approximately same as the average of the variance in all the windows (i.e.) $\langle \text{var}(x^{(k)}) \rangle_k \approx \text{var}(x)$, where $\langle \cdot \rangle$ denotes the average and x denotes 10-minutes of RRis. Based on this relation, the integration of the spectral estimate $P(\omega)$ obtained using the modified approach, will also be one. Further, the power spectrum obtained through this modified scheme will be dimensionless because of the normalization by standard deviation. To compare the spectrum obtained using modified approach with standard approach, we rescaled the former by multiplying it with $\langle \text{var}(x^{(k)}) \rangle_k$. This rescaling allows to express power in the unit of second^2 . Thus, for stationary data, both the standard and modified approaches should yield the same result within the numerical precision of the computation.

However, for non-stationary data, the normalization by standard deviation will ensure that the periodogram corresponding to the non-stationary region (with sudden changes in the signal amplitude) will assume the same or comparable amplitude as rest of the data from stationary regions. Therefore, the periodogram from the non-stationary region will not dominate the average in the calculation of the spectrum. However, the periodogram from the non-stationary region will have a different frequency distribution (i.e. the power may be concentrated in different frequency bands). This effect will be minimized in the subsequent

averaging part, as the periodograms from stationary parts of the signal will have power concentration in a different region of the spectrum.

3.4 Data Analysis

From both standard and modified spectra, we calculate the low-frequency power as the sum of powers in the frequency bands between 0.05 - 0.25Hz [17]. We calculate the high-frequency power as the sum of powers in the frequency bands covering 0.3 - 1Hz [14, 17]. To this end, we divide the low-frequency power and high-frequency power by the total power. We define the total power as the sum of the powers in the frequency band of 0.05 - 2Hz. With this definition, the low-frequency power represents the percentage of the total power explained by the power in the frequency band of 0.05 - 0.25Hz. Similarly, the high-frequency power represents the percentage of the total power explained by the power in the frequency band of 0.3 - 1Hz. The power in the low-frequency band quantifies the sympathetic and parasympathetic components of the ANS, with the former being dominant. In contrast, the power in the high-frequency band quantifies the parasympathetic (vagal) components of the ANS. Further, early work on neonatal RRI analysis has defined the high frequency band as the respiratory frequency of the intubated infants [14]. Based on this work, to accurately quantify the ventilator related changes (parasympathetic component) in the RRI we also computed the ratio of the maximum power between 0.3-0.8Hz to total power (0.05-2Hz). Using both the standard and modified approaches, we also calculated the ratio of low-frequency to high-frequency LF/HF powers to assess the sympatho-vagal balance. We used Kolmogorov-Smirnov test to compare the difference between two power spectra (standard versus modified). Further, we used paired t-test to compare the spectral power obtained from both methods. A value of $P < 0.05$ was considered statistically significant.

4. Results

4.1 Clinical course of the study subject

The infant was supported on highflow nasal cannula oxygen during initial part of the study. Six hours into the study, the baby became apneic requiring intubation and mechanical ventilation. The ventilator frequency was initially set at 30 breaths per minute (0.5 Hz), which was then changed to 25 breaths per minute (0.42Hz) after 47 minutes. After one hour and 15 minutes, the ventilator frequency was changed to 20 breaths per minute (0.33Hz) over the rest of the study: Continuous EEG recording showed voltage suppression at 14 hours of the study and subsequently became isoelectric. Uncal herniation was confirmed by brain imaging at 17 hours and based on the perceived futility of ongoing artificial support, the family requested withdrawal of life support.

4.2 Spectral analysis of RRI during the study period

We present the spectra obtained from the standard and modified approaches for 10 minutes of data selected from (near) stationary region during initial part of the study. Figure 1a shows the RRI for a 10 minute period, and Figure 1b shows the spectra computed using both approaches. The spectra are plotted up to 2Hz. The RRI fluctuates between 0.52-1.03

seconds. There is no significant difference between two spectra ($P=0.37$). The distinct peak around 0.3Hz corresponds to respiratory sinus arrhythmia (RSA).

We present the RRI containing arrhythmic beats in Figure 2a. The inset shows the ECG tracing between 0.23-0.4 minutes containing arrhythmic cycles. This part of the data was taken during the period when the infant was on mechanical ventilation at a frequency of 20 breaths per minute (0.33Hz). We show significant difference ($P=0.02$) in the power spectra computed using two approaches in Figure 2b. The spectrum obtained using the modified approach shows high power in the low-frequency and also shows a distinct peak at the RSA frequency (0.33Hz), whereas the spectrum obtained using standard approach shows high power over a broad frequency band (0.2-0.9Hz).

In Figure 3, we present the results of the spectral analysis of RRI in a 10 minute segment that immediately follows the tracing shown in Figure 2a. This example shows the occurrence of arrhythmic beats in multiple instances. Additionally, the spectrum obtained using the modified approach shows high power in the low-frequency band and distinct peaks at 0.33Hz corresponding to RSA for this case. The spectrum computed using the standard approach shows high power between 0.2-0.8Hz with no discernable peak at the RSA frequency; however, there is a small peak at the first harmonic of RSA frequency (0.66Hz). Again we demonstrate a significant difference between two power spectra ($P=0.02$).

In Figure 4, we present the variation of power in low- and high-frequency bands as a continuous function of time. In Figures 4a and c, we show the low- and high-frequency band powers, respectively, obtained using the standard approach. In Figures 4b and d, we show the low- and high-frequency powers, respectively, obtained using the modified approach. There is a clear decrement in the low-frequency power obtained using the modified approach (Figure 4b), whereas the low-frequency power obtained using the standard approach shows increase in the power in some instances (see Figure 4a). Furthermore, there is a gradual increase in the high-frequency power obtained using the modified approach. The high-frequency power (Figure 4c) obtained using the standard approach also shows an increase in power over time, but the increase was not as gradual as shown in the results obtained by using the modified approach. The low-frequency to high-frequency ratio (LF/HF) calculated from the standard and modified approaches are shown in Figures 4e and 4f, respectively. After 6 hours, LF/HF obtained using the standard approach was lower compared to the same ratio obtained using the modified approach.

The ventilator induced changes obtained as a ratio of the maximum power in the band of 0.3-0.8 Hz to the total power is shown in Figure 5. The modified approach shows a gradual increase in power from 6 hours onward, whereas the standard approach shows an increase in power starting around 5 hours at which time the infant was not on mechanical ventilation (see Figure 5a). There is a significant difference between the ratio of the power at the ventilator frequency to the total power calculated using the standard approach and modified approach ($P<0.01$) with the modified approach displaying higher ratio compared to the standard approach.

5. Discussion

Here we propose a modification that mitigates the inherent vulnerability of power spectral analysis to non-stationary data caused by unstable intrinsic dynamics. In this study, we demonstrate the robustness of our modified approach in the context of a highly unstable clinical scenario with major opportunity for non-stationary data. Specifically, we apply our modified approach to prolonged continuous heart signal recording during the terminal critical illness of an infant exposed to severe hypoxia-ischemia and therapeutic hypothermia. The ECG tracing of this infant evolved from normal sinus rhythm through periods of arrhythmia, and ultimate cardiac arrest. During this relentless physiological deterioration, our modified power spectral analysis approach detects a progressive decrease in low-frequency power and increase in high-frequency power of the RRI features not identified by the conventional power spectral analysis approach.

During periods of clinical stability and stationarity of the data, the modified approach provides similar power spectrum results for the RRI compared to the standard approach (Figure 1). When there is a loss of stationarity, as occurs during periods of arrhythmia, the modified approach identifies distinct spectral peaks while the standard power spectral analysis approach is compromised by the non-stationarity of the data (Figures 2 and 3).

Heart rate variability provides a potentially important window on autonomic function [2, 8, 9, 18-22]. The spectral power of the RRI in the low-frequency band quantifies the sympathetic and parasympathetic components of the ANS, with the former being dominant [7-12]. Recent animal studies suggest that this low-frequency component of RRI reflects the baroreflex activity mediated through coupling between RRI and blood pressure [23-25]. In contrast, the power in the high-frequency band is thought to reflect respiratory sinus arrhythmia (RSA) due to activity in the parasympathetic (vagal) component of the ANS [26]. Earlier studies in human subjects with critical cardiac illness [27], as well as an animal model [28] showed a reduction in the low-frequency component of the RRI indicating the loss of the sympathetic component of the ANS. Based on these findings, the reduced normalized low-frequency power detected by the modified approach (Figure 4b) might reflect impaired autonomic function, which the standard approach failed to capture (Figure 4a).

The higher power values in the high-frequency band observed in the standard approach compared to modified approach during periods of non-stationarity (i.e. arrhythmia) may indicate the spurious redistribution of the power caused by non-stationarity. Further, this spurious high-frequency power is the reason for the low LF/HF values (a measure of sympatho-vagal balance) observed in the standard approach after six hours of the study. Hence, in the presence of non-stationarity the high-frequency power obtained by standard approach may not accurately reflect the sympatho-vagal balance in this infant.

A clear discernable peak at the ventilator frequency observed in the modified approach helps to quantify the RSA, which the standard approach fails to quantify. Since the presence of arrhythmic beats causes redistribution of power to the high-frequency, the power quantified at high-frequency from standard approach (Figure 5b) may not reflect the accurate

quantification of the RSA. Conversely, the modified approach shows a clear increase in the power at the RSA frequency as the infant's condition approaches cardiac arrest.

We believe that the increase in the RRI power at the ventilator frequency reflects increasing ventilator dependency. Emergence of such an increasingly elevated spectral peak around at the ventilator frequency may provide an early biomarker for impaired autonomic function and progressive lower brainstem failure. If validated such a biomarker of brainstem failure might provide valuable prognostic information and potentially drive enhanced neuroprotective management. Such validation studies in this population are currently ongoing. We propose that the modified approach provides a more accurate spectral characterization and is therefore the analytic method of choice for such future studies.

We acknowledge that the issue of non-stationarity in datasets such as this might be handled by time-frequency analysis of RRI using short-time Fourier transform [29], Wigner-Ville distribution [30]. However, when the time-frequency spectrum is integrated over different time and frequency bins to obtain a single representation of power as shown in Figure 4, the non-stationary regions may dominate and obscure the quantification.

One potential limitation of this study is that the comparison between standard and modified approaches was performed on data from a single subject. However, the extreme physiological instability (leading to death) presents a stringent test of the robustness of our modified approach in an enriched milieu for non-stationarity. The assessment of the robustness of this approach to other forms of non-stationarity (such as baseline wandering) needs further investigation. We would also like to emphasize that the modified approach does not overcome the effect of non-stationarity entirely, but rather mitigates its effects.

6. Conclusions

A modification to spectral estimation is proposed to mitigate the effect of non-stationarity in continuous datasets. We have demonstrated its performance in providing enhanced accuracy of RRI spectral power from a critically ill newborn. The modified approach captured the dynamic changes and deteriorating physiology of the infant, while the standard approach failed to capture these features. This approach might therefore enhance our ability to detect the very earliest signs of autonomic failure in critical care. A prospective ongoing study in infants with neonatal hypoxic-ischemic encephalopathy treated with therapeutic hypothermia is in process.

Acknowledgements

This work was supported by the U.S. NIH under Grant K24 NS057568. We would like to thank Ms. Rachael Lipsetts for her editorial assistance.

References

- [1]. Guyton, AC. Textbook of Medical Physiology. 5th ed.. Saunders, W.B.; 1976. 5th ed. ed.
- [2]. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996; 93:1043–1065. [PubMed: 8598068]

- [3]. Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos*. 1995; 5:82–87. [PubMed: 11538314]
- [4]. Ivanov PC, Amaral LA, Goldberger AL, Havlin S, Rosenblum MG, Struzik ZR, Stanley HE. Multifractality in human heartbeat dynamics. *Nature*. 1999; 399:461–465. [PubMed: 10365957]
- [5]. Bauer A, Barthel P, Muller A, Kantelhardt J, Schmidt G. Bivariate phase-rectified signal averaging--a novel technique for cross-correlation analysis in noisy nonstationary signals. *J Electrocardiol*. 2009; 42:602–606. [PubMed: 19665726]
- [6]. Govindan RB, Vairavan S, Sriram B, Wilson JD, Preissl H, Eswaran H. Phase plane based identification of fetal heart rate patterns. *Conf Proc IEEE Eng Med Biol Soc*. 2011:1455–1458. [PubMed: 22254593]
- [7]. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science*. 1981; 213:220–222. [PubMed: 6166045]
- [8]. Appel ML, Berger RD, Saul JP, Smith JM, Cohen RJ. Beat to beat variability in cardiovascular variables: noise or music? *J Am Coll Cardiol*. 1989; 14:1139–1148. [PubMed: 2681319]
- [9]. Cerutti S, Baselli G, Civardi S, Ferrazzi E, Marconi AM, Pagani M, Pardi G. Variability analysis of fetal heart rate signals as obtained from abdominal electrocardiographic recordings. *J Perinat Med*. 1986; 14:445–452. [PubMed: 3820044]
- [10]. Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans Biomed Eng*. 1986; 33:900–904. [PubMed: 3759126]
- [11]. Gordon D, Herrera VL, McAlpine L, Cohen RJ, Akselrod S, Lang P, Norwood WI. Heart-rate spectral analysis: a noninvasive probe of cardiovascular regulation in critically ill children with heart disease. *Pediatr Cardiol*. 1988; 9:69–77. [PubMed: 3399429]
- [12]. Karin J, Hirsch M, Akselrod S. An estimate of fetal autonomic state by spectral analysis of fetal heart rate fluctuations. *Pediatr Res*. 1993; 34:134–138. [PubMed: 8233713]
- [13]. Hamann C, Bartsch RP, Schumann AY, Penzel T, Havlin S, Kantelhardt JW. Automated synchrogram analysis applied to heartbeat and reconstructed respiration. *Chaos*. 2009; 19:015106. [PubMed: 19335010]
- [14]. Andriessen P, Oetomo SB, Peters C, Vermeulen B, Wijn PF, Blanco CE. Baroreceptor reflex sensitivity in human neonates: the effect of postmenstrual age. *J Physiol*. 2005; 568:333–341. [PubMed: 16051623]
- [15]. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005; 353:1574–1584. [PubMed: 16221780]
- [16]. Halliday DM, Rosenberg JR, Amjad AM, Breeze P, Conway BA, Farmer SF. A framework for the analysis of mixed time series/point process data--theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog Biophys Mol Biol*. 1995; 64:237–278. [PubMed: 8987386]
- [17]. Lasky RE, Parikh NA, Williams AL, Padhye NS, Shankaran S. Changes in the PQRST intervals and heart rate variability associated with rewarming in two newborns undergoing hypothermia therapy. *Neonatology*. 2009; 96:93–95. [PubMed: 19252411]
- [18]. Wolf MM, Varigos GA, Hunt D, Sloman JG. Sinus arrhythmia in acute myocardial infarction. *Med J Aust*. 1978; 2:52–53. [PubMed: 713911]
- [19]. Hon EH. The electronic evaluation of the fetal heart rate; preliminary report. *Am J Obstet Gynecol*. 1958; 75:1215–1230. [PubMed: 13545252]
- [20]. Kamath MV, Fallen EL. Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. *Crit Rev Biomed Eng*. 1993; 21:245–311. [PubMed: 8243093]
- [21]. Rimoldi O, Pierini S, Ferrari A, Cerutti S, Pagani M, Malliani A. Analysis of short-term oscillations of R-R and arterial pressure in conscious dogs. *Am J Physiol*. 1990; 258:H967–976. [PubMed: 2109943]

- [22]. Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. *Circulation*. 1994; 90:1826–1831. [PubMed: 7923668]
- [23]. Rahman F, Pechnik S, Gross D, Sewell L, Goldstein DS. Low frequency power of heart rate variability reflects baroreflex function, not cardiac sympathetic innervation. *Clin Auton Res*. 21:133–141. [PubMed: 21279414]
- [24]. Piccirillo G, Magri D, Ogawa M, Song J, Chong VJ, Han S, Joung B, Choi EK, Hwang S, Chen LS, Lin SF, Chen PS. Autonomic nervous system activity measured directly and QT interval variability in normal and pacing-induced tachycardia heart failure dogs. *J Am Coll Cardiol*. 2009; 54:840–850. [PubMed: 19695465]
- [25]. Goncalves H, Henriques-Coelho T, Bernardes J, Rocha AP, Nogueira A, Leite-Moreira A. Linear and nonlinear heart-rate analysis in a rat model of acute anoxia. *Physiol Meas*. 2008; 29:1133–1143. [PubMed: 18784391]
- [26]. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation*. 1991; 84:482–492. [PubMed: 1860193]
- [27]. Shah AJ, Lampert R, Goldberg J, Veledar E, Bremner JD, Vaccarino V. Posttraumatic stress disorder and impaired autonomic modulation in male twins. *Biol Psychiatry*. 2013; 73:1103–1110. [PubMed: 23434412]
- [28]. Piccirillo G, Ogawa M, Song J, Chong VJ, Joung B, Han S, Magri D, Chen LS, Lin SF, Chen PS. Power spectral analysis of heart rate variability and autonomic nervous system activity measured directly in healthy dogs and dogs with tachycardia-induced heart failure. *Heart Rhythm*. 2009; 6:546–552. [PubMed: 19324318]
- [29]. Blain G, Meste O, Blain A, Bermon S. Time-frequency analysis of heart rate variability reveals cardiocomotor coupling during dynamic cycling exercise in humans. *Am J Physiol Heart Circ Physiol*. 2009; 296:H1651–1659. [PubMed: 19252094]
- [30]. Huang HH, Chan HL, Lin PL, Wu CP, Huang CH. Time-frequency spectral analysis of heart rate variability during induction of general anaesthesia. *Br J Anaesth*. 1997; 79:754–758. [PubMed: 9496208]

Figure 1.

(a) RRI tracing for a period of 10 minutes from a stationary region. (b) Power spectra computed using both approaches.

Figure 2.

(a) RRI tracing for a period of 10 minutes from a period containing arrhythmia. The inset shows the ECG tracing from 0.23-0.4 minutes with arrhythmic cycles. (b) Power spectra computed using both approaches.

Figure 3.

(a) RRs containing higher incidences of arrhythmic beats. (b) Power spectra computed using both approaches.

Figure 4.

The variation of percent spectral power with time in (a) low-frequency, (c) high-frequency and (e) the ratio of the power in the low-frequency to high-frequency, obtained using the standard approach. (b), (d) and (f) show the same quantities as shown in Figures (a), (c) and (e) but obtained using modified approach. Low-frequency power is defined as the ratio of the sum of powers in the frequency band of 0.05-0.25Hz to the total power. High-frequency power is defined as the ratio of the sum of powers in the frequency band of 0.3-1Hz to the total power. Total power is defined the sum of the powers in the frequency band of (0.05-2Hz). The quantities plotted in (a-f) are dimensionless by virtue of their definitions.

Figure 5.

(a) The frequency at which the ventilator was delivering the breaths to the infant. During the first six hours and 15 minutes the infant was on the high-flow ventilator. (b) The ratio of the maximum power in the frequency band of 0.3-0.8 Hz to the total power (0.05-2Hz) as a function of time.