UNCOUPLING AND RECOUPLING OF AUTONOMIC REGULATION OF THE HEART BEAT IN PEDIATRIC SEPTIC SHOCK

Running Head: Uncoupling and recoupling in septic shock

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ABSTRACT

Healthy physiologic systems exhibit marked signal variability and complexity while diseased systems generally show a loss of variability, decreased complexity ("decomplexification"), and increased regularity. The goal of this study was to evaluate the uncoupling and recoupling phenomenon in children with septic shock by following serial changes in heart rate variability metrics. Data was collected from 7 children with septic shock using the computer system in the Complex Systems Laboratory at Oregon Health Sciences University. Heart rate time series were constructed and analyzed using the Hales Research System at intervals of 6 hours during PICU hospitalization. These power spectral values were then plotted versus time. Six of seven patients demonstrated an increase over time in low-frequency heart rate power and the low-/high-frequency ratio, while high-frequency heart rate power decreased. We also compared the change in mean heart rate, heart rate standard deviation, and power spectral values during the first 24 hours of PICU hospitalization versus the remainder of the PICU stay (for the 5 patients with a PICU LOS > 48 hours). Compared to the initial 24 hours in the PICU, low-frequency power and the low-/high-frequency ratio increased while high-frequency power decreased over the course of the illness. This report demonstrates the potential value of monitoring the uncoupling and recoupling phenomenon in patients with septic shock. Our results are in agreement with other investigators who report evidence of decomplexification both in experimental models of sepsis and in clinical studies and provide direction for further work.

Key Words: heart rate variability, power spectral analysis, complex nonlinear systems, autonomic nervous system, systemic inflammatory response syndrome, sepsis, multiple organ dysfunction syndrome

ABBREVIATIONS

SIRS	systemic inflammatory response syndrome
MODS	multiple organ dysfunction syndrome
PICU	pediatric intensive care unit
SDN	serial data network
LAN	local-area computer network
PDS	patient data server
ECG	electrocardiogram
LOS	length of stay
nLFP	normalized Low Frequency Power
nHFP	normalized High Frequency Power
Dop	dopamine
Dob	dobutamine
Epi	epinephrine

INTRODUCTION

The systemic inflammatory response syndrome (SIRS) is a life-threatening condition that affects thousands of children and adults each year (1). A subpopulation of patients with SIRS goes on to develop septic shock, multiple organ dysfunction syndrome (MODS), and death. The progression from SIRS to death may result, in part, from an alteration in the interconnectivity of organ systems (2). Despite advances in antimicrobial therapies and intensive care, new paradigms are needed if we are to improve the outcome from this disease state.

Uncoupling has been defined as the loss of interorgan communication (2). This loss of communication can be the result of multiple, varied processes, including the loss of anatomic connections (e.g. following a heart transplant (3) or a surgical parasympathectomy (4)), the loss of autonomic nervous system input (e.g. brain death (5,6)), the effect of pharmacologic autonomic nervous system blockade with atropine or propranolol (7), and other pathophysiologic processes including congestive heart failure (8,9), chronic renal failure (10), diabetes mellitus (11), sepsis (12) and experimental endotoxemia (13). Investigators have shown that all of the above phenomena are associated with a loss of low frequency heart rate variability power. Healthy systems exhibit marked physiologic signal variability and complexity while diseased systems generally show a loss of variability, decreased complexity ("decomplexification"), and increased regularity (14, 15). It has therefore been suggested that the net effect of all these processes (i.e. a loss of communication or uncoupling) may be evaluated with measures of variability.

Power spectral analysis of beat-to-beat heart rate variability is a non-invasive method to assess autonomic nervous system regulation of cardiovascular activity, or the degree of interconnectivity and coupling between these two organ systems. Thus, power spectral analysis of heart rate variability and other time series analysis techniques have the potential for improving the monitoring of disease progression and recovery. We have previously shown that loss of heart rate variability and decomplexification are inversely related and negatively correlated to severity of illness and outcome in critically ill and injured children, including a small sub-population of patients with septic shock (16). We hypothesized that septic shock results in an uncoupling of organ system interconnectivity and that the uncoupling phenomenon can be quantified as a loss in heart rate variability. Furthermore, we suggest that recovery from septic shock is characterized by recoupling with an increase in heart rate variability. The goal of this study was to evaluate the uncoupling and recoupling phenomenon in children with septic shock by following serial changes in heart rate variability metrics.

MATERIALS AND METHODS

Informed Consent

This study was reviewed and approved by the Institutional Review Board at Oregon Health Sciences University, and the requirement for informed consent was waived.

Patient Population

We studied seven patients with septic shock as defined by the 1992 American College of Chest Physicians and the Society of Critical Care Medicine consensus statement of definitions for the systemic inflammatory response syndrome and the continuum of disease states to septic shock (17).

General Patient Management

Patients were managed according to the standards of care in the pediatric intensive care unit (PICU) at Doernbecher Children's Hospital and according to previously reported practice parameters (1).

Data Collection

We used the computer system in the Complex Systems Laboratory to build a library of physiologic signals characterizing the sepsis continuum in children (18). The computer system is based on four components: (a) 16 Hewlett-Packard (HP; Palo Alto, CA) Merlin monitors located in each patient room and connected via a Serial-Data-Network (SDN) to (b) an HP Patient Data Server (PDS) computer located in a telecommunications room connected through a local-area computer network (LAN) to (c) an HP-UX workstation and HP Vectra computer located in the Complex Systems Laboratory within the PICU. All software and workstation programming and maintenance are done over the Internet through (d) the Laboratory for Computational Neuroscience, Dept. of Neurological Surgery, at the Univ. of Pittsburgh Medical Center (**Figure 1**).

Briefly, the HP Patient Data Server is a computer configured with specialized hardware and software that provides a digital programmable interface to the HP Merlin Bedside Monitors connected to the SDN. Attached to both the SDN and to the Complex Systems Laboratory LAN, the patient data server provides a gateway allowing local computer systems access to waveform and parameter data produced by the bedside ICU monitors for real-time display and acquisition. Standard network communications protocols extend this capability via the Internet to the Laboratory for Computational Neuroscience, Dept. of Neurological Surgery, Univ. of Pittsburgh Medical Center.

A program running on the remote computer system from the Complex Systems Laboratory HP-UX workstation communicates with the PDS to learn the status of each bedside monitor and dynamically identifies the physiological data available on each channel. Using this information, the program requests the PDS to capture desired data and forwards it for processing. Two types of physiological data are available through the PDS: *parameter data* that is sampled at a rate of 0.98 Hz; and, *continuous physiologic signal waveform data* that is sampled at either 500 Hz (electrocardiogram, ECG) or 125 Hz (pressure, respiration, oximetry). Data is transmitted by the PDS at a rate of 0.98 Hz. Therefore, each transmission consists of 1, 125, or 500 data points. In addition, subject identification, alarm text, and alert status information are captured.

All data is dynamically stored in an ASCII file format. The system captures data on a 24-hour x 7-day schedule for each bed selected. The data is compressed and archived to CD-ROM each weekday from which it is accessible according to date, subject, and bed number.

Construction of Heart Rate Variability Time Series

For this study, the ECG was downloaded from archived CD-ROM using the Hales Research System (Boston Medical Technologies, Boston, MA). A raw 128 second ECG time series was constructed every 6 hours during PICU hospitalization using R wave detection and filtering techniques embedded in Hales as well as visual inspection for artifact. No time series epoch with > 1% artifact was used. Time series data were linearly detrended and analyzed using a modification of the methodology described by Saul et al. (19) for determining mean values, standard deviation, and power spectral density.

Calculation of Linear, Frequency-Domain Power Spectral Metrics

Power spectral analysis, which reveals the relative frequency-specific contributions of strong periodic signals on the heart beat and provides information about autonomic regulation of heart rate (20), was also calculated within Hales. Spectral analysis of heart rate variability time series derived from the ECG waveform detects and quantifies periodicities in cardiovascular oscillations and deconvolutes the original time series into a sum of component sinusoidal functions of different frequencies (21). Standards defining specific frequency bandwidths commonly used to characterize and study power spectral analysis of heart rate variability in adult humans were followed and normalized power spectral values were calculated and reported for this study (22).

We used total power from the bandwidth between 0.15-1.0 Hz (to allow for the faster respiratory rate observed in children) as a measure of parasympathetically mediated respiratory sinus arrhythmia. While the combined neural control at lower frequencies makes it difficult to separate specific sympathetic and parasympathetic influences in a given subject, if the effects of one or the other autonomic inputs are absent, then the short-term heart rate fluctuations that remain are caused primarily by the other autonomic branch. During stressful conditions, as we have documented in PICU patients, low-frequency heart rate oscillations are predominately mediated by sympathetic input (23). Therefore, we used both low-frequency bandwidth (0.04-0.15 Hz) and the ratio of low-/high-frequency power to provide information about sympathetic modulation of heart beat (16).

RESULTS

Table 1 shows the patient's age, gender, survival, PICU length of stay (LOS), diagnosis and maximum vasoactive drug dose.

In order to evaluate the uncoupling/recoupling phenomenon, we calculated the normalized low-frequency and high-frequency heart rate power for a 128 second segment every six hours for the duration of the PICU stay. These power spectral values were then plotted versus time and trends in the data were illustrated by lines of best fit for each patient. **Figures 2 a-c** shows the results. Six of seven patients demonstrated an increase over time in low-frequency heart rate power and the low-/high-frequency ratio, while high-frequency heart rate power decreased.

The plot of low-/high-frequency heart rate power ratio for the one patient who did not survive is shown in greater detail in **Figure 3**.

We also compared the change in mean heart rate, heart rate standard deviation, and power spectral values during the first 24 hours of PICU hospitalization versus the remainder of the PICU stay. This was done in the 5 patients with a PICU LOS > 48 hours. The results are summarized in **Table 2** and demonstrate that, compared to the initial 24 hours in the PICU, low-frequency power and the low-/high-frequency ratio increased while high-frequency power decreased over the course of the illness.

DISCUSSION

This study specifically evaluated serial changes in heart rate variability in order to more carefully examine the time course of uncoupling and recoupling in children with septic shock. Our main finding was that evidence of recoupling following an acute uncoupling phase was found utilizing serial measures of heart rate variability. Normalized low-frequency heart rate power and low-/high-frequency heart rate power ratio increased over time in 6 of the 7 patients studied. The seventh patient was cared for only briefly in the PICU and it is possible that the trend was not observed due to the small number of data points. These results suggest significant uncoupling and decomplexification between the sympathetic and cardiac systems during the acute phase of septic shock with recoupling during recovery.

The two patients with E. coli sepsis had underlying malignancies that resulted in an immunocompromised state prior to septic shock and PICU admission. However, the five patients with meningococcemia were all previously healthy within hours of PICU hospitalization and can be assumed to have demonstrated normal heart rate variability and coupling. Thus, we suggest that the uncoupling phenomenon may occur rapidly with the onset of septic shock, while the recoupling period may take days or weeks to occur concomitant with clinical recovery. Detailed analysis of the only non-survivor showed a positive slope in sympathetic activity over time, but this may have resulted from one data point (at 66 hours) that was temporally related to a brief clinical improvement or may have simply represented spurious data. Interestingly, from that point until the time of death, heart rate variability decreased demonstrating recurrent uncoupling.

Interpretation of changes in the high-frequency power is difficult as the effects of mechanical versus spontaneous ventilation obfuscate the interpretation of the results (24).

Our results are in agreement with other investigators who report evidence of decomplexification both in experimental models of sepsis and in clinical studies. Experimental studies have demonstrated that endotoxin shock adversely affects neuroautonomic cardiovascular regulatory mechanisms, leading to decreased heart rate and blood pressure variability (25, 26, 27) and uncoupling. Evidence suggests that shock states result in central and peripheral inhibition of the sympathetic and parasympathetic nervous system by a variety of mechanisms, including damaged neuronal transmission, the release of myocardial depressant factors, and inhibition of numerous neurohumoral responses, including the response to endogenous or exogenous catecholamines and parasympathetic attenuation of the release of cytokines (2, 28). Signaling compounds and molecules that appear to affect the inflammatory process may also affect the mathematical physics of the system. Thus, there is evidence that at various neuroanatomic and biochemical levels, the autonomic and cardiovascular systems appear to lose interconnections and uncouple during sepsis.

A growing number of clinical studies have reported specific dynamic characterizations of sepsis, septic shock and recovery states. Clinical studies have demonstrated decreased variability, or decomplexification, in physiologic dynamics during critical illness (29, 30) and in sepsis syndromes. Listeria sepsis reduced normal heart rate variability in 20 maternal-fetal dyads and was associated with poor outcome (31). In 17 patients with sepsis, sympathetically mediated heart rate variability was significantly lower during the sepsis syndrome and showed an inverse correlation with disease severity (32). Using frequency domain metrics, decreased low-frequency heart rate and blood pressure variability was found in 12 patients with septic shock. Variability increased by the time of discharge for patients who recovered (33). Godin and colleagues performed a prospective, randomized crossover trial in which human volunteers injected with endotoxin served as a model of clinical sepsis (13). Using linear and nonlinear metrics, this study demonstrated uncoupling between the neuroautonomic and cardiovascular systems as evidenced by decreased heart rate variability. A recent report demonstrated that the onset of septic shock is characterized by impaired sympathetic modulation of heart and blood vessels, suggesting that central autonomic regulatory impairment contributes to circulatory failure (34). Finally, we recently reported a prospective case series study to evaluate the degree of uncoupling in sepsis and septic shock in 30 PICU patients (12). We found evidence of uncoupling of the autonomic and cardiovascular systems over both short- and long-range time scales during sepsis using heart rate variability metrics. Results from this current study extend these findings and suggest that the degree of uncoupling may help differentiate between septic shock and recovery states.

This report, while limited in its scope, demonstrates the potential value of monitoring the uncoupling and recoupling phenomenon in patients with septic shock. There are a number of limitations in this study, and our laboratory is prepared to address these in future work. Clearly a larger number of patients needs to be evaluated to confirm and extend our findings. For this study, we limited the analysis of the data to 6-hour intervals although raw data was continuously collected. We are currently developing algorithms that will allow analysis in a continuous fashion utilizing a moving window, and will utilize both linear and nonlinear metrics. The use of nonlinear metrics will overcome problems with non-stationarity of the data and may provide additional insight into pathophysiological mechanisms. Finally, the question remains whether variability and regularity metrics are legitimate measures of organ system coupling in both the mathematical and physiological sense.

TABLES

Table 1. Patient summary.

Subject	Age (years)	Gender	Survival vs. Non-survival	PICU LOS (hours)	Diagnosis	Maximum Vasoactive Drug Dose (mcg/kg/min)		
						Dop	Dob	Epi
1	3.5	F	Survival	102	Meningococcemia	20	7	0.2
2	21	F	Survival	318	E. coli	15	5	0.15
3	5	F	Survival	36	Meningococcemia	20	5	--
4	2	F	Survival	24	Meningococcemia	5	10	--
5	1.5	M	Survival	210	Meningococcemia	20	20	0.4
6	0.5	F	Non-survival	198	E. coli, Candida albicans	40	20	2.0
7	17	M	Survival	204	Meningococcemia	15	10	0.2

(Dop - dopamine, Dob - dobutamine, Epi - epinephrine)

Table 2. Heart rate and hear rate variability during the initial 24 hours in the pediatric intensive care unit versus the subsequent ICU stay. (nLFP – normalized Low Frequency Power, nHFP – normalized High Frequency Power)

	Initial 24 hours	Subsequent PICU Stay	p value*
Heart rate (bpm)	149 $\pm$ 7	119 $\pm$ 9	0.02
Heart rate SD	2.46 $\pm$ 0.83	2.02 $\pm$ 0.21	0.59
nLFP	35.0 $\pm$ 5.8	51.7 $\pm$ 5.4	0.01
nHFP	65.0 $\pm$ 5.8	47.9 $\pm$ 5.7	0.01
nLFP/nHFP Ratio	0.60 $\pm$ 0.37	1.22 $\pm$ 0.66	0.02

* Paired *t* test

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FIGURES

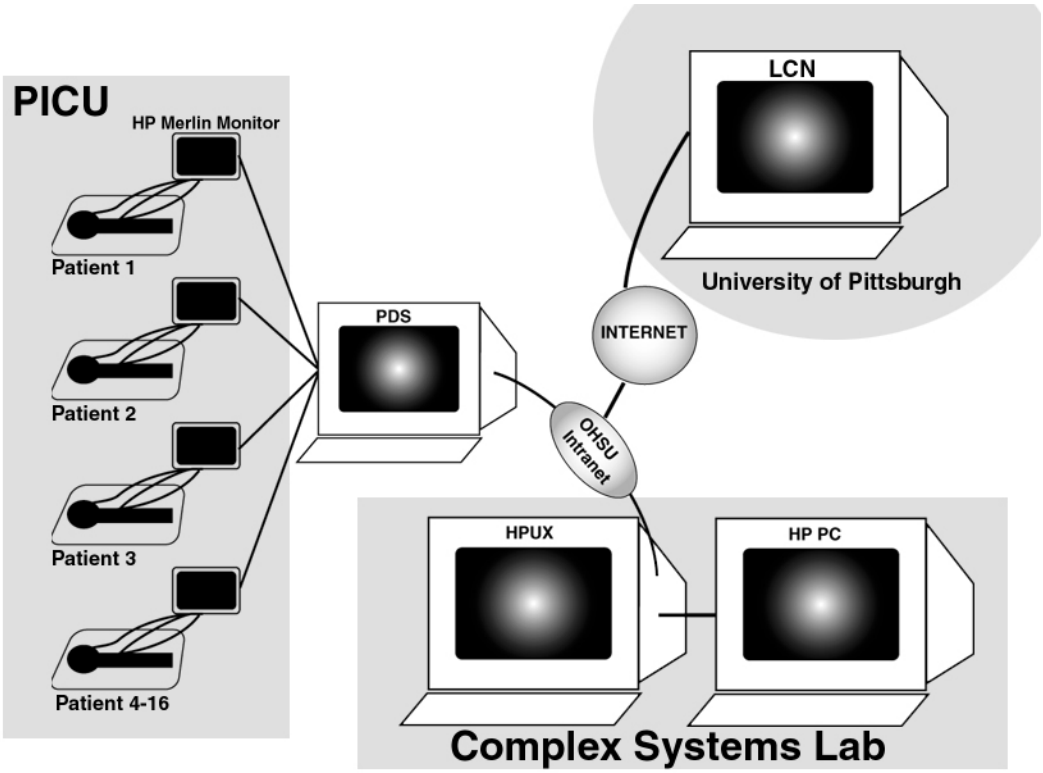

Figure 1. Schematic diagram of the design and communication links of the Pediatric Intensive Care Unit (PICU), the HP-Patient Data Server (PDS), the Complex Systems Laboratory, and the Laboratory for Computational Neuroscience (LCN), Dept. of Neurological Surgery, Univ. of Pittsburgh Medical Center.

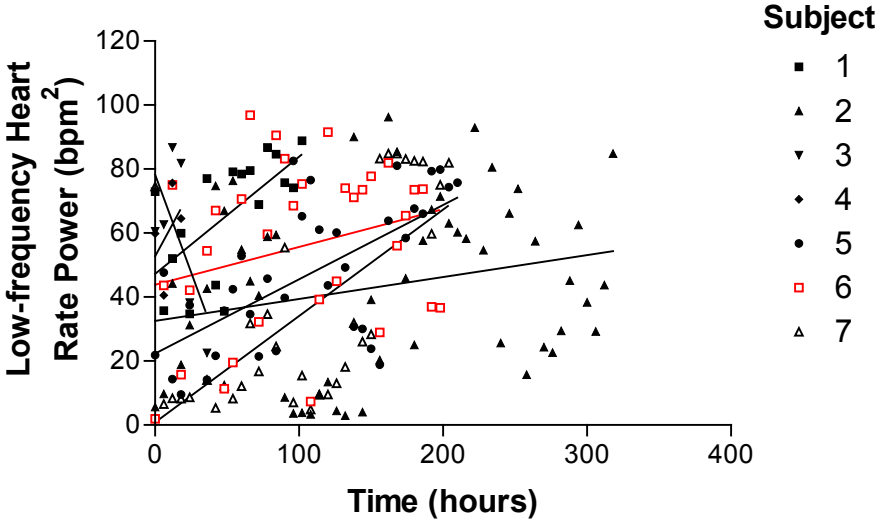

Figure 2.a.

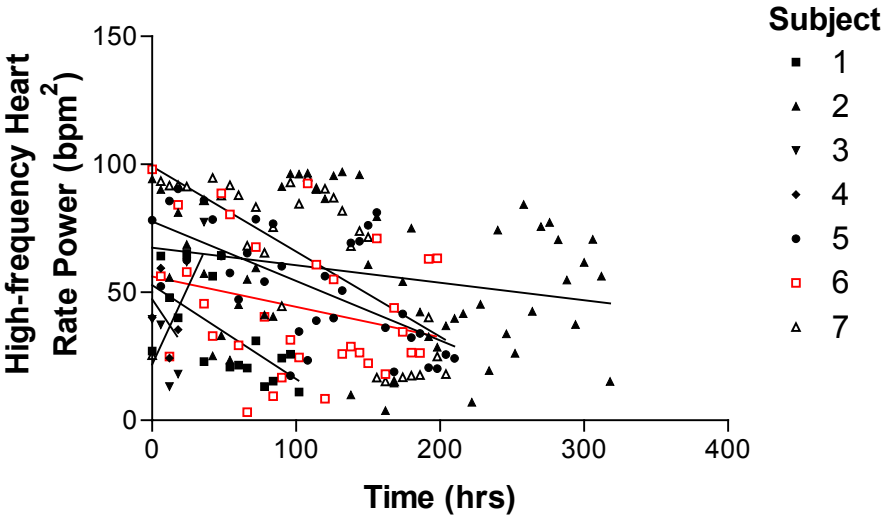

Figure 2.b.

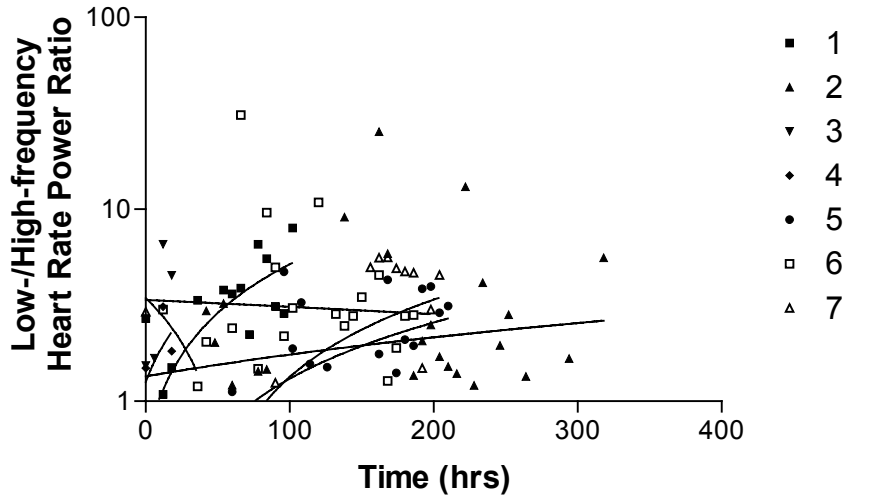

Figure 2.c.

Figures 2 a-c. Low-frequency (a), high-frequency (b), and low-/high-frequency ratio (c – note log scale) heart rate power versus time in seven patients with septic shock. To illustrate trends in the data, lines of best fit have been added. Note the positive slope of the low-frequency and low/high-frequency ratio power trend in 6/7 patients while the high-frequency power shows a negative slope. The one patient with the opposite pattern survived and had a very brief PICU stay of only 36 hours (and thus had a limited number of time epochs evaluated). Six of seven patients demonstrated similar patterns of increasing low-frequency heart rate power, increasing low-/high-frequency heart rate power ratio, and decreasing high-frequency heart rate power over time.

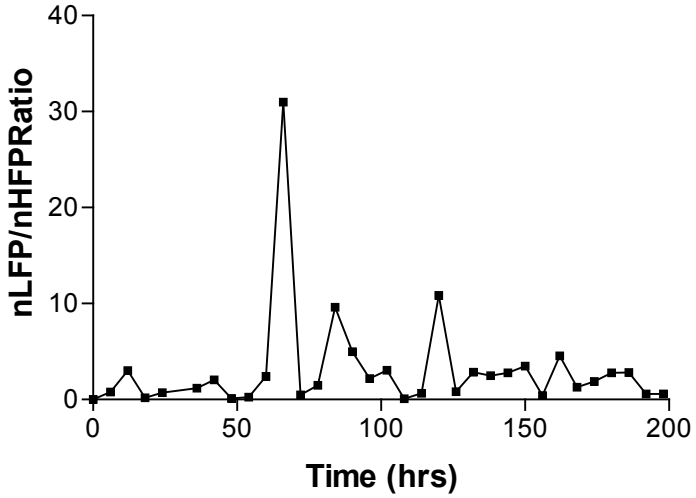

Figure 3. Detailed plot of low-/high-frequency heart rate power ratio in the one patient who did not survive. Note the increased power ratio at 66 hours into PICU hospitalization that correlated with a brief clinical improvement. This caused the overall slope to be positive which otherwise would have been flat.