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Power Spectrum Analysis of Heart Rate Variability in Full-Term and Preterm Neonates

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Objective: Prematurely born infants have been believed to be neurologically less mature than full-term neonates. The purpose of this study was to investigate the regulation and maturation of autonomic nervous systems, in both full-term and preterm neonates of different conceptional ages.

Methods: One hundred and thirteen infants, both clinically and neurologically healthy and with conceptional ages of between 33 and 42 weeks, were enrolled in the study. Power spectrum analyses of heart rate variability were performed under standard conditions when the subjects were in a sleeping state.

Results: Conceptional age did exert a significant influence over heart rate variability. There was a steady increase in total power and in the power of low frequency and high frequency components, along with a progressive decline of low frequency/high frequency ratio, as the conceptional age advanced. Infants of more than 36 weeks conceptional age demonstrated a significantly greater activity of autonomic nervous system than the younger group. However, the maturation of sympathovagal balance needed to take two more weeks with a low frequency/high frequency ratio cut-off age occurring at 38 weeks conceptional age. Gender and postnatal days at the time of the study did not exert a significant impact on the recordings.

Conclusions: The function of autonomic nervous systems in preterm neonates was underdeveloped as compared with full-term neonates. This might account for the vulnerability to stress in this population. Every possible precaution should be taken to avoid jeopardizing their fragile lives, and continuous monitoring of vital signs during medical procedures should be mandatory in order to recognize major stress signs as early as possible. (Tw J Phys Med Rehabil 2007; 35(3): 127 - 135)

Key words: power spectrum analysis, heart rate variability, autonomic nervous system, conceptional age

INTRODUCTION

Physiologic homeostasis, the delicate balance of cardiopulmonary and metabolic functions, is modulated by the autonomic nervous system (ANS). Prematurely born infants are neurologically less mature than full-term neonates. Their autonomic nervous systems are pro-
grammed to function primarily in the intrauterine environment and thus do not completely adapt to the physiologic demands of extrauterine life. Unfortunately, they are exposed to multiple stressors during the period of neonatal intensive care, and the immaturity of their central nervous systems makes them particularly vulnerable to the destabilizing effects of these events. This accounts for the development of physiological stress in this population from even routine activities and medical procedures. Frequently seen autonomic stress signs include episodes of apnea and bradycardia, increased heart rate and blood pressure, color changes (skin mottling to red or cyanotic appearance because of desaturation), sneezing, sweating, trembling, startling, hiccups, yawning, bowel movements, and so on. Some of the major stress signs are highly capable of endangering their fragile lives if they are not recognized and managed immediately. Also, prolonged physiologic instability has been found to be associated with deleterious neurodevelopmental consequences for extremely premature infants at 2 to 3 years of age, independent of the effects of intracranial abnormalities and gestational age.

Heart rate variability (HRV) is affected by numerous factors, including blood pressure, temperature, respiration, the biochemical influence of acid-base balance, state of oxygenation, ventilation, and psychological parameters. Heart rate variations have been used as a means of investigating ANS regulation for a long time. Power spectrum analysis (PSA) is a frequency domain analysis of HRV that displays two main components according to its oscillating frequency and developing mechanism: a low-frequency (LF) one representing sympathetic and parasympathetic influences, with frequency ranging from 0.04 to 0.15Hz; and a high-frequency (HF) one of parasympathetic origin, with frequency ranging from 0.15 to 0.4Hz. The measurement of LF and HF power components is usually made in absolute values of power (milliseconds squared - ms²); but it may also be measured in normalized units, which represent the relative value of each power component in proportion to the total power. This normalization also minimizes the effect of changes in total power on the values of LF and HF components in different testing circumstances. The controlled and balanced behavior between the sympathetic and parasympathetic systems (sympathovagal balance) can be defined as LF/HF ratio. Previous findings suggest that change in the LF/HF ratio, rather than in LF and HF power, best defines shifts in sympathetico-vagal balance.

Some previous researchers have used a baroreflex to study heart rate control in preterm and full term infants. The baroreflex involves minimizing any variation in blood pressure by response of both the heart rate and arterial vascular tone through the mediation of the para-sympathetic and sympathetic system, respectively. A study by Gournay et al. indicated that baroreflex control of the heart rate is present in the premature infant, but is underdeveloped and increases with postnatal age. In the series by Mazursky et al., the authors concluded that the LF/HF ratio progressively decreased with increasing postnatal age, which indicated a maturational change in sympathovagal balance. Cabal et al. studied neonatal HRV in 92 preterm infants and suggested that the decrease in neonatal HRV was significantly related to the severity of respiratory distress syndrome (RDS), and that the reappearance of neonatal HRV in infants with RDS was associated with a good prognosis. Clairambault et al. studied 24 healthy newborns, aged 31 to 40 weeks of conceptional age (CA) and undertook a spectral analysis of the interbeat interval (RR) signal. They documented a steep increase in vagal tone at 37 to 38 weeks CA, with stability afterwards, and a more regular increase in sympathetic tone from 31 to 41 weeks CA. Most previous researchers have agreed that the ANS which mediates HRV is relatively immature in preterm newborns and that maturational change does occur with increasing postnatal age. Nevertheless, their research has been limited by factors which include small sample sizes that stretch across a wide range of CA, and inability to elaborate when the maturational of ANS does actually take place. The purpose of the present study was to investigate the regulation and maturational change of ANS, as assessed by power spectrum analysis of HRV, in both full-term and preterm neonates with different CA. At meanwhile, our team also tried to confirm that the cut-off age of the maturational change of ANS does indeed occur during the postnatal period.

**MATERIALS AND METHODS**

Full-term and preterm neonates of different gestational age (GA) in baby room, and both clinically and
neurologically healthy, were enrolled. We excluded patients with congenital anomalies, cardiac disease, and histories of intraventricular hemorrhage, asphyxia or other complicated medical conditions. No subjects were receiving any medication that might modify the activity of ANS at the time of study. Clinical care was not affected by participation of the study. They were grouped by CA at the time of recording into five different age groups for comparison: group I, >32 and <34 weeks; group II, >34 and <36 weeks; group III, >36 and <38 weeks; group IV, >38 and <40 weeks; group V, >40 and <42 weeks. GA referred to weeks after conception at birth, and CA referred to weeks after conception at the time of HRV recording. The Ethics Committee of the Veterans General Hospital approved this study, and informed consent was obtained from their parents before enrollment.

**Measurement and equipment**

All studies were performed between 10am and 4pm when the subjects were in periods of sleep with few movements and regular respiration, usually 1 to 2 hours after feeding. No further attempt was made to distinguish between the behavioral states (deep or light sleep) of the infants. Precordial electrocardiogram (ECG) recordings were made under standardized conditions, while the subjects were in a supine position for 5 consecutive minutes. Either five consecutive minutes or 24 hours recording were the standardized period of time recommended by the American Heart Association. Since five minutes recording could provide all the information needed in the present study, we chose this recording time for convenience purpose. The raw ECG signals were recorded using an eight-bit analog-to-digital converter with a sampling rate of 256 Hz. The digitized ECG signals were analyzed online, and were simultaneously stored on removable hard disks for offline verification. We used a general-purpose personal computer to perform the signal acquisition, storage and processing.\(^{[12]}\)

**Signal processing**

The computer program for HRV analysis was based on a modified version of software developed by one of authors.\(^{[12,13]}\) In the QRS identification procedure, the computer first detected all peaks in the five-minute digitized ECG signal sequence using spike detection algorithms. Parameters, including amplitude and duration of all spikes, were measured so that their means and standard deviations (SDs) could be calculated as standard QRS templates. Ventricular premature complex or noise was then rejected according to its likelihood in standard QRS templates. The valid RR values were then resampled and interpolated at the rate of 7.11 Hz to accomplish the continuity in a time domain.\(^{[14]}\)

**Frequency domain analysis**

Frequency domain analysis was performed using the nonparametric method of fast Fourier transformation (FFT). The DC component was deleted, and a Hamming window was used to minimize the effects of leakage. For each time segment (288 seconds, 2048 data points), our algorithm estimated the power spectral density using FFT. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window.\(^{[15]}\) The power spectrum was subsequently quantified into various frequency measurements, as previously defined.\(^{[7]}\) Outcome measures in the present study included total power, mean power, LF and HF power, proportion of LF and HF components and LF/HF ratio. All the HRV parameters were expressed in original, square root and natural logarithm forms to correct possible skewness of distribution.\(^{[16]}\) The distributions of total power, mean power, LF and HF power, and LF/HF exhibited acute skewness, which were adjusted by natural logarithm transformation. However, the distributions of proportion of LF and HF components were close to normal distributions and thus were expressed as original forms.

**Statistical Analysis**

Data were analyzed with a Wilcoxon rank sum test and Kruskal-Wallis one-way ANOVA by ranks for comparison between the groups. Spearman’s rho correlation was used to define the correlation between the HRV parameters, gestational age (GA), CA, and postnatal days. The alpha level for all analyses was set at 0.05. All statistical analyses were conducted using SPSSx software (SPSS Inc., Chicago, IL).

**RESULTS**

One hundred and thirteen infants, 65 boys and 48
girls who met the inclusion criteria were enrolled. Their gestational age ranged from 26 to 42 weeks (mean 35.88 ± 4.28) and their birth body weight ranged from 1.4 to 9.9 lb (mean 5.39 ± 1.74). Twenty-nine of them were born before 32 weeks GA, 29 were born between 32 to 37 weeks GA, and 55 were born after 37 weeks GA. The distribution of subjects grouped by CA at the time of recording was 10 in Group I, 30 in Group II, 27 in Group III, 26 in Group IV, and 20 in Group V. Recordings were performed at 1 to 113 days after birth (mean 13.23 ± 19.31). CA was positively correlated with GA (r=0.880, p=0.000) and negatively related to postnatal days at the time of the study (r=-0.609, p=0.000). It implied that subjects born more prematurely tended to be enrolled at earlier CA and needed longer postnatal days to become medically stable so as to meet the criteria of enrollment.

Different CA group did show significant difference in almost all HRV parameters (Table 1) with the LF/HF ratio also reaching borderline significance (p=0.06). Regular increase in mean power, LF and HF components in absolute values of power, total power, and proportion of HF components were noted. Progressive decline of LF/HF ratios and of the proportion of the LF component were also noted as CA advanced (Figures 1 and 2). The cut-off age for mean power, and the LF and HF components, total power in absolute values of power was 36 weeks CA, with infants of more than 36 weeks CA demonstrating significantly greater activity of ANS than the younger group. However, the maturation of sympathovagal balance seemed to take two more weeks, with a cut-off age for LF/HF ratio occurring at 38 weeks CA (Table 2). The proportion of subjects with a more mature LH/HF ratio (negative value after logarithm transformation of the scale) was significantly higher in groups of more than 38 weeks CA (12/46 vs. 6/67, p=0.014). Gender and postnatal days at the time of study did not exert a significant impact on the recordings.

**DISCUSSION**

The management of physiological risk is a major consideration during developmental assessment and intervention procedures. Since prematurely born infants are neurologically less mature than full-term neonates, they are no doubt physiologically more fragile. Moreover, they are almost constantly handled in intensive care units. Routine medical procedures are often stressful and produce periods of physiological and behavioral instability. Common physiological responses include an increase or decrease in heart rate and/or respiratory rate, decrease or increase in vagal tone, and transient decrease in oxygen saturation. The behavioral responses of premature infants to relatively benign interventions include greater wakefulness, crying and more instability. However, some children exhibit prolonged periods of instability, while others are virtually insensitive to the treatment. Although in general, morbidity rates for infants born prematurely have improved over the past decade, these infants remain at significant risk of long-term neurological, cognitive and behavioral abnormalities. Prolonged physiological instability during the early postnatal period has been believed to have at least a partial association with these consequences, which makes the study of stress vulnerability in infants born prematurely of particular importance.

The variation of heart rate have long been used as a functional indicator of the ANS because it is controlled by both the sympathetic and the parasympathetic components of ANS. The sympathetic stimulation leads to acceleration of the heart rate, whereas the parasympathetic impulses through the vagal nerve produce slowing of the heart rate. The end result of their interactions is the R-to-R interval differences of the heart rate, or HRV. Neonatal HRV monitoring is a simple and non-invasive way to assess the newborn, and might be a prognostic tool also. Previous researches have indicated that after birth, HRV is influenced by the behavioral state and maturity of the newborn infant. The heart rate has tended to be fixed depending on the severity of RDS, and the reappearance of normal HRV in these sick babies has been associated with a good prognosis. Brain death, also, has been associated with an extremely small HRV. The study of HRV can be approached through either time domain analysis (R-R interval variation; RRIV) or frequency domain analysis (PSA), both of which are very simple procedures and require only minimal cooperation from the subjects being tested. Although RRIV is perhaps the simplest measurement in analyzing HRV, it is mainly indicative of the parasympathetic function of the vagus nerve and cannot give any information regarding the balance between the sympathetic and parasympathetic...
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Nevertheless, PSA is indicative of both sympathetic and parasympathetic functions, and can concurrently define shifts in sympathetic-vagal balance. This advantage was the major factor in our decision to use PSA, instead of RRIV, to investigate the HRV of our subjects in the present study.

Table 1. HRV Parameters and Different Groups of Conceptional Age

<table>
<thead>
<tr>
<th>Group (No)</th>
<th>I (10)</th>
<th>II (30)</th>
<th>III (27)</th>
<th>IV (26)</th>
<th>V (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BBW (Kg)</td>
<td>1.55±0.32</td>
<td>1.94±0.52</td>
<td>2.15±0.86</td>
<td>3.09±0.49</td>
<td>3.60±0.31</td>
</tr>
<tr>
<td>Female:male</td>
<td>4 : 6</td>
<td>16 : 14</td>
<td>12 : 15</td>
<td>8 : 18</td>
<td>8 : 12</td>
</tr>
<tr>
<td>Mean power (ms$^2$)$^a$</td>
<td>404.6±35.9</td>
<td>403.1±35.2</td>
<td>425.9±52.0</td>
<td>472.4±65.0</td>
<td>456.8±77.8</td>
</tr>
<tr>
<td>(347.7-477.1)</td>
<td>(354.2-475.2)</td>
<td>(336.4-539.1)</td>
<td>(354.6-618.5)</td>
<td>(333.0-653.1)</td>
<td></td>
</tr>
<tr>
<td>LFP(ms$^2$)$^a$</td>
<td>4.7±0.8</td>
<td>4.8±1.2</td>
<td>4.9±1.4</td>
<td>5.8±1.2</td>
<td>5.7±1.3</td>
</tr>
<tr>
<td>(3.6-6.3)</td>
<td>(2.6-8.3)</td>
<td>(2.3-9.5)</td>
<td>(2.8-11.5)</td>
<td>(3.9-8.4)</td>
<td></td>
</tr>
<tr>
<td>HFP(ms$^2$)$^a$</td>
<td>3.4±1.5</td>
<td>3.7±1.7</td>
<td>3.4±1.7</td>
<td>4.9±2.0</td>
<td>5.1±2.1</td>
</tr>
<tr>
<td>(1.7-6.6)</td>
<td>(1.2-8.3)</td>
<td>(0.2-9.2)</td>
<td>(0.9-8.0)</td>
<td>(2.3-8.9)</td>
<td></td>
</tr>
<tr>
<td>Total power(ms$^2$)$^a$</td>
<td>6.2±1.0</td>
<td>6.4±1.2</td>
<td>6.4±1.3</td>
<td>7.5±1.2</td>
<td>7.4±1.4</td>
</tr>
<tr>
<td>(4.9-8.7)</td>
<td>(4.1-9.4)</td>
<td>(3.8-10.5)</td>
<td>(5.7-9.4)</td>
<td>(5.4-10.1)</td>
<td></td>
</tr>
<tr>
<td>nLF(nu)$^a$</td>
<td>64.9±23.0</td>
<td>56.1±19.2</td>
<td>66.9±15.6</td>
<td>53.4±24.7</td>
<td>47.3±24.5</td>
</tr>
<tr>
<td>(22.9-88.4)</td>
<td>(10.6-92.5)</td>
<td>(18.5-92.9)</td>
<td>(14.9-91.5)</td>
<td>(14.2-84.6)</td>
<td></td>
</tr>
<tr>
<td>nHF(nu)</td>
<td>17.7±10.1</td>
<td>19.3±8.3</td>
<td>16.7±7.7</td>
<td>21.6±10.5</td>
<td>23.5±10.0</td>
</tr>
<tr>
<td>(6.22-35.11)</td>
<td>(3.8-40.0)</td>
<td>(4.5-35.6)</td>
<td>(5.2-39.6)</td>
<td>(8.3-37.8)</td>
<td></td>
</tr>
<tr>
<td>LF/HF$^aa$</td>
<td>1.36±1.04</td>
<td>1.09±0.87</td>
<td>1.46±0.76</td>
<td>1.01±0.96</td>
<td>0.64±1.03</td>
</tr>
<tr>
<td>(-0.3-2.7)</td>
<td>(-1.3-3.2)</td>
<td>(-0.66-3.0)</td>
<td>(-0.55-2.9)</td>
<td>(-0.76-2.3)</td>
<td></td>
</tr>
</tbody>
</table>

BBW= birth body weight; LFP= low frequency power; HFP= high frequency power; nLF= proportion of low frequency power; nHF= proportion of high frequency power; nu=normalized units, LF/HF= ratio of LF component to HF component

$^a P<0.05; ^aa P=0.060.$

Figure 1. Steady increase of LF and HF components in absolute value of power, total power, as CA advanced. CA= conceptional age; LFP= low frequency power; HFP= high frequency power; TP= total power.
Figure 2. Progressive decline of LF/HF ratio as CA advanced. CA= conceptional age

Table 2. HRV Parameters at Cut Off Points of 36 and 38 Weeks Conceptional Age

<table>
<thead>
<tr>
<th>CA (No)</th>
<th>≤36weeks (40)</th>
<th>&gt;36weeks (73)</th>
<th>≤38weeks (67)</th>
<th>&gt;38weeks (46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female:male</td>
<td>20:20</td>
<td>28:45</td>
<td>32:35</td>
<td>16:30</td>
</tr>
<tr>
<td>Mean power (ms$^2$)</td>
<td>403.5±34.9$^a$</td>
<td>451.0±66.7</td>
<td>412.5±43.7$^b$</td>
<td>465.6±70.5</td>
</tr>
<tr>
<td>LFP (ms$^2$)</td>
<td>4.7±1.1$^a$</td>
<td>5.4±1.3</td>
<td>4.8±1.2$^b$</td>
<td>5.8±1.2</td>
</tr>
<tr>
<td>HFP (ms$^2$)</td>
<td>3.6±1.6$^a$</td>
<td>4.4±2.1</td>
<td>3.5±1.7$^b$</td>
<td>5.0±2.0</td>
</tr>
<tr>
<td>Total power (ms$^2$)</td>
<td>6.3±1.2$^a$</td>
<td>7.1±1.4</td>
<td>6.4±1.2$^b$</td>
<td>7.5±1.3</td>
</tr>
<tr>
<td>nLF (nu)</td>
<td>58.3±20.3</td>
<td>56.7±22.9</td>
<td>61.8±18.9$^b$</td>
<td>50.8±24.5</td>
</tr>
<tr>
<td>nHF (nu)</td>
<td>18.9±8.7</td>
<td>20.3±4.97</td>
<td>18.0±8.3$^b$</td>
<td>22.4±10.2</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.16±0.91</td>
<td>1.08±0.96</td>
<td>1.28±0.86$^b$</td>
<td>0.85±0.99</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

$^a,b$ Statistically different between groups older and younger than 36 weeks CA, 38 weeks CA, and respectively ($P<0.05$).

Since previous researches have indicated that after birth, HRV is influenced definitely by the behavioral state, all of our recordings were performed when the subjects were in a sleeping state, with no movement or only minimal movement occasionally during the study period, so as to minimize the influence of different behavioral states (such as crying or vigorous movement) on the recordings. Our subjects were fairly evenly distributed in different CA groups, except for fewer cases recruited in Group I. Subjects who were born closer to term tended to be recruited earlier for the recordings. In contrast, the more premature the subjects were, the longer period of time needed before they were medically stable enough to be recruited for the study. According to previous studies, CA, GA, postnatal days and associated medical problems probably would all have exerted a certain impact on the recording. In our observations, postnatal days at the time of the study were greatly influenced by factors such as GA and associated medical complications of the subject. This might account for its lack of significant impact on all HRV parameters. Given that GA, postnatal age and CA were highly related in the present study, we decided to analyze data by CA groups only and to exclude, for simplification, subjects with complicated medical conditions during the postnatal period. Although gender is one of the factors that might influence ANS activities, as...
shown by some previous studies, we did not reach a similar finding here. The possible confounding factors included CA, GA and associated medical conditions of the subjects.

Our observations indicated that CA did exert a significant influence on HRV parameters and that a steady increase of total power, and power of LF and HF components, were demonstrated as CA advanced. This implied that progressively increasing ANS activities, in terms of both sympathetic and parasympathetic functions, did exist during the postnatal period as maturational processes took place, which concurred with previous studies. Moreover, our study further pointed out that those subjects with a CA of more than 36 weeks did have significantly higher ANS activities than the rest – an observation never raised before. Since parasympathetic activities were supposed to be predominant as compared with sympathetic activities during the sleeping state, a steady decline in LF/HF ratios and increase in the proportion of HF components was also observed as CA advanced. This also indicated a maturational change of sympathovagal balance. A cut-off point at 38 weeks of CA for LF/HF ratios was observed in the present study. The finding of significantly more subjects of more than 38 weeks CA did produce a negative LF/HF ratio after logarithm transformation provided further evidence that infants older than 38 weeks are relatively mature in terms of sympathovagal balance. This again raises the need for every medical personnel to be particularly cautious when dealing with younger subjects, considering their relatively underdeveloped ANS and limited capabilities to adapt to the physiological stresses we impose on them when performing assessment and/or intervention procedures in intensive care units. Every possible precaution should be taken to avoid jeopardizing their fragile lives and continuous monitoring of vital signs during medical procedures need to be mandatory so that major stress signs be recognized as early as possible.

CONCLUSION

Preterm neonates was proved to be neurologically less mature than full-term neonates, which might account for the fact that they are physiologically more fragile in dealing with external stimuli during their early postnatal life. PSA of HRV is a simple and non-invasive procedure that provides valuable information on the development of ANS in this particular patient population.

ACKNOWLEDGEMENT

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早產兒及足月兒心跳變異性的頻譜分析

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目的: 一般認為早產兒的神經系統發展不如足月兒成熟。本研究利用心跳變異性的頻譜分析(power spectrum analysis of heart rate variability),來探討不同受孕後週數(conceptional age)的嬰兒其自主神經系統的調節功能是否有差異。

方法: 本研究總共收集了113位臨床現象及神經狀況穩定且受孕後週數33到42週的個案,每個個案在睡眠狀態下接受了心跳變異性的頻譜分析。

結果: 受孕後週數確實影響了心跳的變異性。隨著受孕後週數的增加,在頻譜分析中低頻及高頻的能量(power)也穩定增加,而低頻/高頻比值也呈現逐步下降的趨勢。受孕後週數大於36週的個案他們自主神經系統的活動性顯著高於36週以下的個案；而代表交感與副交感神經系統間的平衡關係的低頻/高頻比值可能要再成熟個兩週,也就是到38週以上才會與早期有明顯的差別。性別與接受測試時的出生天數對研究結果則沒有顯著相關。


關鍵詞: 頻譜分析(power spectrum analysis),心跳變異性(heart rate variability),自主神經系統(autonomic nervous system),受孕後週數(conceptional age)