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Original article

Relationship between frequency spectrum of heart rate variability and autonomic nervous activities during sleep in newborns

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Abstract

Introduction: We analyzed the frequency spectrum of two neonatal sleep stages, namely active sleep and quiet sleep, and the relationship between these sleep stages and autonomic nervous activity in 74 newborns and 16 adults as a comparison.

Method: Active and quiet sleep were differentiated by electroencephalogram (EEG) patterns, eye movements, and respiratory wave patterns; autonomic activity was analyzed using the RR interval of simultaneously recorded electrocardiogram (ECG) signals. Power values (LFa, absolute low frequency; HFa, absolute high frequency), LFa/HFa ratio, and the values of LFn (normalized low frequency) and HFn (normalized high frequency) were obtained. Synchronicity between the power value of HFa and the LFa/HFa ratio during active and quiet sleep was also examined by a new method of chronological demonstration of the power values of HFa and LFa/HFa.

Results: We found that LFa, HFa and the LFa/HFa ratio during active sleep were significantly higher than those during quiet sleep in newborns; in adults, on the other hand, the LFa/HFa ratio during rapid eye movement (REM) sleep, considered as active sleep, was significantly higher than that during non-REM sleep, considered as quiet sleep, and HFa values during REM sleep were significantly lower than those during non-REM sleep. LFn during quiet sleep in newborns was significantly lower than that during active sleep. Conversely, HFn during quiet sleep was significantly higher than that during active sleep. Analysis of the four classes of gestational age groups at birth indicated that autonomic nervous activity in a few preterm newborns did not reach the level seen in full-term newborns. Furthermore, the power value of HFa and the LFa/HFa ratio exhibited reverse synchronicity.

Conclusion: These results indicate that the autonomic patterns in active and quiet sleep of newborns are different from those in REM and non-REM sleep of adults and may be develop to the autonomic patterns in adults, and that parasympathetic activity is dominant during quiet sleep as compared to active sleep from the results of LFn and HFn in newborns. In addition, in some preterm infants, delayed development of the autonomic nervous system can be determined by classifying the autonomic nervous activity pattern of sleep stages.

Keywords: EEG; Autonomic nervous system; Neonatal sleep; Heart rate variability

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1. Introduction

Heart rate variability (HRV) is a cardiac phenomenon in which the RR interval varies between beats. HRV results from regulation by the sinoatrial node, which is the natural pacemaker of the heart, and the parasympathetic and sympathetic divisions of the autonomic nervous system. In adults, spectral analysis of HRV has been used in physiological analyses of autonomic nervous system function, and in analyses of the pathophysiology of psychosomatic disorders [1–3]. Nevertheless, there are only a few reports of use of spectral analysis of HRV to analyze physiological and clinical disorders in the fetus or newborn. Furthermore, there are no reference values available for neonatal autonomic nervous system parameters, such as LFa (absolute low frequency component), HFa (absolute high frequency component), and LFa/HFa ratio. One reason for the paucity of such data is the difference between newborns and adults in terms of cardiac output and lung tidal volume. In fact, the heart and respiratory rates in newborns are approximately twice those in adults. Therefore, reference values for autonomic parameters in adults are not applicable to newborns [4,5].

Newborn sleep is differentiated into two stages: active sleep and quiet sleep. The differentiation between these two sleep stages is based on electroencephalogram (EEG) characteristics, eye movements, respiratory wave patterns, general movements, heart rate and respiratory rhythm [6–9]. In newborns, HRV characteristics and irregular respiratory rhythms, indicating active sleep, are similar to those during rapid eye movement (REM) sleep in adults, whereas quiet sleep is similar to non-rapid eye movement (non-REM) sleep [10,11]. Based on the physiological characteristics of these two sleep stages, it appears that the autonomic nervous system also regulates newborn sleep cycles. However, there is little data on the relationship between neonatal sleep stages and autonomic activity. Thus, we investigated autonomic activity during active and quiet sleep in neonates using physiological characteristics and EEG patterns for the determination of sleep stages, and evaluated autonomic activity by performing Fourier analysis of the ECG-RR interval with the EEG recorded at the same time. We sought to determine whether the power values for the sympathetic nervous system parameter, LFa/HFa, and the parasympathetic nervous system parameter, HFa, and the synchronicity between HFa and LFa/HFa, could be analyzed by a new method of demonstrating the changes with time in the power values of HFa and LFa/HFa.

2. Subjects

Subjects were selected from 431 newborns admitted to the neonatal intensive care unit of Nara Medical University Hospital from January 2007 to January 2011. An EEG was performed for 266 of these newborns at the time of their discharge. From these 266 newborns, we selected those who met the following criteria for study: at least 5 min of EEG recordings were available during both active and quiet sleep stages, and absence of the following disorders: neonatal asphyxia (Apgar score < 7 points at 5 min), intracranial hemorrhage, severe infection, metabolic abnormalities, or congenital malformations. In total, 74 newborns were included in the study (42 males, 32 females). Gestational age was calculated as the number of weeks until birth from the mother's last menstrual period before pregnancy. The mean birth weight (BW, 1642.5 ± 629.1 g) and mean gestational age at birth (GA, 32 weeks $\pm$ 4 days) was calculated for all subjects; GA was corrected based on the date when the EEG was recorded (mean: 37 weeks 2 days; range: 35 weeks 0 days to 43 weeks 6 days). The neonates were categorized into the following four subgroups based on their GA at birth: <28 weeks ($n = 12$), 28 weeks to <34 weeks ($n = 38$), 34 weeks to <37 weeks ($n = 19$), and $\geq$37 weeks ($n = 5$). Sixteen healthy adults with no significant heart disease or neurological disorder (mean age 51.4 years; 10 males, 6 females) were also included in the study as an adult reference. This study was approved by the ethics committee of Nara Medical University as part of the study on environmental care of the newborn.

3. Methods

EEG recordings were performed in a central EEG examination room that was maintained at a constant temperature (24 °C), shielded from electromagnetic waves, and had consistent lighting conditions (0–5 Lx). The digital EEG was recorded with Neurofax EEG (model 1524, Nihon Kohden Co., Tokyo, Japan) using a time constant of 0.3 s, calibration wave of 50 μV/5 mm, 120-Hz high-cut filter, and a 200-Hz sampling frequency. EEGs were recorded with 11 derivation reference electrodes that were fixed to the scalp (10/20 method) with plate electrodes (Ag/AgCl) (Nihon Kohden, Tokyo, Japan), and were recorded simultaneously with right and left eyelid movement, mandibular electromyographic activity (EMG), respiratory waves (thermistor method), and electrocardiograms (ECG, limb lead I).

We recorded EEGs for the entire sleep cycle in the supine position. Active and quiet sleep were differentiated by their EEG patterns, eye movements, and respiratory wave patterns. Adult sleep consists of repeated cycles of non-REM and REM sleep.

Non-REM sleep consists of sleep stages I to IV. Adult REM sleep is readily identified by rapid eye movements. We performed spectral analysis of HRV using 5-min segments of digital ECG data (lead I) recorded in each sleep cycle. Spectral analyses were performed with MemCalc/win (GMS Co., Tokyo, Japan). The

power spectra were calculated in the range of 0.04–0.15 Hz for low frequency (LF) and 0.15–0.7 Hz for high frequency (HF) components, to account for respiratory variability in the newborn [4]. The HF component in adults ranged from 0.15–0.45 Hz. In autonomic activity analysis, the LFa value represents mixed sympathetic and parasympathetic activity, whereas the HFa value represents only parasympathetic activity. Thus, the LFa/HFa ratio represents relative sympathetic nervous system activity. Power values of LFa and HFa were obtained every 30 s during the 5-min ECG recordings. We calculated normalized values of LF and HF (LFn, normalized low frequency power; HFn, normalized high frequency power) by dividing the LFa or HFa value by the sum of LFa and HFa, as LFn = (LFa/(LFa + HFa), and HFn = (HFa/(LFa + HFa) [12–15].

3.1. Statistical analysis

The power values of LFa and HFa to obtain a normal data distribution, statistical analyses were performed with power spectra of LFa and HFa. Statistical analysis of the power values in each sleep stage was performed using the Mann-Whitney *U* test. Values of $p < .10$ were judged as indicating differences, whereas $p < .05$ indicated significant differences.

In addition, the comparison of autonomic activity during active sleep and quiet sleep among the 4 GA groups at birth were statistically analyzed using the Kruskal-Wallis test. Values of $p < .10$ were judged as indicating differences, whereas $p < .05$ indicated significant differences.

4. Results

4.1. Comparison of autonomic activity during quiet and active sleep in all the newborns in the three corrected GA groups classified according to the time of EEG recordings

Neonates were divided into three groups according to the following corrected GAs: 35 to <37 weeks (28 neonates), 37 to <40 weeks (35 neonates), and ≥40 weeks (11 neonates). Our results indicated that the power values of LFa and HFa during active sleep in all three groups were significantly higher than their corresponding values during quiet sleep.

In contrast, the LFa/HFa ratio during active sleep was only significantly higher than that during quiet sleep in the 37- to <40-week group (Table 1).

4.2. Comparison of autonomic activity during neonatal active and quiet sleep and adult REM and non-REM sleep

The power values of LFa during REM and non-REM sleep in adults were also not significantly different. However, the power values of HFa during REM sleep in adults were significantly lower than those during non-REM sleep, contrary to what was seen during newborn sleep.

The LFa/HFa ratio during adult REM sleep was significantly higher than that during non-REM sleep (Table 1).

4.3. Comparison between normalized parameters of autonomic activity, namely LFn and HFn, during active and quiet sleep in all newborns and the three groups based on the corrected GA at the time of EEG recording

The LFn values of all newborns was significantly higher than their HFn values during both quiet and active sleep. Comparison of LFn and HFn in the three corrected GA groups at the time of EEG recording showed that in the ≥40-week corrected GA group, LFn during active sleep was significantly higher than that during quiet sleep ($p < .05$). In the other groups, however, there were no significant differences in LFn between active and quiet sleep.

On the other hand, in all corrected GA groups at the time of EEG recordings, the values of HFn during quiet sleep were significantly higher than those recorded during active sleep ($p < .01$) (Fig. 1).

4.4. Comparison between autonomic activity during active sleep and quiet sleep in groups classified according to gestational age at birth

Subgroup analysis of groups classified according to GA at birth, instead of the corrected GA, indicated that the power values of LFa during active sleep in the <28-week, 28- to <34-week, 34- to <37-week and ≥37-week GA groups were also significantly higher than their respective values during quiet sleep (Table 2).

Further, the power values of HFa during active sleep in the <28-week, 28- to <34-week, and 34- to <37-week GA groups were also significantly higher than their respective values during quiet sleep. There were, however, no significant differences in HFa between active and quiet sleep in the ≥37-week GA group. LFa/HFa ratios were significantly higher during active sleep than quiet sleep in the <28-week and 28- to <34-week GA groups. However, there were no significant differences in LFa/HFa ratio between active and quiet sleep in the 34- to <37-week and ≥37-week GA groups (Table 2).

4.5. Comparison of autonomic activity during active and quiet sleep in newborns classified according to gestational age at birth versus gestational age corrected for the time of EEG recordings

We also compared autonomic parameters between the groups classified according to GA at birth; <28-

Table 1
Comparison of the absolute values of autonomic nervous activity during the two stages of neonatal sleep in groups classified according to the corrected gestational age (in weeks) at the time of EEG recording.

Corrected GA (weeks)	n	LFa		
		Active sleep	Quiet sleep	*p*
35 to <37	28	107.56 ± 60.95	55.62 ± 32.34	<.01
37 to <40	35	105.96 ± 72.33	45.85 ± 36.10	<.01
≥40	11	110.35 ± 79.40	35.28 ± 24.56	<.01
Total number of neonates	74	104.40 ± 68.54	47.15 ± 34.17	<.01
Adults	n	LFa		
		REM	NREM	*p*
	16	289.68 ± 204.66	267.34 ± 169.23	.88
Corrected GA (weeks)	n	HFa		
		Active sleep	Quiet sleep	*p*
35 to <37	28	29.80 ± 26.54	15.93 ± 10.28	<.01
37 to <40	35	23.97 ± 16.75	12.57 ± 12.89	<.01
≥40	11	25.54 ± 12.78	13.19 ± 8.52	<.05
Total number of neonates	74	26.06 ± 20.93	13.72 ± 11.56	<.01
Adults	n	HFa		
		REM	NREM	*p*
	16	91.12 ± 63.00	225.29 ± 183.16	<.05
Corrected GA (weeks)	n	LFa/HFa		
		Active sleep	Quiet sleep	*p*
35 to <37	28	6.02 ± 2.97	4.91 ± 3.25	.08
37 to <40	35	6.73 ± 3.09	5.23 ± 2.48	<.01
≥40	11	4.95 ± 2.29	3.38 ± 1.40	.14
Total number of neonates	74	6.23 ± 3.04	4.84 ± 2.75	<.01
Adults	n	LFa/HFa		
		REM	NREM	*p*
	16	5.79 ± 4.94	2.93 ± 2.43	<.05

Values are presented as mean ± SD.
Mann-Whitney *U* test, Significant difference: p < .05 (HFa: absolute high frequency power, LFa: absolute low frequency power).

week, 28- to <34-week, 34- to <37-week and ≥37-week GA groups, and corrected GA at the time of EEG recordings. In the <28-week GA group, EEGs were recorded at 39 weeks ± 12 days (mean ± SD), in the 28- to <34-week and 34- to <37-week GA groups, EEGs were recorded at 37 weeks ± 7 days and 37 weeks ± 10 days, respectively, while in the ≥37-week GA group, EEGs were recorded at 40 weeks ± 13 days. The difference between the times at which EEGs were recorded among the 4 GA groups was analyzed by the Kruskal-Wallis test. No significant differences were observed between them (p=.10). However, the power values of LFa and HFa during active and quiet sleep were both significantly different among the 4 GA groups. On the other hand, the LFa/HFa ratios during active and quiet sleep were not significantly different among the 4 groups (p=.617 and p=.170, respectively) (Table 2). From these results, it seems that the autonomic activity of preterm newborns does not reach the level seen in full-term newborns, even when data are corrected for GA.

4.6. Synchronicity of the power values of HFa and the LFa/HFa ratio during active and quiet sleep in newborns and the two adult sleep stages (REM sleep and non-REM sleep)

A periodic change and synchronization between the power values of LFa and HFa and the LFa/HFa ratio were seen during the two stages of neonatal sleep (Fig. 2A). The power value of HFa reflects parasympathetic activity, whereas the LFa/HFa ratio reflects relative sympathetic activity. These two parameters exhibited reverse synchronicity, i.e., the lowest LFa/HFa ratio occurs at the peak power value of HFa.

This reverse synchronicity between the power values of HFa and the LFa/HFa ratio is seen during both adult and newborn sleep (Fig. 2B). Greater fluctuation and higher power values of HFa and the LFa/HFa ratio were seen in the power values of LFa, HFa, and the LFa/HFa ratio during adult REM and non-REM sleep than that seen during neonatal active and quiet sleep.

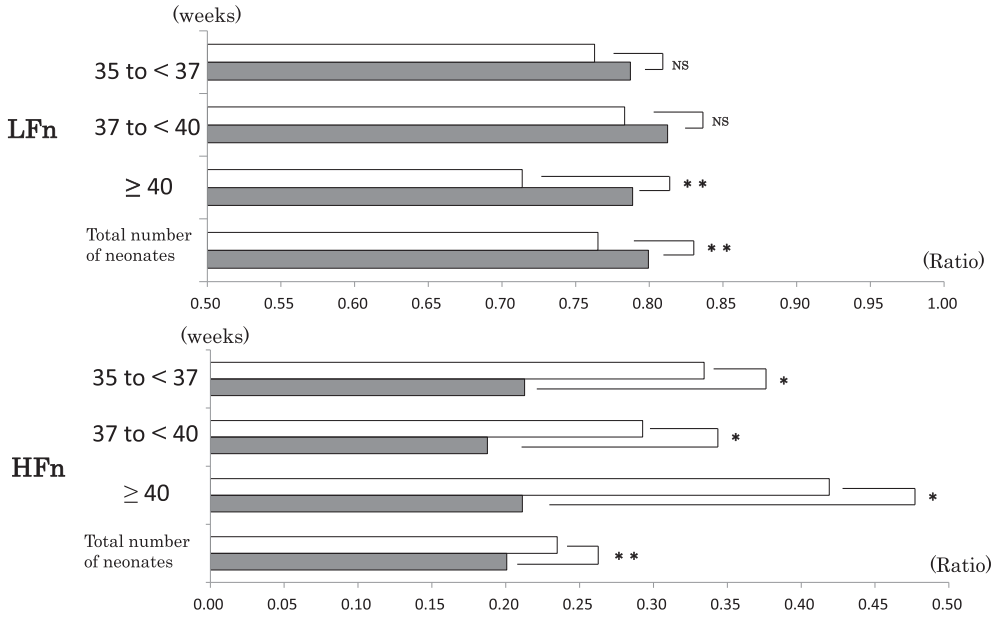

Fig. 1. Comparison between normalized parameters of autonomic activity during active and quiet sleep among the corrected GA groups at the time of EEG recording. The calculated normalized values of LF and HF (LFn, normalized low frequency power; HFn, normalized high frequency power) were obtained by dividing the LFa or HFa values by the sum of LFa and HFa, as LFn = (LFa/(LFa + HFa), HFn = (HFa/(LFa + HFa). The open squares indicate quiet sleep, and closed squares indicate active sleep. A significant difference was observed between active and quiet sleep, as shown in the figure. ($^{*}p < .01$, $^{**}p < .05$, NS: not significant difference).

Table 2
Comparison of autonomic nervous activity during the two stages of neonatal sleep in groups classified according to gestational age at birth.

Gestational age at birth (weeks)	LFa					
	n	active sleep		quiet sleep		p
<28	12	75.73 ±32.63	∗ (p<0.01)	36.22 ±30.41	∗ (p<0.01)	<0.05
28 to <34	38	108.25 ±75.71		46.08 ±33.30		<0.01
34 to <37	19	101.99 ±53.71		49.24 ±30.82		<0.01
≥ 37	5	194.77 ±62.26		85.76 ±28.10		<0.01
Total number of neonates	74	104.40 ±68.54		47.15 ±34.17		<0.01

Gestational age at birth (weeks)	HFa					
	n	active sleep		quiet sleep		p
<28	12	19.56 ±9.99	∗ (p<0.05)	11.06 ±6.37	∗ (p<0.05)	<0.05
28 to <34	38	23.03 ±13.67		11.81 ±9.39		<0.01
34 to <37	19	30.88 ±30.86		15.09 ±12.54		<0.05
≥ 37	5	51.54 ±13.12		32.58 ±13.07		0.12
Total number of neonates	74	26.06 ±20.93		13.72 ±11.56		<0.01

Gestational age at birth (weeks)	LFa/HFa					
	n	active sleep		quiet sleep		p
<28	12	5.29 ±2.33	∗ (p=0.617)	3.56 ±1.41	∗ (p=0.170)	<0.01
28 to <34	38	6.71 ±2.84		5.41 ±3.15		<0.05
34 to <37	19	6.15 ±3.52		4.85 ±2.39		0.30
≥ 37	5	4.67 ±2.15		3.38 ±1.24		0.46
Total number of neonates	74	6.23 ±3.04		4.84 ±2.75		<0.01

Values are presented as mean ± SD.
Mann-Whitney *U* test, Significant difference: p < .05.
*Kruskal-Wallis test: p < .05.

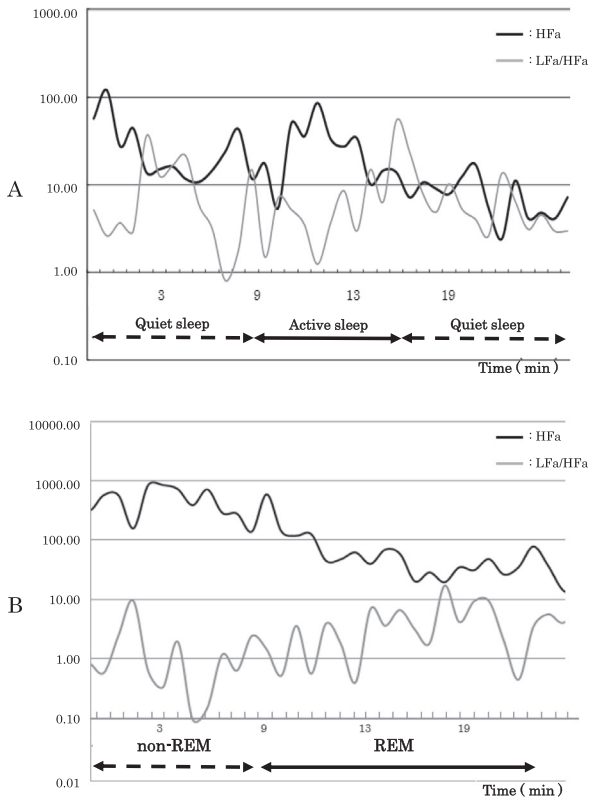

Fig. 2. Synchronicity between the power values of HFa and the LFa/HFa ratio during active and quiet sleep. A: Chronological changes in power values of HFa and the LFa/HFa ratio during active sleep and quiet sleep in the newborn. B: Chronological changes in power values of HFa and the LFa/HFa ratio during REM and non-REM sleep in adults. Both figures A and B demonstrate the changes in autonomic parameters during the sleep cycle over time. The black curves indicate HFa, representative of parasympathetic function, and the grey curves indicate the LFa/HFa ratio, which is representative of sympathetic function. The vertical axis is the logarithmic value of HFa (ms^2) and LFa/HFa (ms^2/ms^2) and the horizontal axis is time (min).

5. Discussion

We observed that, in newborns, the power values of LFa, HFa, and the LFa/HFa ratio during active sleep are significantly higher than those during quiet sleep. During adult sleep, however, the power values of LFa during REM sleep, considered as active sleep, were not significantly different from those during non-REM sleep, considered as quiet sleep. Further, contrary to neonatal sleep, the power values of HFa during REM sleep were significantly lower than those during non-REM sleep, while the LFa/HFa ratio during REM sleep was significantly higher than that during NREM sleep, as in newborn sleep.

The comparison between active and quiet sleep in newborns and REM and non-REM sleep in adults revealed that the power values of HFa and LFa were more dissimilar in the newborns, and the absolute power values in newborns were lower than those in adults. These results indicate that the newborn autonomic nervous system is in a state of transition, and that this state of transition continues throughout further development after birth. Previous studies reported that the power values of LFa and HFa increase between 10 to 14 years of age, but increase at a slower rate between 40 and 49 years of age [4,17,18]. Such changes in the autonomic nervous system appear to be important for physiological and environmental adaptation in the newborn, especially in terms of heart rate and respiratory rate.

Furthermore, we revealed high LFn values and low HFn values during neonatal active sleep, with the opposite seen during neonatal quiet sleep.

Van Laar [12] examined autonomic activity during fetal movements by calculating the power values of LFa, HFa, and the LFa/HFa ratio from fetal HRV monitoring. They observed that the power values of LFa, HFa, and LFa/HFa ratio during fetal active sleep were higher than those during fetal quiet sleep. Furthermore, they also found high LFn values and low HFn values during fetal active sleep. They concluded that the sympathetic nervous system is active during fetal active sleep, while the parasympathetic nervous system is active during fetal quiet sleep.

In the present study, we evaluated neonatal sleep stages using their EEG patterns, eye movements, respiratory waveforms, and mandibular electromyography activity during the neonatal period. Our results are similar to those observed by van Laar et al. in their study on fetuses, and confirmed their results [12].

Furthermore, we analyzed autonomic activity during active and quiet sleep in newborns sub-classified according to gestational age corrected for the time of EEG recordings, and also those classified according to gestational age at birth.

We found that the autonomic activities of premature infants might be different from those in term infants.

Analyses of the GA subgroups revealed that the power values of LFa were significantly higher during active sleep than quiet sleep in all GA subgroups. However, the power values of HFa were significantly higher during active than quiet sleep in the <28-week, 28- to <34-week, and 34 to <37-week GA subgroups, but not in the ≥37-week GA subgroup.

The LFa/HFa ratio was significantly different in the <28-week and 28- to <34-weeks GA subgroups, but not in the 34 to <37-week and ≥37-week GA subgroups.

These results suggest a difference in the level of development of the autonomic nervous system between preterm and term infants.

Subgroup analyses according to GA indicated that autonomic nervous system development in preterm infants seems to be delayed, even when they reach the

correct term age (Table 2, Kruskal-Wallis test analysis). The power values of HFa in the early GA groups were lower than those in the late GA groups. The power values of LFa in the early GA groups were also lower than those in the late GA groups, in spite of a similar GA at the time of EEG recordings. These data support the previous reports showing that preterm birth appears to delay maturation of HRV in preterm and low BW infants, which may increase the risk of SIDS, as suggested by Fyfe et al. [16].

The power values of HFa and the LFa/HFa ratio obtained during active and quiet sleep stages in the newborn, and during REM and non-REM sleep stages in adults demonstrate reverse periodic synchronization. This reverse synchronization is lost or disrupted in individuals with West syndrome and in children with severe brain injuries (data not shown). We believe that our novel method for analyzing synchronicity between the power values of HFa and the LFa/HFa ratio may be useful for physiological analysis of the autonomic nervous system. Further studies are required to evaluate various pathophysiological conditions related to the autonomic nervous system in the newborn, including delay in autonomic nervous system development in preterm and low BW infants.

6. Conclusion

Sleep stages should be assessed when evaluating the autonomic nervous system in neonates. Autonomic activity changes during active and quiet sleep, which is reflected in EEG patterns, heart rate, and respiratory rhythms. In addition, autonomic nervous system activity in some preterm and infants fails to reach the activity levels seen in full-term newborns. We objectively evaluated autonomic activity in newborns by comparing not only numerical values of HRV, but also its periodicity and synchronicity, which enabled detection of disturbances in several newborns. Further research is needed to elucidate the mechanisms behind these differences in autonomic activity. Careful physiological observation is, therefore, required for physiological and developmental assessment of preterm infants and infants with delayed autonomic nervous system activity.

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