論　文　題　目

Effect of environmental music on autonomic function in preterm infants in intensive and growing care units

（新生児集中治療室(NICU)・回復治療室(GCU)の音環境

ー入院児の心拍変動による交感神経・副交感神経活動の観察ー）

名古屋大学大学院医学系研究科

リハビリテーション療法学専攻

長　谷　川　陽　子

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// Declaration of conflict of interest //

The author has no conflicts of interest relevant to the content of this study.

1. Introduction

1-1. Background and Objective

Survival rates of premature and low-birth-weight (LBW) infants, including extremely premature infants less than 28 weeks gestation, have recently increased with the development of perinatal medical care (Myrhaug et al., 2017). The premature infants need medical treatments for a number of months in neonatal intensive (NICU) and growing care (GCU) units. As the period of medical treatments is prolonged in the NICU and GCU, roles of therapists in the units have also increased (Ross et al., 2017). In such a situation of hospitalization for preterm infants, environmental conditions during the period of intensive care should be evaluated and controlled by therapists. Temperature, humidity, and brightness around infants are automatically controllable, but it is difficult to control sound environment around infants in NICU and GCU. The importance of the sound environment has been emphasized in care units for infants (Anderson, 1986; Pineda et al., 2017). The auditory environment, including ambient sound, for infants in those units might cause stressors and be associated with developmental risks (Thomas & Uran, 2007; Shimizu & Matsuo, 2016; Lejeune et al., 2016). However, because of the priority of medical treatments for infants, mechanical and artificial sounds in the intensive care units are usually unavoidable and the auditory environmental setting has not been sufficiently considered (Marik et al., 2015; Shoemark et al., 2016). Although the American Academy of Pediatrics recommended a noise level between 45 and 65 dB in the NICU (American Academy of Pediatrics, 1997), such levels are not always adhered to in hospitals (Parra et al., 2017).

On the other hand, parents of infants often request their babies' favorite music as background music (BGM), expecting the positive effects of music on perinatal infants (O'Toole et al., 2017). Music might have positive effects on the physical condition of infants, and it could be a sensory intervention given with other interventions, such as positioning and sensory-motor intervention (Palazzi et al., 2018). A recent study reported that music in premature infants enhanced cognitive function (Lordier et al., 2019). However, the effects of music on the physical condition of infants have not been clarified. It is difficult to evaluate the effects of music on infants, especially in the NICU and GCU, since the responses of infants are not interpretable, except for crying in response to unpleasant stimuli. Only a few studies have been carried out regarding the effect of music on the physical condition of newborns, e.g., on sleep evaluated with electroencephalography (EEG) (Olischar et al., 2011) and vital signs (Amini et al., 2013). We considered that BGM could be an important factor in the environmental setting of the NICU and GCU. Other modalities of intervention, e.g., intervention with touching or visual stimulation are limited when infants are in incubators, although the combination of stimuli was effective for infants (Qiu et al., 2017).

Therefore, the objective of the present study was to identify the effect of music on the physical condition of preterm infants in the NICU and GCU. To assess the physical condition of preterm infants, we measured heart rate variability (HRV) and observed the physical condition of the infants through the changes in autonomic function.

1-3. Heart rate variability (HRV)

One of the problems when evaluating the effects of an intervention is that the outcome of the intervention is not clearly identifiable in preterm infants. We assessed HRV as a biomarker of the infant's condition obtained by electrocardiography (ECG) (Burdick, 1978; Cardoso et al., 2017). One of the advantages of the present method, measuring HRV, was that ECG monitoring is routinely used in the NICU and GCU for preterm infants to evaluate their physical condition. No additional equipment was needed to obtain biological signals for HRV calculation other than ECG.

Three major components of HRV, low- (LF, 0.05-0.15 Hz) and high- (HF, 0.15-0.4 Hz) frequency HRV components and LF/HF ratio, are calculated from variation of hear rate. HRV can be described as a fluctuiation of heart rate, i.e, R-R interval of ECG. Two major peaks of frequency, LF and HF, are observed in frequency analysis of sequential R-R interval for several minutes (Burdick, 1978; Cardoso et al., 2017) (Fig. 1). The LF and HF components reflect the autonomic function with information on the balance between sympathetic and parasympathetic activities in adults and infants (Burdick, 1978; Cardoso et al., 2017). The HF is considered a major contributor to the efferent vagal tone, while the LF component represents a quantitative index of the sympathetic and parasympathetic activities (Task Force of The European Society of

Cardiology and The North American Society of Pacing and Electrophysiology, 1996). Consequently, the LF/HF ratio was considered to reflect the balance between sympathetic and parasympathetic functions (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996; Zaza & Lombardi, 2001; Cardoso et al., 2017). We considered that the HRV measurement could be suitable to monitor the infant's condition with changes in the autonomic function. Since the effect of music might include wakefullness, pleasantness, or unpleasantness in infants, observation of the autonomic function may be suitable to observe the effect of music, although the HRV does not simply indicate stressful or pleasant conditions in infants.

2. Methods

2-1. Participants

Thirty premature or low-birth-weight (LBW) infants in the NICU or GCU in Nagoya City West Medical Center were involved in the present study. The mean gestational period was 249.2 ± 16.9 (SD) days (range, 185 - 270 days). The present experiment was applied to the participant once in the NICU or GCU with a mean corrected gestational period of 275.6 ± 70.9 days (range, 235 - 278 days). The corrected gestational period indicated the sum of the gestational period at birth and days after birth. Profiles of participants are shown in Table 1. The participants did not suffer from diseases or organ failure, but were preterm or LBW. Infants under complete mechanical ventilation were excluded. Infants with brain damage and auditory disturbance, which were revealed by magnetic resonance imaging (MRI) and auditory brainstem response (ABR), respectively, were also excluded.

Written informed consent was obtained from their parents with an agreement for participation in the present study after receiving a document exploring the study. The present study was approved by local ethical committees at the Faculty of Medicine, Nagoya University, and Nagoya City Hospital (No. 15-604), based on the Declaration of Helsinki (World Medical Association, 2013).

2-2. Procedure

2-2-1. ECG recording condition

The present experiment was carried out for 30 minutes between 1:30 and 4:00 p.m. between feeding time and approximately 30 minutes after feeding time. The behavioural condition of each infant at the time of the experiment was drowsy or quiet but alert, as assessed by the neonatal behavioural assessment scale of Brazelton (Brazelton, 1973; St Clair, 1978). The ECG signals were obtained by two electrodes attached to both shoulders via an electrocardiogram monitor (M8004A, Philips), and heartbeats at the peak of the QRS complex of the ECG were recorded by a digital recorder at a sampling rate of 500 Hz (RR-US310, Panasonic, Japan). The ECG signals were sequentially recorded under three conditions for 10 minutes each: 1) environmental condition with only ambient noise (Con-1), 2) environmental condition with BGM (BGM condition), and 3) environmental condition with only ambient noise 10 minutes after BGM (Con-2). The ECG recording for 10 minutes included more than 512 beats of ECG, which could be applied to

HRV analysis. The songs used for the BGM were lullabies for a baby with sounds of a music box. The BGM was delivered through a speaker placed in the incubator. The mean sound intensity at the head of the infant was 55 dB, and the sound was always less than 65 dB. The recording was carried out three times on different days within a period of four weeks for each infant.

2-2-2. Data analysis

All data on heartbeat recording were transferred off-line to a signal processor (Spike-2, CED, UK), and the sequence interval of each heartbeat was obtained from each recording. Frequency analysis was applied to each sequence of the heartbeat interval by fast Fourier transform, and summations of power values between 0.05 and 0.15 Hz and between 0.15 and 0.40 Hz were defined as LF and HF components of HRV, respectively. The LF/HF value was the ratio of LF to HF. Each value of the HRV component was compared among the three environmental conditions using one-way repeated measures analysis of variance (ANOVA) followed by Bonferroni-Dunn correction for multiple comparisons. The relationship between the HRV values and corrected gestational period or birth weight on participation in the experiment was calculated. The correlation between values was tested by Pearson’s test. A p-value less than 0.05 was considered to be significant.

3. Results

Heartbeats were recorded successfully in all infants. There was no complication or unexpected effects of the experimental settings. The body weight was correlated with the gestational period, but the body weight at the time of the experiment was not correlated with the corrected gestational period at that time (Fig. 2). The mean heart rate was 141.2 ±13.2 (SD) beats per minute under the Con-1 condition at the time of the experiment. The mean heart rate at the time of the experiment (Con-1) was negatively correlated with the body weight at birth and gestational period, but it was not correlated with the body weight or corrected gestational period at that time (Table 2).

The mean HR did not change among conditions of the present experiment ($F (24, 2) = 1.158$, $p = 0.322$) (Fig. 3). The LF and HF values decreased under the BGM condition compared with the Con-1 condition ($p<0.05$, Bonferroni-Dunn's correction, Fig. 4), but the difference between the BGM and Con-2 conditions did not reach significance for LF ($p = 0.07$) or HF ($p = 0.06$). The LF/HF ratio did not change among the conditions ($p = 0.21$). The LF, HF, and LF/HF values under the Con-1 condition were not correlated with the body weight or corrected gestational period at the time of the experiment (Table 2). The LF and HF at the time of the experiment (Con-1) were not correlated with the body weight or gestational period at birth. However, the LF/HF at the time of the experiment was correlated with the body weight at birth ($r = 0.39$, $p = 0.025$), but not with the gestational period at birth (Table 2).

4. Discussion

The present results indicated that the values of the LF and HF components decreased under the BGM condition without a significant change in the LF/HF ratio. With the interpretation of HRV components in previous studies (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1996; Zaza & Lombardi, 2001; Cardoso et al., 2017), the decrease in the LF and HF values without LF/HF change under the present experimental conditions suggested decreases in parasympathetic tone and levels of sympathetic and parasympathetic activities without a change in balance between activites.

4.1. Auditory environment with music affected the autonomic function

One piece of evidence from the results of the present study was that the auditory environment with music affected the autonomic condition of preterm infants. We could not decide on a positive or negative effect of music based on the change in the HRV components in the present study. Although effecive outcomes following sensory-motor intervention with music have been reportred for children (Miller, 1948; Gee et al., 2014), precise strategies for preterm infants have not been established. However, a recent study reported that intervention with music for preterm infants was positive in general, although some exceptional results were obtained (Pineda et al., 2017). We concluded that an environmental setting with music for preterm infants modulated the autonomic function during the intervention, possibly with a positve effect. Since there was an effect on the autonomic function in preterm infants in the present study, therapists could consider BGM as a factor during intervention.

4.2. BGM could not stressful stimulation

The HRV components could be a marker of stress (Thayer et al., 2012), and a decrease in parasympathetic activity generally occurred with a reciprocal increase of sympathetic activity under mental and physical stressors (Taylor et al., 2009). However, the heart rate did not change among conditions in the present study, which indicated stable sympathetic activity among conditions at least regarding the effect on the heartbeat. We considered that the BGM condition was not a stimulus that unsettled the infants because of the stable heart rate during BGM. We considered that the contents and intensity of BGM in the present study were within acceptable ranges for the care of infants in the NICU and GCU.

Interpretation of the HRV values was controversial in a recent study (Cardoso et al., 2017). The HRV components were affected by sleep stages (Villa et al., 2000), the ambient temparature (Stéphan-Blanchard et al., 2013), and attention (Richards & Casey, 1991) in infants. The awake-sleep condition and attention may have influenced the present results, from based on a previous report of a decrease in HRV values during attention (Richards & Casey, 1991). However, interpretation in the change of HRV components of infants should be carefully addressed, as mentioned above.

4.3. Development of the autonomic function in preterm infants

Another finding regarding HRV in infants was that the development of the autonomic function in preterm infants was slower after birth than the increase in the body weight. The body weight of the preterm infants was correlated with the gestational period in the present study, and the infants gained weight until the experiment, when the body weight was not correlated with the corrected gestational period at the time of the experiment. However, their HR and LF/HF values were still correlated with the body weight at birth. Ferber et al. (2006) reported that infants with a higher heart rate achieved significantly greater weight gain in the first days of life. We considered that the infants with a low body weight at birth gained weight, but their pattern of autonomic function was still the same as at birth, at least within the period of the present experiment. The discrepancy between the body weight and HR and LF/HF suggested that the autonomic function was still as immature as it was at birth, while the body weight solely increased. The HF showed an increase with the gestational age in previous reports (Cardoso et al., 2017). Among the infants examined in the present study, there was no correlation between the HRV components and body weight or gestational period. A possible reason may be that we did not measure HRV at birth but at 1-10 weeks after birth.

5. Conclusions

We observed a change in the autonomic function during the first days of life in preterm infants in the NICU and GCU using HRV analysis. There was a significant change in the autonomic function based on HRV among environmental conditions with BGM. The present results showed that an environment with a range of BGM affected the autonomic condition of infants. Therapists should consider the positive or negative effects of sound on the physical and mental conditions of infants during intervention in the NICU and GCU.

6. Limitation

In the present study, experimenal conditions were limited to two pieces of music. Since we should avoid unnecessary risks to infants, relatively low-level intervention was planned. Additional studies are needed to clarify which acoustic environment is suitable for infants, an important issue affecting care given by mothers to infants. How to interpret the HRV changes remains unclear, especially for preterm infants, and so further studies are needed regarding the development of autonomic functions.

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Table 1. Profiles of the participants

Male/female	10 males and 20 females	
	Mean ±SD	range
Gestational period	249.2 ±16.9 (days)	185 - 270
Corrected gestational period on participation in the present experiment	261.4 ±9.7 (days)	235 - 278
Days of the experiment after birth	14.9 ±17.6 (days)	3 - 89
Birth weight	1,936.6 ±340.8 (g)	946 - 2,440
Birth weight on participation	2,031.7 ±233.8 (g)	1,576 - 2,538

Corrected gestational period: sum of gestational period at birth and days after birth.

Table 2. Correlation between HRV values (Con-1) and body weight and gestational period in the experiments.

r value (p-value)	HR	LF	HF	LF/HF
Gestational period	-0.41 (0.021)*	0.013 (0.53)	0.0035 (0.99)	0.32 (0.11)
Body weight at birth	-0.58 (0.0012)*	0.27 (0.19)	0.12 (0.57)	0.39 (0.025)*
Corrected gestational period	-0.11 (0.31)	0.049 (0.82)	0.019 (0.93)	-0.051 (0.41)
Body weight at experiment	-0.072 (0.37)	0.099 (0.64)	-0.0044 (0.98)	0.053 (0.40)

HR: heart rate, LF: low-frequency heart rate variability (HRV) component, HF: high-frequency HRV component. Corrected gestational period: sum of gestational period at birth and days after birth. * $p < 0.05$, gray cells, Pearson's test.

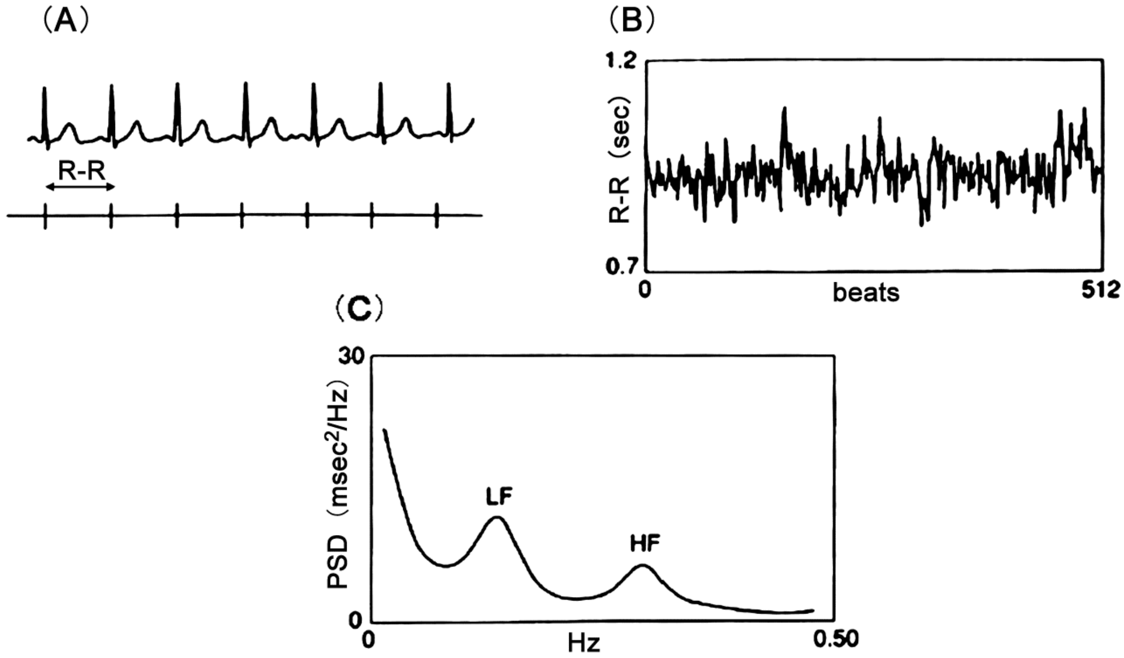

Figure 1: Processing heart rate variability (HRV). (A) R-R intervals (R-R) were obtained from continuous electrocardiogram recorded from participants. (B) Sequential R-R intervals for 512 heart rates (beats) were plotted. Fluctuation of R-R intervals were seen on the graph. (C) The power spectral density (PSD) was obtained at each frequency by frequency analysis, fast Fourier transformation. Low- (LF) and high- (HF) frequency components were seen on the results of frequency analysis.

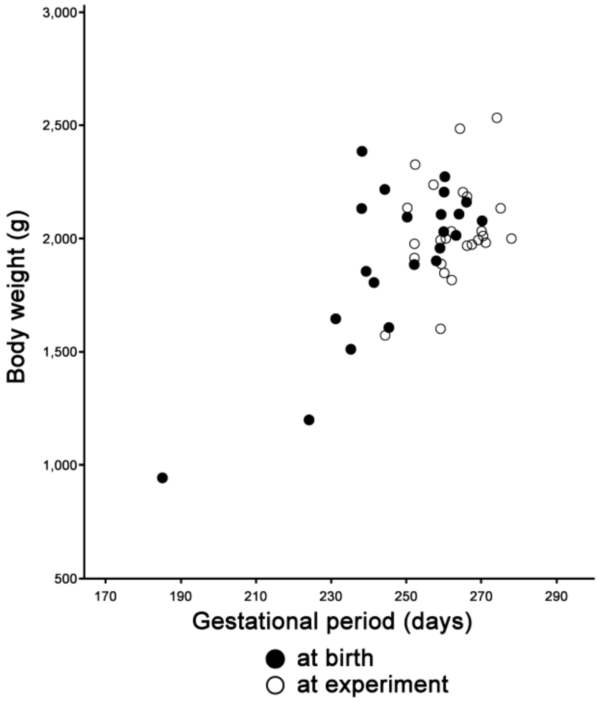

Figure 2: Correlation between the body weight and gestational period at birth (●) and at the time of the experiment (○). The body weight was correlated with the gestational period ($r = 0.74$, $p = 0.0001$, Pearson's test), but the body weight at the time of the experiment was not correlated with the corrected gestational period at that time ($r = 0.32$, $p = 0.061$).

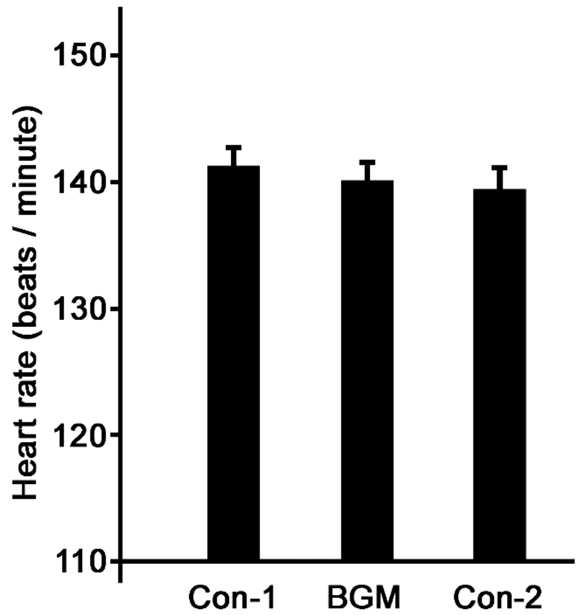

Figure 3: Mean heart rate (HR) among auditory environmental conditions. There was no difference in the mean HR among experimental conditions: control condition before background music (BGM) (Con-1), BGM, and 10 minutes after BGM (Con-2).

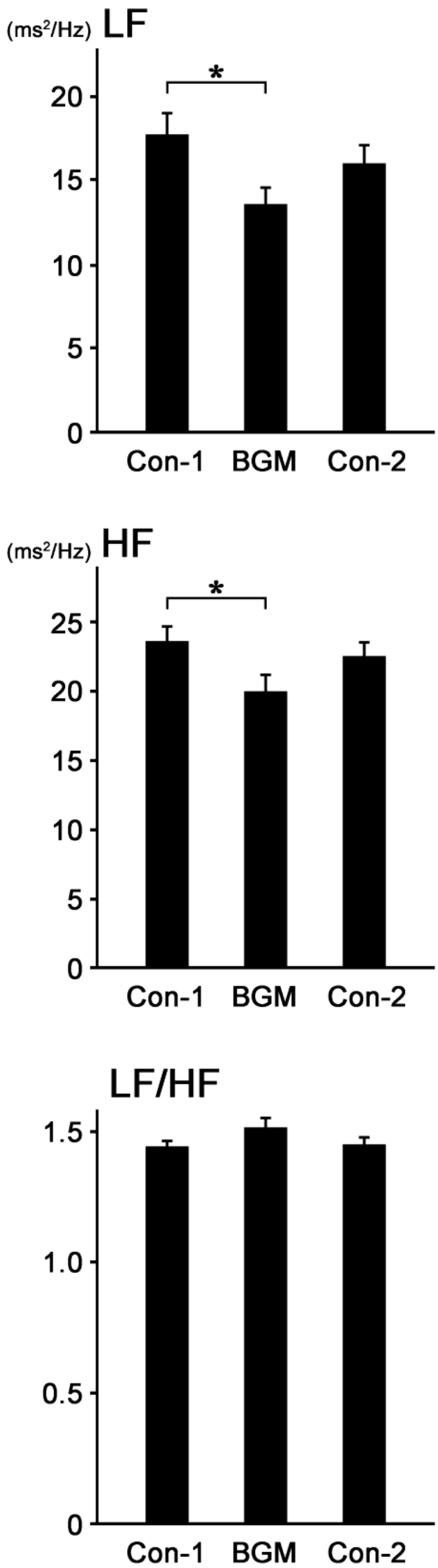
(ms2/Hz) LF
20
15
10
5
0
*
Con-1
BGM
Con-2
(ms2/Hz) HF
25
20
15
10
5
0
*
Con-1
BGM
Con-2
LF/HF
1.5
1.0
0.5
0
Con-1
BGM
Con-2

Figure 4: Difference in HRV values among auditory environmental conditions. The low- (LF) and high- (HF) frequency HRV components under the background music (BGM) condition were lower than under the control condition before BGM (Con-1). Under the control condition 10 minutes after BGM (Con-2), LF and HF values tended to increase to those of Con-1, but the change was not significant. The LF/HF ratio was not significantly changed. *$p<0.05$, Bonferroni-Dunn's correction.