The Emergence and Development of Physiological Regulatory Systems of Newborn Infants in a Neonatal Intensive Care Unit

Motoki Bonno, Esmot Ara Begum and Hatsumi Yamamoto
Fetal – Neonatal Physiology Research, Clinical Research Institute,
National Hosiptal Organization, Miechuo Medical Center, Mie,
Japan

1. Introduction

In the life of a human being, the early neonatal period is the most prone to life-threatening events. After birth, following the transition from the intra- to the extra–uterine environment, babies experience dramatic hemodynamic changes. Once babies begin life in the extra-uterine environment, they must regulate their own homeostasis in order to survive. Preterm, low birth weight, newborn are even more vulnerable and require the mechanical support for proper tissue oxygenation and nutrition in order to grow and survive in the extra-uterine environment. The adaptation to extra-uterine life is a slow and difficult process for these babies because of their prematurity.

At this critical period, hypothermia, apnoea, respiratory distress, and cardiac instabilities such as bradycardia and hypotension are common features in these newborn babies (Bhatt et al., 2010; Di Fiore et al.,2001; Dransfield et al., 1983; Tirosh et al., 2010; Trevisanuto et al., 2005; Upton, et al., 1992), and the resulting hypoxia may lead to brain damage and cardiac arrest if the medical support of a special incubator equipped with a ventilator and systemic monitoring is not provided a as a "primary life support system". Therefore, the continuous monitoring of heartbeat, respiration, oxygen saturation, blood pressure and temperature has been integrated into the neonatal intensive care unit (NICU) as a mandatory tool to support the fragile clinical conditions of these infants.

Monitoring data collected using non-invasive electrocardiograms have been used to understand the physiological regulatory system of these vulnerable infants. The measurement of heart rate variability has been widely examined using various analytic methods (Ardura et al., 1997; Baldzer et al., 1989; Katona et al.,1980; Patural et al., 2004; Yiallourou et al., 2010). Among them, circadian rhythms have been documented to be a prognostic marker of physiological stability and the maturation of the physiological regulatory system, which can be defined as the long-term regulatory system. The endogenous circadian rhythm is generated by the endogenous biological clock located in the anterior hypothalamic suprachiasmatic nuclei (Panda et al., 2002) and may be modulated by exogenous factors (Reppert & Weaver, 2002). It has been documented in the growing foetus

(Patrick et al., 1982) controlled by maternal circadian signal (Seron-Ferre M et al). In full-term neonates, circadian rhythm are documented after birth, subsequently disappear and are not detectable within 3 or 4 weeks of postnatal age (Dimitriou et al., 1999; Mirmiran & Kok, 1991). However, in preterm neonates, the development of circadian rhythms is still controversial (Ardura et al., 1997; Begum et al, 2006; Bueno et al., 2001; Dimitriou et al., 1999; Korte et al., 2001; Mirmiran & Kok, 1991; Schimmel et al., 2002; Updike et al., 1985; Weinert et al., 1994) and the clinical relevance remains obscure.

Heart rate variability (HRV), derived from fast Fourier transform analysis of the R to R interval (RR interval) using an electrocardiogram, is another popular method to assess the autonomic nervous system (ANS) (Akselrod et al., 1981; Danguole et al., 2001; Finley et al., 1987; Kamen, 1996; Malik, 1996; Mazurak et al., 2010; Pontet et al., 2003; van Geijn et al., 1980). Continuous changes in sympathetic and parasympathetic neural impulses in the ANS induce changes in heart rate and cause oscillations around the mean, which is the HRV (Malik, 1996). In a frequency-based analysis of HRV, the low frequency (LF) band (0.04-0.15Hz) derived from the frequency domain analysis expresses the activity of both the sympathetic nervous system (SNS) and parasympathetic nervous system, and the high frequency (HF) band (0.15-0.5Hz) expresses the parasympathetic nervous system (PNS) activity of the ANS (Akselrod et al., 1981). The LF to HF ratio reflects the sympathovagal balances. Reports regarding the relevance of HRV to cardiac-health-related events that contribute to the ANS in the foetus, such as asphyxia (Bocking, 2003), foetal distress (Karin et al., 1993); in infants, such as respiratory distress, apnoea, sepsis, bradycardia (Bennet & Gunn, 2009; Frasch et al., 2009; Li et al., 2005; Logier et al., 2008 ; Sampson et al., 1980), and hypotension (Di Fiore et al., 2001; Dransfield et al., 1983; Fairchild & O'Shea, 2010; Frasch et al., 2009; Upton et al., 1992; Wennergren et al., 1986); and adults, such as stroke and myocardial events (Faber, 1996; Korpelainen et al., 1999; Sosnowski et al., 2002), are numerous and well-documented. In foetuses and preterm infants, the ANS is highly dependent on the SNS while the PNS is immature (Chatow et al., 1995), and the role of the PNS increases with the increase in gestational age (Van Leeuwen et al., 2003). Evidence of the effect of HRV on the adaptation of the ANS in preterm, low birth weight infants during the early neonatal period is not widely available, although it is known that an immature ANS is one of the factors contributing to the vulnerability of these infants.

In this research review, developmental and adaptation changes will be described based on heart rate records from ECG monitors. This description will provide an important perspective on the developmental physiological homeostasis of preterm infants during the early neonatal period in the intensive care unit.

2. Utilisation of the electrocardiogram - analytical methods of heart rate assessment

2.1 Monitoring and data recording through NICU local area network (LAN) system

All infants hospitalised in the NICU are monitored via electrocardiogram (ECG) for heart rate (HR) and respiration rate (RR), with a pulse oxymeter on the wrist or foot for pulse rate (PR) and oxygen saturation by pulse oxymetry (SpO_2), and arterial blood pressure (ABP) using a catheter manometer system occasionally. In our study, the monitored physiological information is transformed to measurement variables using the Wave Achieving System (WAS) or Clinical Database Engine (CDE) (Philips Electronics Japan, Tokyo, Japan) through NICU LAN system (Fig. 1) (Begum et al., 2006). In this report, we will explain the circadian

rhythmicity of neonate as long-term regulatory system and HRV as short-term regulatory system of physiological homeostasis.
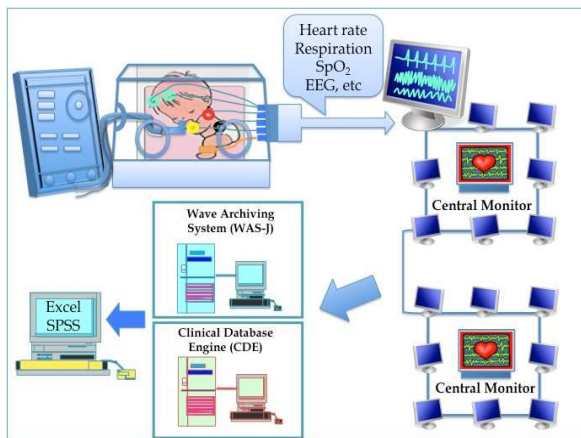

Fig. 1. NICU LAN system for recording physiological parameters.

2.2 Analysis of the heart rate circadian rhythm as a long-term regulatory system
2.2.1 Data acquisition and trend removal

For each patient, the heart rate was continuously recorded for 24 hours for the four postnatal periods (P): P1: 0-3, P2: 4-6, P3: 7-13, and P4: 14-21 postnatal days. Subjects with a continuous disruption in the data of more than 1 minute were excluded from the study. Any linear trend was removed using least square regression methods.
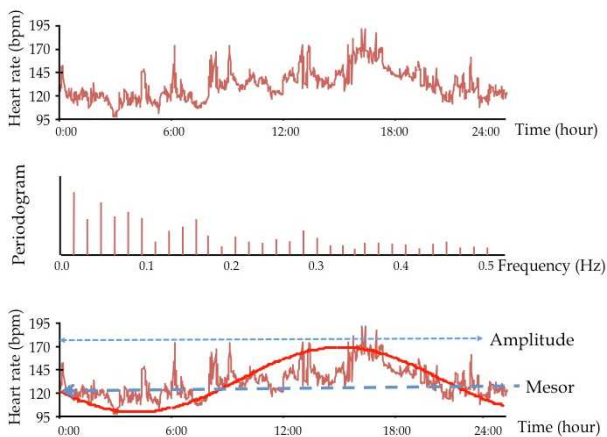

Fig. 2. Determination of the dominant cycle using spectral analysis. *A*: Plot of original data for heart rate (HR). *B*: Periodogram intensities for HR. The largest peak of the periodogram was selected as the cycle component. *C*: The intensity of the cycle corresponding to the largest peak in the periodogram was reconstructed to fit the sinusoidal function. The bold red line is the detected cycle superimposed on the original data.

2.2.2 Analysis of circadian rhythm

Circadian rhythmicity can be analyzed using various methods such as chi square periodogram, cosinor analysis.In our study, the existence of rhythmicity was analysed using power spectral analysis (periodogram) with SPSS 11.5 software (SPSS Inc. Chicago, IL) (Warner, 1998). Briefly, 24-hour sessions in 10-second intervals were run and aggregated into 1-minute time blocks. A periodogram analysis was performed using a time series of 1440 minutes. The Fisher test was used to assess the statistical significance of the cycle components ($N = 1440$, $\alpha = 0.05$) (Russell, 1985). In our study, the cycle with the largest peak in the periodogram was considered to be the dominant cycle for each time series among the significant cycles. All dominant cycles were confirmed by Fourier analysis, further circadian cycles were confirmed by cosinor analysis with a significance of $p < 0.05$ by least squares analysis (Fig. 2) (Nelson, 1993).

2.3 Analysis of heart rate variability (HRV) as a short - term regulatory system
2.3.1 Data acquisition of RR interval and the detection of outliers

To calculate R to R intervals in our study, for each patient, the heart rate wave was digitally transported to the CDE system, and the digital data for the heart rate was exported as a CSV file at a sampling rate of 500Hz. The RR interval was calculated by using MemCalc (GMS, Tokyo, Japan) which is statistical software specialised for entropy-based spectral analysis (Fig. 3).
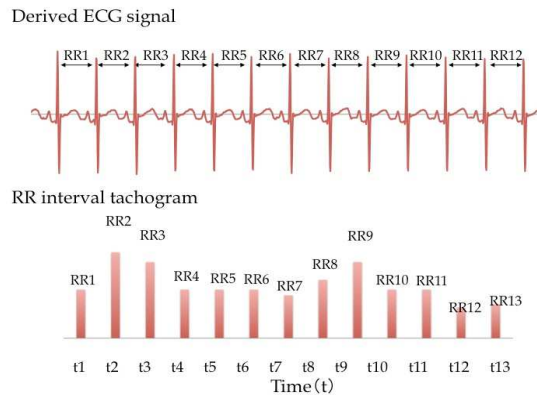

Fig. 3. Transformation of the RR interval from the waveform of a heart rate signal.

The data set obtained for the RR interval was visually inspected to identify any abnormal R – waves or artefacts. The presence of outliers in the RR interval data set can adversely effect both the time and the frequency domain analyses of HRV. Data outside of three standard deviations from the mean of RR interval data set were assumed to be statistically irrelevant and were tagged as outliers unless they were part of a trend (Niles, 2003). The missing values were replaced by the mean of the total data set.

2.3.2 Methods for HRV analysis - time domain analysis, frequency domain analysis and Poincare plot of the RR interval

Heart rate variability can be analysed in two ways: time domain and frequency domain analyses (Akselrod et al., 1981; Malik, 1996). For a geometric representation of the RR

interval, the non-linear Poincare plot can be analysed (Brennan et al., 2002). In this study, we have used the Heart Rate Variability Software (Kubios HRV, version 2.0) to analyse the time domain and frequency domain analysis as well as Poincare plot also.

2.3.2.1 Time domain analysis

Time domain measurements can be easily described using the RR interval data. From the time domain analysis, the standard deviation of RR (SDRR), and the root mean square of successive differences (RMSSD) were calculated as follows:

Standard deviation of RR interval (SDRR) $= \sqrt{\frac{1}{N-1} \sum_{n=1}^{N} (RR_n - RR)^2}$

The root mean square of successive differences (RMSSD)

$$= \sqrt{\frac{1}{N-1} \sum_{n=1}^{N-1} (RR_{n+1} - RR_n)^2}$$

2.3.2.2 Frequency domain analysis of the RR interval

For the frequency domain analysis, a spectral analysis of the RR interval was performed using fast Fourier transformation (FFT). The frequency domain analysis is widely used and is well recognised for analysing HRV. The low frequency (LF: 0.04 - 0.15 Hz) band and the high frequency (HF: 0.15 - 0.50 Hz) band were calculated.

2.3.2.3 Poincare plot of the RR interval

Poincare plots were calculated for the geometric representations of the RR intervals. The non-linear Poincare plot presents a figure with each RR interval plotted against the previous RR interval (RR_{n+1}, RR_n) and provides a detail of beat-to-beat information for the total data set (Brennan et al., 2002).
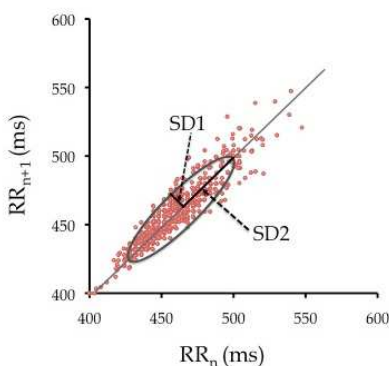

Fig. 4. An example Poincare plot: A standard Poincare plot of the R-R intervals of a healthy neonate born with 35 weeks of gestational age (GA). SD1 and SD2 represent the dispersion along the minor and major axes of the fitted eclipse.

The SD1, the width of the Poincare plot (the dispersion of points perpendicular to the line of identity), expresses the level of short-term heart rate variability, and SD2, the length (the dispersion along the line of identity), expresses the level of long-term heart rate variability (Fig. 4) (Brennan et al., 2001). The equations for SD1 and SD2 are as follows:

Width of RR_n vs. $RR_{(n+1)}$ distribution $(SD1)^2 \frac{1}{2} SDSD^2$

Length of RR_n vs. $RR_{(n+1)}$ distribution $(SD2) = 2SDSD^2 - \frac{1}{2} SDSD^2$

3. Evidence of circadian rhythmicity during the early neonatal period with clinical relevance

3.1 The development of a circadian rhythm in the neonatal period

Infants admitted in the NICU are vulnerable because of their physiological instability, and hypothermia, apnoea, respiratory distress, bradycardia and hypotension are common features for them. Frequent medical examination and therapy are common for them. Within this fragile environment, how do they adapt a physiological homeostasis? In our study, we have observed the circadian rhythmicity of preterm and full-term infants at four postnatal periods to observe their adaptation and developmental processes. The circadian rhythms of the heart rate were analysed in 187 neonates. The median GA was 34 weeks (range: 23–42 weeks). (Begum et al, 2006).

By analysing the distribution of circadian rhythmicity (Fig. 5), circadian rhythms were observed to be dominant among preterm infants (40%, < 28 wks of GA) compared to full-term infants, and a similar tendency was observed in other periods. These results partially support the previous studies (Dimitriou et al., 1999; Mirmiran & Kok, 1991).
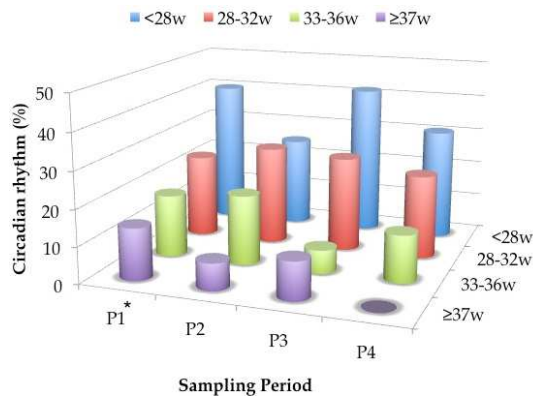

Fig. 5. The distribution of circadian cycles according to gestational age groups

In examining the relationship between circadian rhythmicity and post-conceptional age (PCA), an analysis of the correlation coefficient was performed using the amplitudes of each period. The amplitudes of the heart rate circadian rhythms were positively correlated with PCA in all four periods (Fig. 6).

The higher percentages for the existence of circadian rhythms in preterm infants compared to full-term infants suggest that the maternal influence on circadian rhythm may persist in preterm infants more strongly than in full-term infants during the neonatal period. However, the observed increase in circadian amplitude with PCA implies that the magnitude of circadian rhythmicity parallels the maturation of neonates.

Further, we analysed the heart rate circadian rhythmicity of infants born with small weight for gestational age (SGA: birth weight and height bellow < -2SDs) during 0-2 postnatal days

and compared with infants born with average weight for gestational age (AGA: > -1.5 to < 1.5SDs). In the cases for which significant circadian rhythms were observed, significant differences were not observed between SGA and AGA infants, however, the amplitudes of the heart rate circadian rhythms were significantly smaller in SGA infants compared to AGA infants showed in Fig 7(Begum et al., 2010).
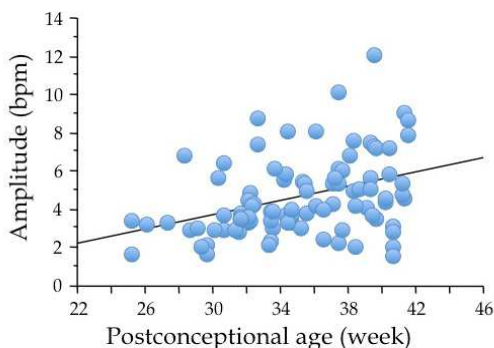

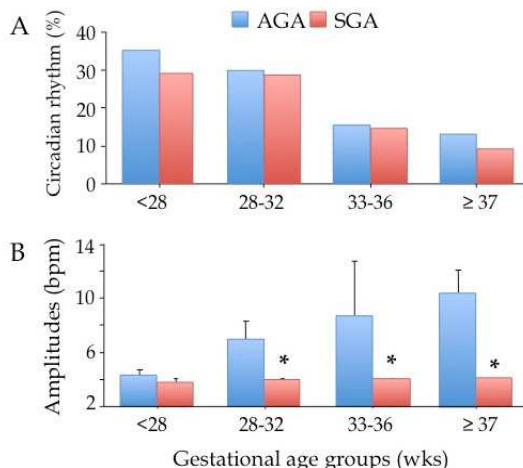Fig. 6. The relationship between rhythmicity and PCA in P1: r = 0.38, P < 0.0001

Fig. 7. The existence and amplitude of circadian rhythms in AGA and SGA neonates. A: Distribution of the infants with significant circadian rhythm and significant differences was not observed between AGA and SGA. B: Distribution of circadian amplitudes for AGA and SGA. The amplitudes were significantly smaller in SGA infants compared to AGA infants. * p <0.05, AGA vs. SGA

A decreased amplitudes in the circadian rhythm of SGA infants as shown above, intrauterine growth retardation might have influences on the quality of circadian rhythm rather than its existence.

4. Evidence of HRV in the early neonatal period and the clinical relevance

4.1 Experimental observation of alterations in HRV during the hourly neonatal period in extremely premature infants

The ANS plays an important role in the control of the physiological regulation. However, an immature ANS has been reported in the preterm infants after birth which prolongs to the later life also (De Rogalski Landrot et al., 2007). In preterm infants, particularly in extremely premature infants, the early neonatal period is a life-threatening period when cardiac failure, shock, loss of variability is frequently occurs to them. Numerous studies on ANS have been reported the GA based information with longitudinal evidences (Chatow et al., 1995; Longin et al., 2005, 2006) in preterm and full-term infants. However, the capacity and the recovery of ANS activity of extremely preterm infants immediate birth remain unclear. Thus, experimentally we observed the ANS activity of preterm infants born less than 28 weeks of GA from 3 hours after birth to 7 days to understand the changes into the capacity and recovery of ANS. For a micro-observation, ANS activity was observed at 3-hours, 6-hours, 12-hours, 24-hours, 72-hours and 7-days after birth using a dynamic analytic approach of HRV and observed the alterations in ANS through this critical period.

For analysis of HRV, a 30-minutes ECG signal data set was recorded for the calculation of RR interval from 13 extremely premature infants during a rest time at 3-hours, 6-hours, 12-hours, 24-hours, 72-hours, and 7-days after birth. From time domain analysis of HRV, mean RR, Mean HR, SDNN and RMSSD was calculated shown in Fig. 8. With the increase of time after birth, heart rates were decreased while RR intervals increased and this relation indicates the increase of the ability of the heart to function economically. Further, the increases in SDNN and RMSSD with the increase of the time after birth, might be indicated an increase in the amount of HRV. The increase in variability, which in turn indicates the significant interplay between SNS and PNS of the ANS.
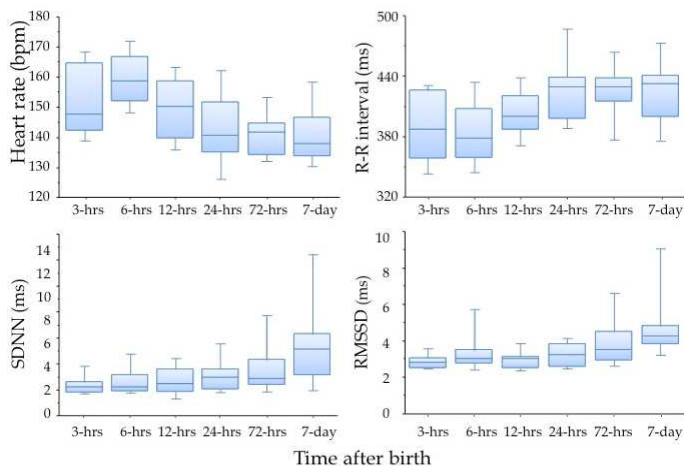

Fig. 8. Alterations in the parameters for the time domain analysis of the RR interval for HRV through the early neonatal period in extremely preterm infants (n=13). The RR interval was obtained for 30 minutes at each time point.

The power of LF region and HF region from the frequency domain analysis and SD1 and SD1 from Poincare plot analysis was calculated for each session. The power of both the LF and the HF was significantly lower at 3 hours or 6 hours after birth compared to the highest value at 7-days and the increase of LF and HF with the time after birth may indicate the maturation of the ANS. In the Poincare plot analysis, SD1 and SD2 also increased with the time after birth (Fig.9).
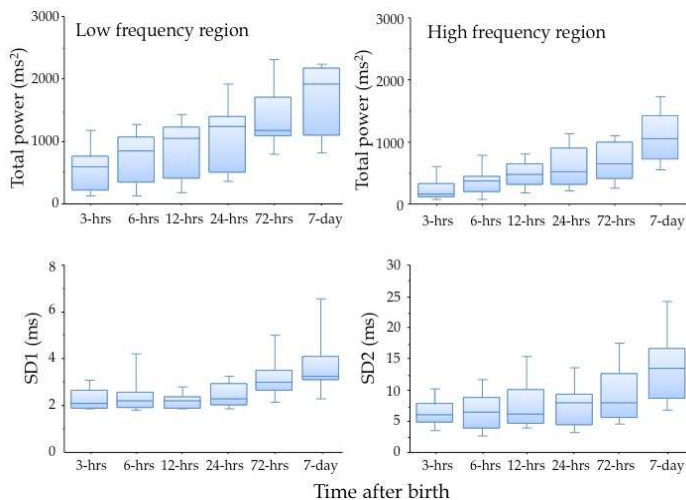

Fig. 9. Alterations in the parameters from the frequency domain analyses and Poincare plot analysis of HRV through the early neonatal period (n=13, mean gestational age = 27weeks, mean birth body weight = 875g).

The decreased HRV till 12 hours of birth may indicate the loss of variability immediate birth and transition of adaptation period for the short - term regulatory system and the increase of HRV from 24-hour to 7-days after birth might be indicated the increase in the ability of the adaptation capacity and as a sign of maturity.

4.2 Experimental observation of pain response during the early neonatal period: Three case analyses for three different gestational ages

The adverse consequences of pain response during the early neonatal period have been documented by numerous study (Grunau et al., 2006), and an emphasis has been placed on pain responses in the NICU (Brown, 2009; Johnston et al., 2010; Stevens et al., 2006, 2010). The most common pain event in NICU is blood procurement including heel lance and venepuncture (Carbajal et al., 2008). Changes in facial expression, sleep states, heart rate and SpO$_2$ are used as indicator of pain response in term infants, not in preterm infants (Stevens et al., 1996). The measures calculated from HRV provide sensitive indices to investigate the response of stressful stimuli. These indices are very helpful to investigate the pain response in preterm infants (Lindh et al., 1999; Morison et al., 2001; Oberlander & Saul, 2002; Padhye et al., 2009). The intensity of pain response in infants has been thought to be related with ANS activity maturation (Grunau et al., 2006). We have experimentally observed three cases with different GA (26, 31, 35 weeks) to analyse the differences in the intensity of the response to the pain stimuli during blood sampling. A heel lance episode was divided into 5 sessions as follows: A: 0-30-second (prior to needle puncture); B: 30-60 second (start of

needle puncture); C: 60-90 second (squeezing for blood collection); D: 90-120 second (30 second after the end of blood collection); E: 120-150 second (after 60 second of blood collection). The RR interval data were analysed separately for each session.

Frequency domain analyses and Poincare plot analyses were applied to interpret the intensity of the response to pain. The distribution of the Fourier plot and Poincare plot is shown in Fig 10 and Fig. 11. The total spectral power increased after the pain procedure in all cases; however, it was low in the case of a 26-week GA neonate. The spectral power of the LF quickly increased following the needle puncture and gradually decreased with the cessation of the procedure in a 35-week GA infant. In contrast, the power of the HF was delayed in a 31-week GA infant and was low in a 26-week GA infant (Fig10).
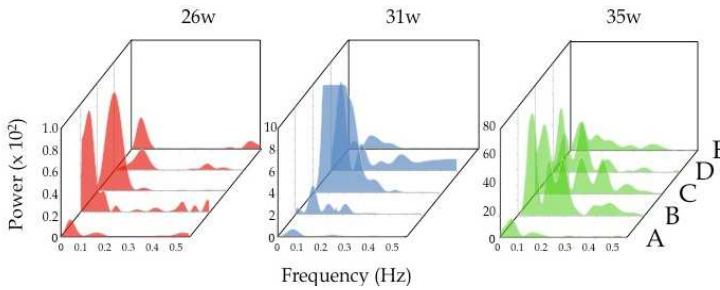

Fig. 10. A Spectral plot on the intensity of pain response during blood sampling for three different GA during early neonatal period. A: 0-30-seconds (prior to needle puncture); B: 30-60 second (start of needle puncture); C: 60-90 seconds (squeezing for blood sampling); D: 90-120 seconds (30 seconds after the end of blood sampling); E: 120-150 second (after 60 seconds of blood sampling).
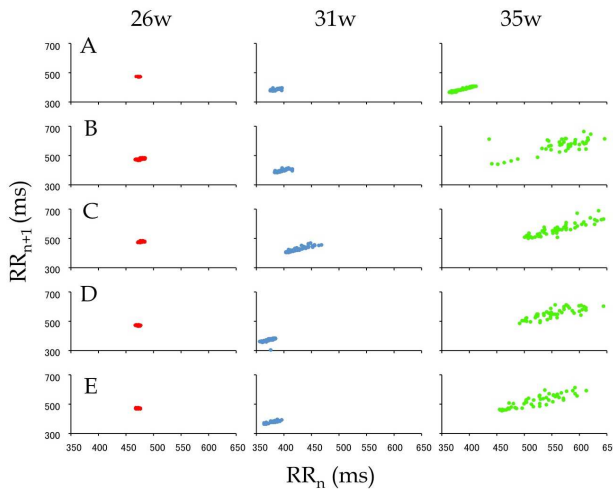

Fig. 11. Poincare plot analysis of the RR interval during blood sampling. A: 0-30 second (prior to needle puncture); B: 30-60 second (start of needle puncture); C: 60- 90 second (squeezing for blood sampling); D: 90-120 second (30 seconds after the end of blood sampling); E: 120-150 second (after 60 seconds of blood sampling).

By Poincare analysis of the RR interval, the response of the painful procedure was well recognized (Fig. 11). The Poincare plot was strongly shifted to the upper right quadrant in the 35-week GA infant, and the shift was small in the 31-week GA infant, while almost no shift was observed for the procedure in a 26-week GA infant.

Based on these findings, we suggest that an increased physiological response to painful events is related to the maturity of the ANS, and late preterm infants may be affected more strongly than extremely premature infants by painful events. Because of the immaturity of the ANS in infants <26 weeks, the response to pain was comparatively lower than that of other infants.

4.3 Kangaroo care for preterm infants as physiological relaxation

Kangaroo care (KC) has been widely practiced for preterm and low birth weight (LBW) infants in the neonatal intensive care unit (NICU). KC is now practiced not only in developing countries, but also in developed countries as developmental care because improved outcome in mortality and morbidity have been reported in infants who undergo KC. There have been many studies performed to evaluate the psychological and physiological responses during KC in preterm infants. Although still there is some contradiction on the influences of KC in infants, positive influences also reported by many literature (Bauer et al., 1997; Fohe et al., 2000; Acolet et al., 1989; Cattaneo et al., 1998; Feldman & Eidelman, 2003; Messmer et al., 1997).

In our study on the physiological responses during kangaroo care, significant differences was observed in the spectral power of heart rate within the different sessions (the %LF was significantly increased during KC, while %HF was decreased, without significant changes in the ratio of LF/HF, Fig. 12). Behavioural states were observed during kangaroo care using the Brazelton Neonatal Behaviour Assessment Scale (Brazelton, 1984). The percentage of infants with quiet sleep states remarkably increased during KC compared to those before KC. This percentage increased further at the end of KC and decreased again 30 minutes after KC (Fig. 13).
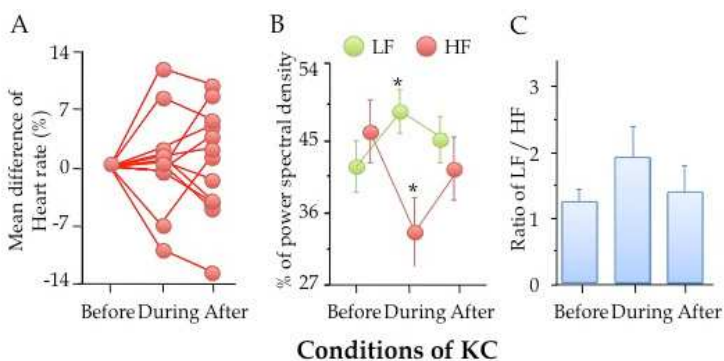

Fig. 12. Changes in heart rate variability during KC. A: mean difference in heart rate; B: power spectral density of LF and HF; C: ratio of LF/HF. *P < 0.05 (Repeated measures ANOVA)
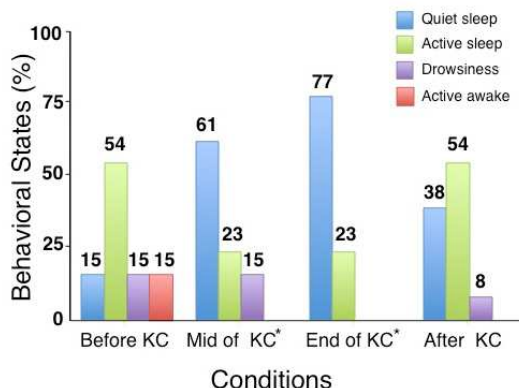
Fig. 13. Changes in the behavioural states of infants during KC. Five different behavioural states were observed: 1) Quiet sleep; 2) Active sleep; 3) Drowsiness; 4) Alert inactivity; and 5) Active awake.

As shown above, an increase in %LF during KC was observed without fluctuation of the LF/HF ratio, and infants tended to sleep deeply during KC. These findings suggest that parasympathetic nerve activity may be suppressed during KC and that decreased parasympathetic nerve activity may induce deep sleep. Improved outcome and health status with KC may be due to relaxation of vagal tone.

5. Conclusion

In this chapter, we explained the emergence and development of the ANS as physiological regulatory systems of new- born infants. Circadian rhythm, we defined it as long-term regulatory system, exist immidiate birth and persist through the neonatal period in preterm infants, while it does not persist after birth in full-term infants. On the contrary, the heart rate variability of extremely premature infants is suppressed on the day of birth and increases with time in the early neonatal period. The maternal influence on circadian rhythms may be important for extremely premature infants because the autonomic nervous system is not fully developed in these infants, as has been shown in the session on physiological response to pain.

In infants with later gestational ages, however, the physiological response to pain is stronger. During hospitalisation, infants with later gestational ages may be more sensitive to stressful stimuli. Developmental support such as Kangaroo care may offer relief from the stressful stimuli of the NICU, and relaxation during their stay in the NICU may be an important aspect for improved outcomes and later health status.

Finally, understanding the development of auto-regulation in newborn infants during the early neonatal period provides new information on the factors that influence the vulnerability of newborn infants in the NICU. Bedside monitoring of physiological hemodynamics and the implications of these monitored variables are key tools for neonatologists, not only for improving survival, but also for improving the quality of life for these vulnerable infants.

6. Acknowledgment

7. References

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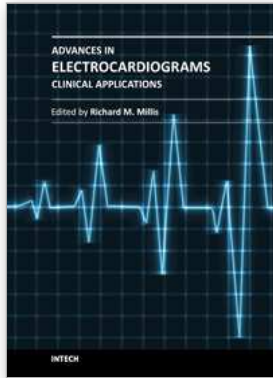
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