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The development of the circadian heart rate rhythm (CHR) in Asian infants★

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Abstract

Objective—To test the hypothesis that term-born Asian infants, at reduced risk to die of Sudden Infant Death Syndrome (SIDS) exhibit a circadian heart rate rhythm (CHR) at a later age than non-Asian term infants.

Method—Repeated overnight heart rate (HR) traces obtained with a battery-operated Polar S810i heart-rate monitor at home in 17 Asian Torajan infants in Indonesia, were compared with those of 52 non-Asian infants monitored as part of the Collaborative Home Infant Monitoring Evaluation (CHIME). HR was determined using a moving window averaging technique. A comparison of median HR during quiet sleep (QS) episodes (identified by minimum HR variability), established the presence of CHR.

Results—Seventy three percent of non-Asian CHIME infants < 7 weeks exhibited CHR compared to 45% of Asian Torajan infants. Between 8 and 12 weeks, 94% of non-Asian CHIME infants exhibited CHR, compared to 33% of Asian Torajan infants ($p < 0.001$). Forty seven and 56% of Asian Torajan infants exhibited the CHR at the age intervals of 16–20 weeks and 21–25 weeks respectively. Active wakefulness percentages as a function of the entire recording and median QS HR were not significantly different in the two groups.

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Conflict of Interest

This was not an industry-supported study. The authors have no financial conflict of interest.

Conclusion—Despite the fact that Asian Torajan infants were on average a week older than non-Asian CHIME babies, between two and three months of age only one in three exhibited the CHR, compared to virtually all non-Asian CHIME infants. We speculate that the cause of this difference rests in the infants' environment rather than their genetic origin.

Keywords

Circadian heart rate rhythm (CHR); SIDS risk factors; Heart rate; Maturation; Breast feeding

1. Introduction

Although the human fetus can follow the maternal circadian rhythm, the entrained expression of the circadian clock, based in the suprachiasmatic nucleus (SCN) of the hypothalamus awaits postnatal maturation of the retinal hypothalamic tract, and melatonin neurotransmission [1,2]. After birth, evidence of this maturing nucleus is found in the emergence of a 24-hour sleep wakefulness cycle that supplants the typical poly-phasic sleep wakefulness pattern of the neonate [3]. In less than 10 percent of infants, one finds an intervening brief period of a free-running sleep wakefulness rhythm [4–7] suggesting that the infant brain has not yet learned to synchronize its neural clock mechanism in the SCN with typical *Zeitgebers* such as ambient temperature, light and darkness and human social behavior. The infant will accomplish this synchronization of the clock and its “hands” between one and three months of age, when numerous indicators such as minimum and maximum of heart rates, breathing, body temperature, metabolic rate, salivary melatonin and cortisol can be measured during the typical 24-hour day [8–15]. Further maturation of the circadian rhythm manifests as an increase in amplitude and a shift in most troughs toward the early morning hours [8,9,14].

Wailoo's research team in England noted that Asian infants in their study sample exhibited a delay in the appearance of a circadian temperature modulation [16]. Compared with the 2–3 month appearance of the circadian temperature modulation in Caucasian infants the temperature rhythm of the Asian infants only appeared between 4 and 5 months. Lodmore et al [17] identified variables that seemed to hasten the appearance of the circadian temperature rhythm: female sex, being firstborn, supine sleeping, affluent families, breastfeeding and older mothers.

The primary objective of this study was to test the hypothesis that the nightly portion of the circadian heart rate rhythm (CHR) in Asian infants in Indonesia appeared later than that of a non-Asian control group. Under the protocol of the Collaborative Home Infant Monitoring Evaluation (CHIME), carried out during the 1990s, a sizable number of subjects underwent an overnight polysomnogram (PSG) that yielded continuous nightly heart rate (HR) values. The available tracings from non-Asian subjects in CHIME were used as controls.

2. Methods

2.1. Participants

Twenty mothers of term born infants between one and two months of age (10 males and 10 females) were recruited for the overnight HR studies in Toraja, Indonesia. These volunteers were drawn from various areas of Toraja consisting of approximately 3000 km² of mountainous terrain, inhabited by 446,661 people who live in two provincial towns and 311 villages. The sample included a cross-section of maternal education in Toraja that ranged from two years of elementary school to two years of a vocational school after high school. This variable was chosen as an estimate of socio-economic status. HR studies were carried out in 2007.

The protocol was approved by the Institutional Review Board (IRB) of Childrens Hospital Los Angeles, with a waiver of written informed consent, based on the culture in which the study was to be carried out. Instead, an explanation of the study preceded each HR monitoring session followed by an oral consent. Lembaga Ilmu Pengetahuan Indonesia (LIPI), the official agency that oversees research by foreigners in Indonesia, gave permission for the study and directed the search for a complete set of approvals from national and local agencies in Indonesia. These permissions guaranteed collaboration from health professionals in the field.

In addition, HR derived from PSGs of 64 term born non-Asian infants from the CHIME study (34 boys and 30 girls) were available for comparison with Torajan tracings. In the early 1990s, IRBs at clinical centers in Cleveland, Chicago, Toledo, Honolulu and our own University, in Los Angeles had approved these CHIME PSG studies and informed consent was obtained from all parents or caregivers.

2.2. Instrumentation

Some of the infants in Indonesia lived in remote areas where electricity was unavailable. A team of biomedical engineering students at Michigan Technological University adapted a battery-powered Polar HR Monitor (S810i) designed for runners, to work with infants. A band around the chest holds a transmitter that sends the HR data to a storage watch, placed in the vicinity of the baby. This data was subsequently downloaded to a laptop computer via an infrared USB interface port and stored using specially designed software.

For the CHIME protocol in the US, the ALICE 3 data acquisition and analysis system was used to obtain overnight PSGs in the various sleep laboratories [18]. This system included a 486/33 IBM computer, a 20-inch monitor and optical disk storage (Healthdyne, Marietta, GA).

2.3. Procedures

In Toraja, three trained research assistants visited mothers and infants at home between 5 and 7 PM for application of the transmitter bands around the chest, just under the arms. Mothers were instructed to follow their usual routines including changing clothes and breastfeeding as long as they kept the watch in the vicinity of the infant (at a distance of no

more than one meter). These units were removed in the morning between 6:00 and 8:00 AM by one of the three research assistants who visited the home again for that purpose. This procedure was initiated in all infants between three and seven weeks of age and repeated either two or three times (Table 1). This was thus a longitudinal CHR study.

As part of a different study, a systematic in-home interview with mothers by two of the authors (TH, SS; 19) revealed that in Toraja most infants are wrapped in a sarong (long cotton cloth) or a blanket, including their heads. They are placed supine on a hard kapok mattress on the floor where they sleep with their mother and often the father and other siblings. These mothers do not smoke, and they tend to recline with their infants and report going to sleep before 9:00 PM. Feeding information was also obtained during this interview and classified as either exclusive breastfeeding or breastfeeding with some addition of solids. Formula feeding is rare in rural Toraja [19,20].

In the US, CHIME PSG's were gathered in a cross-sectional manner. In the five laboratories, personnel were trained in a standardized protocol for obtaining PSG data [21] to ensure comparability of the results. Monitoring onset could be as early as 6:00 PM or as late as 9:00 PM and the monitoring would continue for at least eight hours. Throughout the night a demand-feeding schedule was followed with opportunity for breastfeeding. In some laboratories mothers were offered a recliner in the room with the instruction to be as quiet as possible; in others, the mother or caretaker was offered a separate room to rest.

The youngest infants were typically wrapped in a blanket while arm movements of older infants were limited with gauze bands secured with safety pins to the diaper. Infants were placed in a supine or side-lying position, and, in most laboratories they were observed with the help of a low-illumination or infrared video camera and monitor. Behaviors such as closing and opening of eyes, crying and movements were charted to establish episodes of wakefulness.

Besides two EEG derivations, a chin electromyogram, two electrooculograms and a movement sensor, abdominal and chest movements were recorded as well as expired CO₂. The electrocardiogram was recorded with 2 disposable electrodes placed under the clavicle and equidistant from the midline. For the present study only the HR data across the night were used while, in selected cases, the sleep states derived from visual inspection of the tracings were employed [21]. Feeding behavior at the time of the PSG was classified as exclusive breastfeeding, formula and breastfeeding or exclusive formula feeding.

Most CHIME infants had their PSG between one and three months of age, leaving an inadequate sample size (N = 5, Table 1) available for comparison beyond three months of age. Similarly, too few Asian CHIME infants with a PSG and adequate HR tracings were available to use as a US Asian sample.

3. Data analyses

3.1. Heart rate

The sampling rate of the Polar HR monitor used in Indonesia was one value/5 s. The beat-to-beat HR data derived from the CHIME PSGs were converted to this same sampling rate. To

each nightly HR trace, we applied a moving median filter with a width of 15 min, and with the window being translated forward in time every 5 min. Another filter was used to remove episodes of active wakefulness. These episodes were identified as segments in which the HR levels exceeded the mean HR for wakefulness for these age groups plus or minus one and a half standard deviation (Fig. 1, trace #2); [22]. The percentage active wakefulness of the total recording of Asian Torajan and non-Asian CHIME groups identified by that filter was subsequently compared.

4. State selection

The purpose of the study was to identify the first evidence of a circadian HR modulation during sleep. Quiet sleep (QS) is characterized by low heart rate variability as measured by interquartile range (Fig. 1, trace # 3); [22]; this state could be readily recognized in all heart rate traces, even when PSG's were unavailable. These QS heart rates were used for a comparison of HR in the Asian Torajan and non-Asian CHIME infants.

5. Identification of CHR

All HR tracings were lined up with chronological time beginning at 6:00 PM and ending at 6:00 AM. The night was divided into four intervals: 6 PM–9 PM; 9 PM–12 AM; 12 AM–3 AM and 3 AM–6 AM. QS episodes 6 min in infants 2 months and 10 min in infants > 2 - months were identified. The number of eligible QS episodes during each interval varied between one and two. The HR tracings were considered too short for establishing the presence of the CHR if more than one of these intervals had no QS episode. For instance, several infants had no QS episode after 3 AM and prior to 9 PM. These infants were excluded for the CHR analysis. Of the 64 non-Asian CHIME infants, the tracings of 12 infants had to be excluded, compared to two for the Asian Torajan recordings.

The CHR was considered present if the lowest median QS HR was lower than a QS median HR both prior to and occurring after it. In 20 Asian Torajan tracings, recordings lasted beyond 6 AM. Those cases were examined separately to see whether a HR decline during the last nightly interval between 3 AM and 6 AM would turn to a rise if more data were available. With two exceptions none of them did.

In addition, median HR values during the QS episodes of the two groups of infants were submitted to fit to the quadratic model $As^2 + Bs + C$, where A, B, and C are the best fit coefficients and s is the time from the beginning of the recording. A positive coefficient of the quadratic term ("A" in the above equation) was considered evidence that the CHR was present. This positive coefficient "A" correlated in 39/40 (98%) of the CHIME traces with the presence of CHR as visually identified (Fig. 2). A negative coefficient correlated with the absence of the CHR in 5/12 cases (42%). The comparable numbers in the 48 Torajan traces examined were: 16/24 (69%) and 19/23 (83%). Visual identification of the lowest median QS HR was unambiguous. Because of the relatively high numbers of mismatches, the presence of the CHR in HR traces was based ultimately on visual scrutiny of the computer generated QS HR medians. To ensure that a bias did not affect the statistical comparison between Asian Torajan and non-Asian CHIME infants, the mismatches were scrutinized further (see below).

6. Statistical treatment of the data

Age differences were determined with a T-test. A Fisher Exact Test compared median time in active wakefulness and median overall QS HRs in the two study groups. This same test established the presence of the CHR in male and female infants during the first two age intervals. A Chi square test was used to examine the issue of sex for the larger sample consisting of all age intervals in both study groups.

A Fisher Exact Test was used to compare the CHR in non-Asian CHIME and Asian Torajan infants at the first two age intervals 7 weeks and between 8 and 12 weeks, as well as the influence of exclusive breast feeding (Table 1). In Asian Torajan infants beyond three months of age, the presence of the CHR was established for infants between 16–20 weeks (at a mean age of 18 weeks plus 1 day, SD 10.5 days) and 21–25 weeks (mean age 23 weeks plus 4 days SD 7 days, Table 1). A comparison between the CHR in Asian Torajan infants between 8–12 weeks and these last two age intervals was performed with a Fisher Exact Test as well.

7. Results

On average, during the age interval of 8–12 weeks, Asian Torajan infants were one week and five days older than their non-Asian counterparts ($t = 3.3$ df 1, 30, $P < 0.003$).

Male and female infants exhibited no difference in the timing of the CHR in either of the study groups examined separately across all age intervals (Asian Torajan male: 47%, female 42%, NS; non-Asian CHIME male 80%, female 93%, NS) or in the study groups combined for the first two age intervals (51% of the male infants exhibited CHR compared to 49% of female infants NS).

Twenty four percent of active wakefulness during the nightly recording in the non-Asian CHIME cohort 7 weeks did not differ significantly from the 20 percent in Asian Torajan infants at a similar age, nor did the 20% of active wakefulness and the 15.8% in the same groups between 8 and 12 weeks. Overall median QS HR in these two groups at the two ages did not significantly differ either (135.5 vs 134.8 bpm and 131 and 130.9 bpm).

In 7 week- infants, the CHR was present in 73% of the non-Asian CHIME HR traces and 45% of the Asian Torajan HR traces, a nonsignificant difference. In Asian Torajan infants between 8 and 12 weeks of age the CHR was observed significantly less frequently (33% vs 94%, $p < 0.001$; Figs. 3 and 4). During the two older age periods in Asian Torajan infants (16–20 and 21–25 weeks), the percentages with CHR were 47 and 56% respectively (Fig. 4). This represents a non-significant increase from the 8–12 week interval.

Exclusive breastfeeding was observed in 91% of Asian Torajan infants at 7 weeks, compared to 43% in non-Asian CHIME infants ($p < 0.02$). These numbers were 93% and 18% respectively between 8 and 12 weeks ($p < 0.0001$, Table 1). During this latter interval, a combination of breast and formula feeding was seen in 59% of the non-Asian CHIME infants, with 24% receiving only formula.

No significant correlation between exclusive breastfeeding and the timing of the CHR could be found. A measure of such a correlation would be the simultaneous presence of exclusive breastfeeding and the CHR and the simultaneous absence of both. Of the 97 tracings examined, 41(42%) fit these characteristics. For comparison, in 56 (58%) of the tracings exclusive breastfeeding was practiced while the CHR was absent and the CHR was present without exclusive breastfeeding ($p = 0.029$). Between 8 and 12 weeks, for instance, all Asian Torajan infants, with one exception were exclusively breastfed, yet only one in three exhibited the CHR.

8. Discussion

Between three and seven weeks of age the CHR is emerging in many non-Asian CHIME infants and Asian Torajan infants. Between 8 and 12 weeks, the CHR in non-Asian CHIME infants is ubiquitous as was also shown in a previous study from our laboratory and other reports [8,10,13]. By contrast, the CHR in Asian Torajan infants was observed in only one out of three infants; the CHR begins to rise in the Asian Torajan infants between four and six months of age, similar to Petersen and Wailoo's finding [16] of a late appearance of the circadian temperature rhythm in Asian immigrants in Britain. No other comparable cross-cultural studies can be found in the literature that deal with this phenomenon.

In this study we focused on the earliest appearance of the CHR. We elected to compare the HR levels during QS episodes that are easily identified by low HR variability, in contrast to rapid eye movement sleep (REM) episodes. The location of data gathering begs the question whether the findings presented here are unbiased. For the non-Asian CHIME cohort this was in the PSG laboratory, whereas the Asian Torajan infants were monitored at home. The results from the CHIME cohort replicate the findings for infants monitored in our laboratory in the 1980s [10]. This one to three-month age benchmark seems robust. Petersen and Wailoo [16] monitored both their Asian and non-Asian infants at home, lending credence to the finding of a delay in the appearance of the CHR in Asian infants.

In the youngest age interval where the difference between the groups was not significant, three of the Asian Torajan traces were designated as exhibiting the CHR based on visual analysis despite a negative s-coefficient, compared to four of the non-Asian CHIME group. Between the ages of 8 and 12 weeks, when the difference between the groups was highly significant, one trace of the Asian Torajan group was designated as having no CHR despite a positive s-coefficient. One trace of the non-Asian CHIME infants was designated as exhibiting CHR based on visual analysis, despite a negative s-coefficient and two traces were designated as having no CHR despite a positive s coefficient with a net group change of one. Irrespective of the analysis strategy, with or without the quadratic fit, the differences between the groups remained significant.

Whether the circadian HR rhythm is in sync with the temperature and other “hands” of the clock such as cortisol and melatonin rhythms, has not been firmly established even though each tends to appear around the same age. In an old report, Hellbrügge reported that circadian water excretion awaits the maturation of the glomeruli of the kidney whereas that of potassium and sodium requires the maturation of the tubules that occurs later [8]. Both

happen after the 24-hour sleep–wakefulness rhythm has been established. McGraw et al [23] followed one infant for six months and found that the temperature rhythm appeared first, followed by the wakefulness and melatonin rhythms (45 days) with a sustained nightly sleep rhythm at 56 days. Glotzbach and colleagues [13] examined the rectal temperature and HR periodicities simultaneously and revealed that their correlation increased between one and three months of age. These studies suggest that synchronization of the “hands” is an emerging phenomenon, perhaps also influenced by maturation of neurons in the SCN [7].

It is premature to ascribe these CHR differences to genetic influences. After all, in infants 7 weeks, the differences between the Asian and non-Asian cohorts were not significant. Moreover, a study by Custodio et al [24] in monozygotic and dizygotic twins found little support for a genetic influence upon the timing of a circadian rhythm appearance.

Wailoo's group was the first to suggest specific variables, including infant illness that hastened the appearance of the circadian temperature rhythm [17,25]. A number of these are not supported in the present study. Lodemore et al [17] reported an earlier appearance of the circadian temperature rhythm in the supine sleeping position. The PSG laboratory protocol in our study specified supine or side-lying with a preference for the former. Supine is the cultural imperative for Torajan infants; this study found both an earlier and a later appearance of the CHR in the supine sleeping position depending on ethnicity. Exclusive breastfeeding was far more prevalent in this group than in the non-Asian CHIME infants at comparable ages, yet this did not hasten the appearance of the CHR as it did in Lodemore's cohort [17]. Similarly, girls did not exhibit their CHR at an age prior to boys. Given that there were no HR differences between the two groups, it is unlikely that the time frame of the 1990s when the CHIME infants were monitored and the first decade of the new century for the Torajan infants, influenced the results.

Based on findings from the infant sleep literature, there are a number of candidate variables that may or may not interact with one another to affect the emergence of the CHR; among these sleep architecture, ambient light and feeding behaviors, including formula and breastfeeding are the most important.

QS episodes are brief prior to two months of age but lengthen with age [26].

Heart rates are lowest during QS compared to REM and quiet and active wakefulness [22]. In older studies or in studies that did not measure sleep states, the first HR minimum appeared as early as one or two hours after monitoring onset around 8:00 or 9:00 PM, a time that in all likelihood coincided with sustained QS. Moreover, with increasing age, QS episodes become longer and their HR from beginning to end reaches progressively lower levels [26,27]. In other words, any lengthening of the duration of QS favors a trough in HR.

In young infants Harper et al. [28] showed that during QS epochs prior to awakening for any feeding, the HR decreased. By contrast, QS HRs prior to awakening without feedings, increased. When subsequently infants return to sleep, awakenings accompanied by feedings initially elevated subsequent HR, but these HR levels tapered off over the next hour and a half in QS.

We did not find any direct influence of formula and breastfeeding on the appearance of the CHR. Some investigators, however, have found that these affect sleep architecture differently and could indirectly affect the CHR. Breastfed infants have shorter sleep bouts than bottle fed infants, spend more time in QS, and have shorter REM sleep epochs [29]. We did not find such differences between our two groups in either active wakefulness or QS, making this explanation less likely. These authors also noted significantly lower HR in breast-fed infants, a finding not replicated in this study nor in the one by Petersen et al. [30].

Lastly, all Asian Torajan infants were exposed to lighting conditions different from their non-Asian CHIME controls. Mothers typically reclined for sleep with their children around 9:00 PM and rose around 5:00 AM. Being close to the equator, they lacked variation in natural light due to seasonal influences. Moreover, before bedtime infants were typically exposed to very dim artificial light [19]. Thus, potential complicated effects of interactions may explain the variability in the appearance of the CHR that some investigators have alluded to [31,32].

In conclusion, despite the fact that they were on average a week older, Asian Torajan infants lagged behind the non-Asian CHIME infants in the presence of the CHR between two and three months of age. Even at six months the CHR was still not reliably present in almost half of these infants.

Speculation: The clinical entity, sudden infant death syndrome (SIDS) lends significance to these studies. The incidence of SIDS is significantly lower in Asian than Caucasian infants and the investigative team of Blackwell in Australia has proposed that infants with a later appearance of circadian rhythms may be protected from infections typically associated with SIDS [33]. Prone sleeping, maternal smoking and formula feeding constitute modifiable risk factors for SIDS and were virtually absent in Asian Torajan infants; however, these variables, as well as male sex, bore no relationship with the delayed appearance of the CHR.

Abbreviations

CHIME	Collaborative Home Infant Monitoring Evaluation
CHR	Circadian Heart Rate Rhythm
HR	Heart Rate
IRB	Institutional Review Board
LIPI	Limbaga Ilmu Pengetahuan Indonesia
PSG	Polysomnogram
QS	Quiet sleep
REM	Rapid eye movement sleep
SCN	Suprachiasmatic Nucleus
SD	Standard Deviation
SIDS	Sudden Infant Death Syndrome.

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Fig. 1.

The top tracing shows the raw HR data from an 8-week old non-Asian CHIME infant. In the second tracing, the active wakefulness is removed with a filter described in the method section. The third tracing depicts the HR variability as measured by the interquartile range. The period of low variability coincides with episodes of quiet sleep (QS) determined through visual analysis (tracing # 4). Tracing # 5 is a plot of the median HR during QS throughout the night with a clear minimum between 1:00 and 2:00 AM.

Fig. 2.
Overnight HR recordings in the same Torajan infant at 16 and 24 weeks of age with the trend analysis and the best quadratic fit plotted under it. Notice the absence of a circadian influence at 16 weeks and its presence at 24 weeks.

Fig. 3.
Four examples of overnight HR tracings at 12 weeks in Torajan infants.

Fig. 4.
Comparison of the presence of CHR in non-Asian CHIME and Asian Torajan infants.

Table 1

Monitoring age and exclusive breast feeding.

	N	Mean (SD)	Range	# (%) Exclusive breast feeding
Non-Asian CHIME [*]	30	39 ^{**} (7.6) 5 weeks + 4 days	27–49 weeks	13 (43%) ^{†‡}
	17	64 (9.0) 9 weeks + 1 day	53–84 weeks	3 (18%) [§]
Asian Torajan infants	11	39 (7.3) 5 weeks + 4 days	29–49	10 (91%) ^{†‡}
	15	76 (11.4) 10 weeks + 6 days	57–86	14 (93%) [§]
	15	127 (10.5) 18 weeks + 1 day	112–139	14 (93%)
	9	165 (7.0) 23 weeks + 4 days	153–170	8 (89%)

^{*} 5 infants were older than 14 weeks and excluded from group comparisons; one was exclusively breastfed, two formula-fed and two received both.^{**} Days.[†] Asian Torajan infants were on average 1 week and 5 days older than non-Asian CHIME infants ($t = 3.3$ df 30, $P < 0.003$).^{‡‡} $P < 0.02$;[§] $P < 0.0001$.