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Original Article

Normal ranges for the variability in heart rate in young infants while sleeping

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Abstract *Objective:* Measurements of the variability in heart rate are increasingly used as markers of cardiac autonomic activity. We sought to establish the development this variability in healthy young infants while sleeping. *Patients:* We carried out polygraphic studies with electrocardiographic recording in 587 healthy infants aged from 5 to 26 weeks. *Methods:* We determined several variables over a period of 400 minutes sleeping: mean RR interval, 5 time-domain (SDNN, SDNNi, SDANNi, RMSSD, and pNN50) and 5 frequency-domain indexes (spectral power over 3 regions of interest, total power and low-to-high frequency ratio). Frequency-domain indexes were also assessed separately for the periods of quiet sleep and those of rapid eye movement sleep. *Results:* Our data showed a significant correlation between the indexes of heart rate variability and the mean RR interval, the breathing rate, and the corrected age of the infants. We also demonstrated the importance of the maturation of the sleeping patterns. *Conclusion:* These data in a large cohort of healthy infants confirm a progressive maturation of the autonomic nervous system during sleep, and may be used to examine the influence of physiological and pathophysiological factors on autonomic control during polygraphic studies.

Keywords: Cardiac rate; infants; normal ranges; sleep; physiology

THE HEART RATE FLUCTUATES WITH TIME, AND its variation is closely related to changes in the neural activity influencing the heart. Variability in heart rate, therefore, represents a non-invasive measure of cardiac autonomic control, and is recognised as a sign of cardiac health.

Considerable postnatal development of central neural regulation of cardiovascular function has been demonstrated in mammals.[1–3] It has also been suggested to occur in infants,[4–12] but ethical difficulties considerably limit the potential for clinical investigations. Non-invasive measures are commonly used, but physiologic correlates to explain changes in those measures are very complex, as the autonomic nervous system is highly integrated. Only very large studies could yield additional information on the nature of the dynamics of heart rate. That is why we assessed this variability in a large cohort of infants during polygraphic studies, in order to determine the differences in variability as a function of age, mean RR interval and mean respiratory rate, and to analyse the maturation of those correlations across the various states of sleep.

As opposed to normal ranges during 24-hour Holter recordings,[12,13] the normal ranges of variability in heart rate during polygraphic recordings have not been documented for a large cohort of infants. Our study provides the necessary ranges and equations for reference. Their use has increased our understanding of the influence of autonomic control on the heart, and may contribute to our understanding of the cardiac autonomic control in a number of physiological settings and diseases.[14–18]

Patients

We examined the indexes of variability in heart rate in 587 healthy, full-term infants. Their weight at birth

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was 3213 ± 447 g (mean ± standard deviation), and their length was 49.5 ± 2.3 cm (mean ± standard deviation). Of the infants, 286 were males and 301 were females, and their age, adjusted to a postmenstrual age of 40 weeks, varies from 5 to 26 weeks. They were prospectively recruited between January 1998 and June 1999. All had a normal medical history, normal clinical and neurological examinations, normal electroencephalographic patterns for conceptional age, polygraphic results without cardiac or respiratory abnormalities, and sinus rhythm on a surface electrocardiogram. Of the group, 135 had been breast-fed since birth, 184 were formula-fed since birth, and 268 were formula-fed after a period of breastfeeding. Of the mothers, 182 had smoked cigarettes during and after pregnancy. None took medications, except vitamin supplements, between birth and the date of recording. The study had been approved by our Institutional Review Board, and all parents gave their informed consent.

Methods

Polygraphic recordings

The infants were admitted for an overnight session of monitoring, from 6.00 p.m. until 8.00 a.m., in our sleep laboratory. The data were gathered in the course of polysomnograms performed as part of different programs of research into sleep, or to alleviate parental anxiety for sudden infant death syndrome, with no impact on the subjects. The efficiency of such testing in asymptomatic infants is more than controversial, and it has been abandoned in the majority of the countries. Campaigns generating public awareness of the test became so important in Belgium a few years ago that many parents still request the test for the purposes of reassurance. All infants were normally dressed in a room temperature of 20°C. They were placed in their usual sleep position, supine in 485 infants, on the side in 85, and prone in only 13. The data were collected on a computerised polygraph recording system (Morpheus system, Medatec, Belgium). We simultaneously recorded 2 leads of electroencephalogram, electrooculograms, the electrocardiogram (DII), chin electromyogram, thoracic and abdominal respiratory movements by means of inductive plethysmography, transcutaneous oxygen saturation by pulse oxymetry, oro-nasal airflow by thermistors taped under each nostril and on the side of the mouth, actigram on one arm to measure body movements, and, when available, infrared videorecording.

Data analysis

Each 30-second epoch of data was classified as quiet sleep, rapid eye movement sleep, waking, or an indeterminate state by the software provided with the sleep recorder (Morpheus, Medatec, Belgium), according to previously published criterions.[19] All events detected were checked and visually controlled by a trained observer examining the tracings on screen. There had to be 400 minutes of analysable sleep data for the recording to be accepted for the study.

Analysis of electrocardiographic recordings

We analysed the electrocardiographic data with use of a computer program which identified and labelled each QRS complex. All data were reviewed by the same paediatric cardiologist. Complexes classified as noise or ectopic, because of artefacts, non-sinus beats, or blocks due to disturbances in conduction, were rejected. The intervals between successive R waves of the electrocardiogram, the RR intervals, were calculated with an accuracy of 1 millisecond. Measures of variability in heart rate were calculated employing normal-to-normal intervals over the 400 minutes of sleep data. Where intervals were rejected, RR intervals were interpolated over the invalid area. Interpolation was used, rather than simple omission, so that non-stationarities were not introduced to the time series prior to transforming to the frequency domain. In addition to the beat filter and guard range, there is logic to reduce the influence of miss-triggers and abnormal timing. There were 3 levels of trigger adjustment:

- A missed R wave was detected as an RR interval which was within 10% of 2 previous RR intervals. When detected, an R wave was inserted at the mid point of the long period.
- An additional R wave was detected when the current plus next RR intervals were within 10% of the previous interval. When detected, the current and next intervals were merged into 1 interval.
- A misplaced R wave was detected when the average of the current and next RR intervals were within 10% of the previous RR interval, and the current and next RR intervals are different by more than 35%. When detected, the current and next RR intervals were set to be equal to the average of the 2 intervals.

For the analysis of the frequency-domain indexes, beat-to-beat fluctuations were transformed to the frequency domain by fast Fourier transformation, and the specific measures were computed as the square root of the areas under the power spectrum. The recommendations of the Task Force of the European Society of Cardiology were respected.[20]

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Time-domain analysis of heart rate variability

We calculated the mean of all filtered RR intervals and 5 time-domain measures over the length of the analysis:

- SDNN: standard deviation of all filtered RR intervals in the entire recording.
- SDNNi: mean of the standard deviations of all filtered RR intervals for all 5-min segments of the analysis.
- SDANNi: standard deviation of the means of all filtered RR intervals for all 5-min segments of the analysis.
- RMSSD: square root of the mean of the sum of squares of differences between adjacent filtered RR intervals over the length of the analysis.
- pNN50: percentage of differences between adjacent filtered RR intervals that are greater than 50 milliseconds for the whole analysis.

Frequency-domain analysis of heart rate variability

The spectral analysis was computed by 5 minute epochs throughout the duration of the recording, and the mean spectral power was determined over frequency regions of interest. Five minutes was selected as the duration as being a compromise between the mutually exclusive wishes for optimal determination of both low and high frequency components. For each period of sleep, and for their combination, we determined the mean spectral power over 3 frequency regions of interest:

- Very low frequency index or VLF (0.004–0.04 Hz).
- Low frequency index or LF (0.04–0.15 Hz).
- High frequency index or HF (0.15–0.4 Hz).

We also determined the total spectral index (0.004–0.4 Hz) and the low- to high-frequency index, or balance.

Statistical analysis

Linear and non-linear (logarithmic, exponential, quadratic and power) regression models were used to study the relationship between the parameters of heart rate variability and age, mean RR interval or mean respiratory rate over the length of the analysis. Correlation coefficients (r-values) were calculated and the minimal level of significance accepted was $p < 0.05$. Multiple regression analysis was then performed and normal ranges were established by the Altman's method.[21] This is a simple approach to the parametric derivation of reference ranges, which avoids the creation of arbitrary age groups, copes easily with a non-linear relation between the variables, and is computationally simple. Normality was carefully verified. After the mean was modelled as a function of age, mean RR interval and breathing rate, specific standard deviation was estimated by regressing the absolute residuals on those parameters. All data were expressed as mean value ± standard deviation.

Results

We found a strong positive linear correlation between mean RR interval over the length of the analysis and all indexes of heart rate variability (Fig. 1a), except the low- to high-frequency index, for which we found a negative linear correlation. The independent effect of mean RR interval was confirmed by multiple regression analysis for all the indexes (Table 1).

We also found a significant correlation between age and all variables. It was quadratic for spectral indexes during rapid eye movement sleep (Fig. 1b), and linear in the other cases (Fig. 1c). The independent effect of the age was confirmed for most of the indexes (Table 1).

Finally significant linear correlations were also found between the variables and the mean breathing rate (Fig. 1d). An effect of this variable, independent from the mean RR interval and from the age, was only confirmed for some indexes (Table 1). The greatest influence of the breathing rate is observed for the high frequency component and the low- to high-frequency index for each period of sleep and for their combination.

Equations for the mean and standard deviation of the normal ranges established by Altman's method[21] are given in the Table 1. Ninety and 95 per cent reference interval can be obtained by multiplying the standard deviation respectively by 1.645 and 1.96. The coefficients of determination r^2 of the multiple regressions are also given in Table 1 and demonstrate a level of significance $p < 0.0001$ for all the equations.

Subgroup analysis showed no significant differences of variability in heart rate according to the position during sleep or the maternal smoking habits.

Discussion

The variation and variability in heart rate depend on the influence of sympathetic and parasympathetic activity on the sinus node, with the variability reflecting spontaneous changes in autonomic activity. Interpretation of the analysis of such variability, however, has been controversial because specific components may be related to different mechanisms

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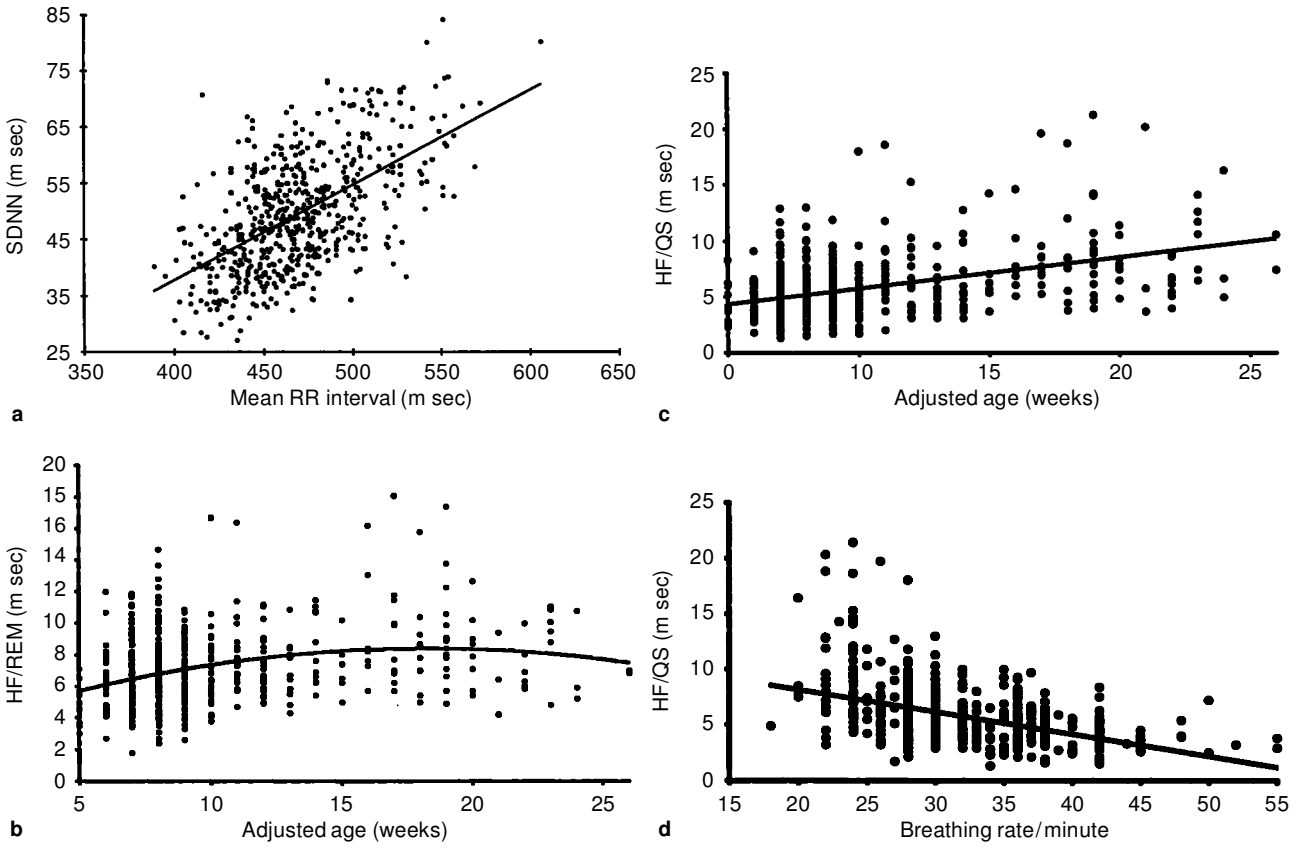

Figure 1.
Examples of regression curves according to the mean RR interval, the mean breathing rate and age. (a) Linear correlation between SDNN (milliseconds) and the mean RR interval over the length of the analysis (milliseconds); (b) Quadratic correlation between the high frequency index (HF) during rapid eye movement sleep (milliseconds) and the patients' age (weeks of adjusted age); (c) Linear correlation between the high frequency index during quiet sleep (milliseconds) and the patients' age (weeks of adjusted age); (d) Linear correlation between the high frequency index during quiet sleep (milliseconds) and the mean breathing rate/minute.

under different conditions, and because interactions between heart rate, respiration, blood pressure and other biological signals have to be considered.[3]

The extent of variability is tightly linked to the basal heart rate during sleep. This relationship is evident[10,12,13] because that association is determined largely by commonality of neural mechanisms controlling heart rate and its variability. It has often been ignored, but is of considerable importance in infants, because mean heart rate widely varies with age as well as between individuals.

We demonstrated that high-frequency oscillations are correlated with the respiratory cycle, so-called respiratory sinus arrhythmia. Our findings are similar to those of previous studies.[22]

Correlation between variability and age has been previously described in infants,[4,5,7,12,14] as well as in children at other ages.[12,13] Considerable postnatal development of central nervous regulation of cardiovascular function is observed in infants. Our findings suggest that developmental changes of sympathetic mediation of heart rate are an important determinant during infancy of the dependence of variability during sleep. Heart rate and breathing rate are important in the developmental changes of parasympathetic mediation, but an effect of age, independent of both factors, is suggested during normal infants' sleep. Interestingly, the linear correlation between frequency domain indexes and the age during quiet sleep indicates that the extent of heart rate variability during quiet sleep increases from 1 through 6 months of age (Fig. 1b). The quadratic correlation between frequency domain indexes and the age during rapid eye movement sleep indicates that the extent of the variability during that particular state of sleeping steeply increases from 1 to 3 months of age, whereas a steadying followed by a decrease is noted from that age through 6 months (Fig. 1c). Our finding, that the extent of variability is similar in all states of sleep during the second and third months of life, may

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Table 1. Normal ranges of heart rate variability during sleep in infancy.

Indexes	r^2	Mean value	Standard deviation
SDNN	0.39	$11.48 - 0.72A - 0.0023B^2 + 0.0002RR^2$	7.88
SDNNi	0.42	$-0.39 - 0.44A + 0.0002RR^2$	$1.36 + 0.00002RR^2$
SDANNi	0.20	$13.64 - 0.57A - 0.0031B^2 + 0.0001RR^2$	7.12
RMSSD	0.13	$111 + 0.001RR^2 - 0.93RR + 0.04A^2 - 0.25A$	$5.44 + 0.02A^2$
Ln pNN50	0.30	$-10.21 + 0.0218RR$	0.97
VLF/QS	0.26	$-1.23 + 0.00006RR$	2.55
LF/QS	0.33	$43.46 - 0.064A^2 + 1.21A + 0.0003RR^2 - 0.212RR - 0.0454B$	$36.44 + 0.0002RR^2 - 0.153RR$
HF/QS	0.53	$62.11 + 0.0003RR^2 - 0.24RR + 0.006B^2 - 0.51B$	$23.71 + 0.0001RR^2 - 0.0084RR + 0.0033B^2 - 0.26B$
BAL/QS	0.32	$1.84 - 0.00098B^2 + 0.09B - 0.0038RR$	0.35
TOT/QS	0.43	$80.39 - 0.0026A^2 + 0.00047RR^2 - 0.35RR - 0.078B$	$34.51 + 0.0002RR^2 - 0.146RR$
VLF/REM	0.26	$-52.27 - 0.014A^2 - 0.0002RR^2 + 0.23RR$	$-18.65 + 0.24A + 0.07RR$
LF/REM	0.30	$-1.29 + 0.00006RR^2 - 0.025A^2 + 0.46A$	$1.31 - 0.0017A^2 + 0.000008RR^2$
HF/REM	0.36	$13.35 - 0.011A^2 + 0.255A + 0.0001RR^2 - 0.067RR - 0.0256B$	$15.54 - 0.0667RR + 0.00008RR^2$
BAL/REM	0.25	$3.31 + 0.007B - 0.018A - 0.0026RR$	$2.33 - 0.0082RR + 0.000008RR^2$
TOT/REM	0.31	$-24.62 - 0.0162A^2 + 0.109RR$	$0.3 + 0.00002RR^2 - 0.0044A^2$
VLF/ALL	0.38	$-40.11 - 0.0001RR^2 + 0.1858RR - 0.4A$	$1.243 - 0.00245A^2 + 0.00001RR^2$
LF/ALL	0.39	$-2.59 + 0.00007RR^2 - 0.0143A^2 + 0.265A$	$1.27 + 0.000005RR^2$
HF/ALL	0.48	$65.36 + 0.00033RR^2 - 0.264RR + 0.004B^2 - 0.349B$	$39.66 + 0.0002RR^2 - 0.168RR - 0.025B$
BAL/ALL	0.32	$1.6 - 0.00047A^2 - 0.000003RR^2 - 0.000645B^2 + 0.063B$	0.34
TOT/ALL	0.44	$0.54 + 0.00012RR^2 - 0.386A$	$1.6 + 0.00001RR^2$

Abbreviations: RR = mean RR interval in milliseconds; A = adjusted age in weeks; B = breathing rate/minute; SDNN = standard deviation of all filtered RR intervals in the entire recording in milliseconds; SDNNi = mean of the standard deviations of all filtered RR intervals for all 5-min segments of the analysis in milliseconds; SDANNi = standard deviation of the means of all filtered RR intervals for all 5-min segments of the analysis in milliseconds; RMSSD = square root of the mean of the sum of squares of differences between adjacent filtered RR intervals over the length of the analysis in milliseconds; Ln pNN50 = Neperian logarithm of the percentage of differences between adjacent filtered RR intervals that are greater than 50 milliseconds for the whole analysis. VLF = very low frequency index in milliseconds; LF = low frequency index in milliseconds; HF = high frequency index in milliseconds; TOT = total spectral index in milliseconds; BAL = low- to high-frequency index. /QS; /REM and /ALL mean that the spectral index was determined respectively for the quiet sleep period, the rapid eye movement sleep period and for their combination

reflect immaturity of the differentiation of the states of sleep themselves during this period. It must also be mentioned that Schechtman et al.[6] previously noted a decrease of heart rate variability in all frequencies over the first month of life, before increasing thereafter, suggesting a general decrease in parasympathetic control of the heart during the postnatal period. Further increase of heart rate variability during quiet sleep, and its decrease during rapid eye movement sleep beyond 3 months of age, may anticipate the greater extent of heart rate variability during quiet sleep relative to rapid eye movement sleep demonstrated in adults[23] and suggested in infants.[8] These findings are similar to those of previous studies,[4,6,8,11] except that the high-frequency components increased steeply during the first 3 months, but showed only minor changes after 3 months of age respectively during quiet sleep as assessed by Harper et al.,[4] and rapid eye movement sleep in the study of Schechtman et al.[6] These differences may result from the manner in which high-frequency components are quantified, the use of spectral analysis rather than peak/trough methods,[6] and that of a wider bandwidth than used by Harper et al.[4] In a previous study,[24] we had analysed the appearance of significant circadian variation in heart rate variability during infancy. In this way, we demonstrated that sleep itself, and the maturation of its biological clock, are

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implicated in the mechanism of autonomic regulation. That clock, which resides in the hypothalamic suprachiasmatic nucleus, plays an important role in the organisation of sleep, and in the coordination of sleep with other physiological rhythms. The main consequence of its maturation on the autonomic balance seems to be sympathetic withdrawal rather than a parasympathetic effect. That sympathetic modulation may be mediated through a direct nervous effect, a reduction in circulating catecholamines, but it could also affect vagal effects on the cardiac cycle.[24,25] In adult animals, some forebrain influences over autonomic function are interrupted during rapid eye movement sleep.[26] This loss of forebrain control may strengthen the reflexive negative correlation between heart rate and heart rate variability imposed by brainstem regions. This relationship may be less apparent before many inhibitory, as well as excitatory, forebrain connections are made in infants. These depend on the myelination of limbic pathways, which occurs largely during the first months of life.[27]

All indexes of heart rate variability followed very similar maturational patterns, suggesting that similar mechanisms influence all the components of the autonomic nervous system and that the maturation of the mechanisms contributing to heart rate variability is concomitant. During the neonatal period, vital functions are controlled reflexively via brainstem mechanisms. As forebrain connections develop, the reflexes, which protect the infant, may be modulated, allowing for a wider and more complex range of reactions. The effects of heart rate, respiration and age have been demonstrated. The coefficients of determination r^2 of the multiple regressions, nonetheless, were less than 0.50 for most indexes of heart rate variability. The maturation of forebrain influences widely varies between individuals, and the coordination of heart rate, heart rate variability and respiratory measures develops at variable rates during early life.[8,10] That finding also suggests that other factors probably influence the level of heart rate variability. Those mechanisms are not clearly identified, but blood pressure and thermoregulation certainly play a role. Changes in breathing pattern and body movements associated with the behavioural state could also influence heart rate variability, especially during respiratory pauses, sucking, and crying behaviours.[28] It could also be that the random part remains important in heart rate variability.

The overall complexity of heart rate dynamics, therefore, is high whilst infants are sleeping. Our findings indicate the importance of age-, heart rate- and respiration-related differences in heart rate dynamics, and illustrate an increase of cholinergic and a decrease of adrenergic modulation of heart rate variability with age, confirming the progressive maturation of the autonomic nervous system during sleep in infancy.

We expect that analysis of heart rate variability, by providing non-invasive evaluation of autonomic neural balance, will be used increasingly once commercially available computer programs are developed. Our data provide normal ranges identified in a large cohort of infants aged from 1 to 6 months. We hope this will contribute to research in a number of physiological settings, and to clinical and experimental protocols in infants whose disease or therapy might affect cardiac autonomic control.

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