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Normal Ranges of Heart Rate Variability During Infancy and Childhood

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Abstract. Heart rate variability is a noninvasive index of the neural activity of the heart. The present study examined heart rate variability indices in 210 infants and children aged 3 days to 14 years to obtain normal ranges for all age classes. Heart rate variability was measured by calculating mean RR interval over the length of the analysis, mean RR interval during quiet sleep, 5 time-domain (SDNN, SDNN-i, SDANN-i, r-MSSD, pNN50), and 4 frequency-domain (VLF, LF, HF, LF/HF ratio) indices. Our data show a significant positive correlation between all indices and the mean RR interval over the length of the analysis, except for the LF/HF ratio for which the correlation was binomial. A positive power correlation was also found between all parameters and age. The multiple correlation analysis confirmed the independent effect of age and mean RR interval on the heart rate variability. These data in a healthy pediatric population confirm a progressive maturation of the autonomic nervous system during childhood and may be utilized to examine the effects of underlying disease processes or therapeutic interventions on cardiac autonomic tone during infancy and childhood.

Key words: Heart rate variability — Time-domain measurements — Frequency-domain measurements — Infants — Children

It is well known that the heart rate fluctuates with time and that this variation is closely related to changes in the neural activity influencing the heart. Therefore, heart rate variability, as determined from 24-hour Holter recordings, represents a noninvasive parameter for studying the cardiac autonomic control and is recognized as a sign of cardiac health. Since the first report on the use of heart rate variability parameters in 1978 [35], impaired variability was found in adult patients with myocardial infarction [18, 21], left ventricular dysfunction [23, 34], low cardiac output [17], chronic heart failure [23, 28, 33], panic disorder [36], and diabetic neuropathy [7]. A few reports are available in the pediatric literature on the heart rate behavior in premature infants [6, 27], newborns [6, 32], full-term infants at risk for sudden infant death syndrome [2, 14, 16, 25, 31], normal infants and children [10], diabetic children [1, 20, 22, 38, 39], children with atrial septal defect [9], and critically ill children following cardiac surgery [15]. Most of these reports compared a group of ill children with age-matched healthy children, so that well-documented normal ranges of heart rate variability for most parameters, to assess the behavior of the autonomic function during infancy and childhood, are not yet available.

The aim of this study was to assess the heart rate variability in 210 infants, toddlers, and schoolchildren during 24-hour ambulatory electrocardiographic monitoring, and to determine the differences in variability as a function of age and mean RR interval over the length of the analysis.

Patients

The present study examined indices of heart rate variability in 210 healthy, full-term neonates, infants, toddlers, and schoolchildren, aged 3 days to 14 years (108 females and 102 males). Twenty-one age groups of 10 infants or children, aged respectively 3 to 7 days, 8 to 14 days, 15 to 21 days, 22 days to 1 month, 1 to 3 months, 3 to 6 months, 6 to 12 months, and then each year of age, were constituted. All of them had a normal medical history and physical examination. None used tobacco products or took medications (including estrogen). Sinus rhythm was confirmed before entering the protocol.

Methods

Holter Monitoring

Continuous ambulatory ECG monitoring was recorded using an MR45 Oxford recorder type. The tape recording consisted of 2 channels of

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electrocardiographic data. The data were typically gathered while the child went about his daily activities.

Analysis of Recordings

All Holter tapes were subsequently analyzed with use of a Medilog Excel computer program to identify and label each QRS complex. All data were reviewed by one analyst and were edited to validate the system's QRS labeling for the duration of the Holter recording. This stage is a crucial precursor to heart rate variability analysis because quality analysis is contingent upon accurate QRS detection and labeling. There had to be more than 23 hours of analyzable data for the 24-hour recording to be accepted for the study. Complexes classified as noise or ectopic were rejected. Measures of heart rate variability were calculated employing only normal-to-normal intervals and were printed for the entire 24 hours. For the analysis of the frequency-domain indices, 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.

Mean Heart Rate

Twenty-four hour mean RR (mean of all filtered RR intervals over the length of the analysis) and nighttime mean RR (mean of all filtered RR intervals for 5 consecutive hours during quiet sleep of the subject) were calculated.

Time-Domain Indices

Five measures [19] were examined: (1) SDNN: standard deviation of all filtered RR intervals in the entire 24-hour ECG recording, (2) SDNN-i: mean of the standard deviations of all filtered RR intervals for all 5-min segments of the analysis, (3) SDANN-i: standard deviation of the means of all filtered RR intervals for all 5-min segments of the analysis, (4) r-MSSD: square root of the mean of the sum of squares of differences between adjacent filtered RR intervals over the length of the analysis, and (5) pNN50: percentage of differences between adjacent filtered RR intervals that are greater than 50 msec for the whole analysis.

Frequency-Domain Indices

We determined the spectral power (5) over 3 frequency regions of interest: (1) VLF: very low frequency index (0.004–0.04 Hz), (2) LF: low frequency index (0.04–0.15 Hz), and (3) HF: high frequency index (0.15–0.4 Hz). We also determined the low- to high-frequency power or LF/HF ratio.

Statistical Analysis

All time-domain and frequency-domain indices are automatically calculated by the commercially available Medilog Excel computer program.

Linear and nonlinear (logarithmic, exponential, binomial, and power) regression models were used to study the relationship between the parameters and age or mean RR interval over the length of the analysis. Correlation coefficients (*r*-value) and regression equations were calculated; *r*-values were analyzed using Student's *t*-test. The minimal level of significance accepted was $p < 0.05$. Standard deviation of all parameters for each age group and the corresponding regression equation were calculated. All data were then expressed as mean value ± standard deviation. Multiple correlation analysis was used to separate the effects of age and mean RR interval because they are not independent parameters.

Table 1. Correlation between heart rate variability parameters and mean RR interval over the length of the analysis

Parameter	Correlation equation	*r*-Value	Standard deviation equation
SDNN	0.39 × mRR − 112.9	0.91	0.04 × mRR − 2.0
SDNN-i	0.21 × mRR − 57.6	0.89	0.03 × mRR − 6.5
SDANN-i	0.33 × mRR − 97.0	0.90	0.04 × mRR − 1.7
r-MSSD	0.21 × mRR − 69.2	0.82	0.06 × mRR − 18.5
pNN50	0.10 × mRR − 42.4	0.91	0.02 × mRR − 5.6
nighttime RR	1.45 × mRR − 145.3	0.98	0.09 × mRR − 17.9
VLF	0.13 × mRR − 32.2	0.75	0.04 × mRR − 9.4
LF	0.07 × mRR − 14.9	0.84	0.01 × mRR + 0.7
HF	0.09 × mRR − 27.5	0.81	0.02 × mRR − 3.5
LF/HF	0.00001124 × mRR^2 − 0.0156 × mRR + 6.4	0.82	−0.00000067 × mRR^2 + 0.00056 × mRR + 0.13

mRR, mean RR interval over the length of the analysis.

Results

There was a strong positive linear correlation between mean RR interval over the length of the analysis and all parameters, except the ratio of low- to high-frequency components for which the correlation was binomial. The relations between measurements and mean RR interval are tabulated in Table 1 and examples are shown in Figures 1 to 3.

We also found a significant power correlation between age and all variables. The relations are tabulated in Table 2 and examples are shown in Figures 4 to 6.

The multiple correlation analysis confirmed the independant effect of age and mean of all RR intervals on the heart rate variability.

There is a strong linear correlation between the mean RR interval during quiet sleep and the mean RR interval over the length of the analysis (Table 1). There is a strong binomial correlation between age and mean RR interval over the length of the analysis and between age and mean RR interval during quiet sleep (Table 2).

There is a similar correlation between the mean RR interval during quiet sleep and the different parameters, such as with the mean RR interval over the length of the analysis; this is to be expected because of the strong correlation between 24-hr mean RR interval and nighttime mean RR interval. We present in Table 3 the cor-

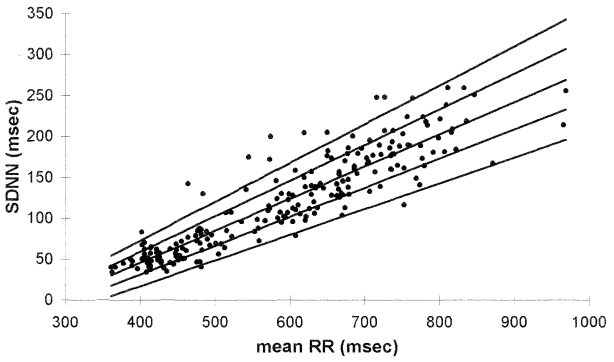

Fig. 1. Normal ranges for the standard deviation of all filtered RR intervals (in msec) in the entire 24-h ECG recording (SDNN) with respect to mean RR interval over the length of the analysis (in msec). Lines are regression line ±1 SD and ±2 SD.

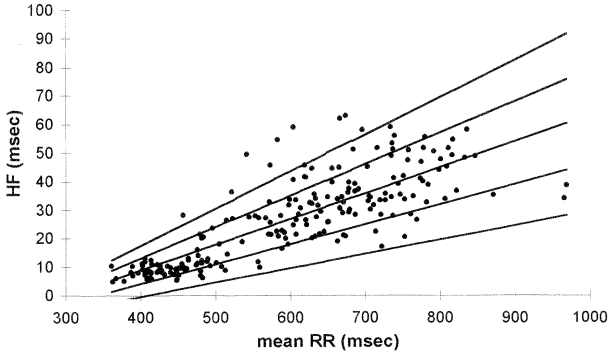

Fig. 2. Normal ranges for the high-frequency component (in msec) of the frequency–domain analysis (HF) with respect to mean RR interval (in msec) over the length of the analysis. Lines are regression line ±1 SD and ±2 SD.

relation between mean RR interval during quiet sleep and the parameters that are mainly influenced by the vagal activity [r-MSSD and pNN50 in the time-domain analysis, high-frequency component (HF), and ratio of low- to high-frequency components (LF/HF ratio) in the frequency-domain analysis].

Discussion

Heart rate variation and variability depend on the influence of sympathetic and parasympathetic activity on the sinus node and variation and variability reflect spontaneous changes in autonomic activity. Heart rate variability measures have received a great deal of attention with regard to the autonomic control of heart rate. However, interpretation of the results is sometimes controversial because specific components may be related to different mechanisms in different conditions and because interactions between heart rate, respiration, blood pressure, and other biological signals have to be considered [13, 24, 29, 30].

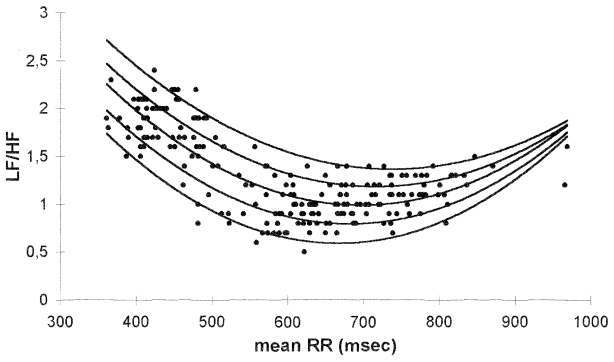

Fig. 3. Normal ranges for the ratio of low- to high-frequency power in the frequency–domain analysis (LF/HF ratio) with respect to mean RR interval (in msec) over the length of the analysis. Lines are regression line ±1 SD and ±2 SD.

Table 2. Correlation between heart rate variability parameters and age

Parameter	Correlation equation	*r*-Value	Standard deviation equation
SDNN	$97.2 \times A^{0.20}$	0.86	$24.9 \times A^{0.22}$
SDNN-i	$53.0 \times A^{0.17}$	0.79	$14.7 \times A^{0.25}$
SDANN-i	$78.0 \times A^{0.22}$	0.86	$22.1 \times A^{0.18}$
r-MSSD	$39.9 \times A^{0.22}$	0.75	$16.5 \times A^{0.29}$
pNN50	$6.5 \times A^{0.53}$	0.82	$5.0 \times A^{0.40}$
VLF	$38.1 \times A^{0.14}$	0.68	$11.7 \times A^{0.28}$
LF	$25.1 \times A^{0.14}$	0.76	$6.2 \times A^{0.17}$
HF	$19.3 \times A^{0.25}$	0.84	$6.1 \times A^{0.29}$
LF/HF	$1.3 \times A^{-0.1}$	0.73	$0.2 \times A^{-0.04}$
24 hr-mRR	$-1.87 \times A^2 + 47.89 \times A + 435.4$	0.90	$-0.28 \times A^2 + 6.9 \times A + 33.4$
nighttime mRR	$-2.90 \times A^2 + 72.8 \times A + 479.4$	0.91	$0.86 \times A^2 + 2.3 \times A + 49.9$

A, year of age.

Preliminary investigations in healthy adults [5, 19] suggested that the high-frequency component of the frequency-domain analysis and pNN50 and rMSSD, which reflect the short-term heart rate variability (high-frequency power) in the time-domain analysis, are predominantly a response to changes in vagal tone and can be heavily influenced by respiration. The low-frequency component of the frequency-domain analysis and the parameters of the time-domain analysis (SDNN, SDNN-i, SDANN-i), which express the long-term heart rate variability (low-frequency power), are dually influenced by cholinergic and adrenergic activity, as well as by other physiologic inputs. These parameters reflect the overall

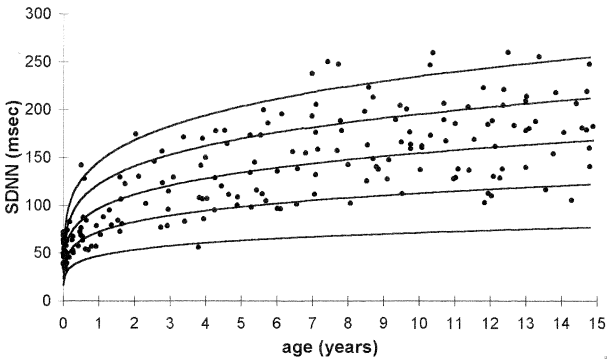

Fig. 4. Normal ranges for the standard deviation of all filtered RR intervals (in msec) in the entire 24-h ECG recording (SDNN) with respect to age (in years). Lines are regression line ±1 SD and ±2 SD.

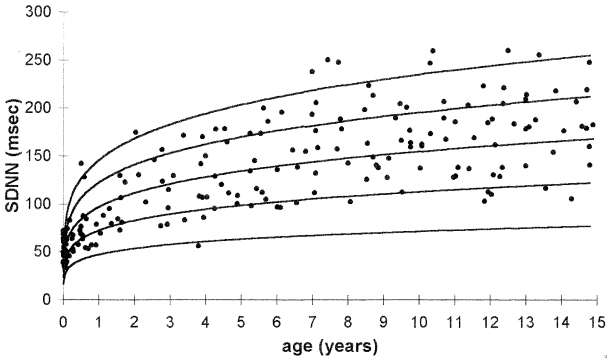

Fig. 5. Normal ranges for the high-frequency component (in msec) of the frequency–domain analysis (HF) with respect to age (in years). Lines are regression line ±1 SD and ±2 SD.

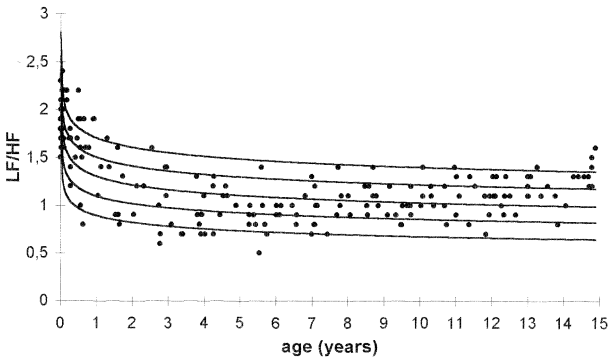

Fig. 6. Normal ranges for the ratio of low- to high-frequency power in the frequency–domain analysis (LF/HF ratio) with respect to age (in years). Lines are regression line ±1 SD and ±2 SD.

Table 3. Correlation between heart rate variability parameters and nighttime mean RR interval

Parameter	Correlation equation	*r*-Value	Standard deviation equation
r-MSSD	0.14 × nRR − 47.1	0.82	0.04 × nRR − 12.7
pNN50	0.07 × nRR − 30.6	0.89	0.014 × nRR − 4.5
HF	0.06 × nRR − 18.3	0.82	0.013 × nRR − 1.6
LF/HF	$0.000005 \times nRR^2 -$ 0.009 × nRR + 4.9	0.82	$-0.0000007 \times nRR^2 +$ 0.0009 × nRR − 0.038

nRR, nighttime mean RR interval.

flexibility of the autonomous nervous system. The sympathovagal balance is best reflected in the ratio of low- to high-frequency components. The physiological meaning of the very low-frequency component of heart rate variability is still not clear, but it appears to be related to thermoregulatory mechanisms, peripheral vascular tone, and circadian humoral changes.

The results of the present study demonstrate that age is an important determinant of heart rate variability in normal subjects. This correlation had been described in newborns [3, 6, 26, 32], in infants [2, 10, 14, 16, 31], and in schoolchildren and young adults [8, 10, 37]. Southall and coworkers analyzed changes of heart rate variability during infancy, which is a period of rapid sympathetic nervous system development, and demonstrated a delayed or deficient cardiovagal development in infants who subsequently succumbed to the sudden infant death syndrome [2, 14, 31]. Considerable postnatal development of central neural regulation of cardiovascular function in mammals has also been suggested by the results of various studies in different species, especially by these of Ph. Gootman and coworkers in developing swine [4, 11, 12, 13]. Continual data during infancy and childhood are only available for the low- and high-frequency components of the frequency-domain analysis [10]; that study showed an age dependence of heart rate variability, being in general an increase in both low- and high-frequency components from 1 month to 6 years, followed by a decrease to 24 years. The authors concluded that developmental changes of parasympathetic and sympathetic mediation of heart rate are an important determinant of age dependence of heart rate variability. We only partially agree with these results and the authors' conclusion; we could not confirm the trend of the low- and high-frequency components as described by those authors: the power correlation that we found involves a steadying of the sympathovagal balance during childhood but no decrease of the parameters. We could also exclude by multiple regression analysis that the age dependence is caused by modification of mean heart rate with age.

The relation between heart rate variability and mean RR interval over the length of the analysis is linear. This relationship between heart rate and heart rate variability

is often ignored in the literature. It is, however, of considerable importance in children because mean heart rate is variable individually but also with age. The difficulty is that heart rate and heart rate variability both depend on the autonomic nervous system so that they are not independent variables; mean 24-hour heart rate corresponds to the product intrinsic heart rate × intrinsic heart rate variability, whereas the heart rate variability indices reflect the circadian flexibility of the autonomic nervous system. The binomial correlation between mean RR interval over the length of the analysis and the LF/HF ratio expresses the complexity of the relationship between heart rate, autonomic nervous system, and heart rate variability. This fact was also emphasized by Schechtman et al. [31] in the analysis of the dynamic patterns of cardiac rate in infants who succumb to sudden infant death syndrome.

There is a strong correlation between mean RR interval over the length of the analysis and over 5 hours in quiet sleep. Therefore, the correlation between mean RR interval and the various indices of heart rate variability during sleep usually does not add important information to the correlation of the same parameters over 24 hours. However, the study of the correlation between mean RR interval during sleep and parameters that are influenced by the vagal activity could be more sensitive in pathological conditions with withdrawal of the vagal activity and loss of harmony between heart rate and heart rate variability.

In summary, the overall complexity of heart rate dynamics is high in children. These findings indicate the importance of age- as well as mean RR interval-related differences in heart rate dynamics in children 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.

Various diseases are accompanied by the heart's altered neural activity. This can be examined by the study of heart rate variability, which is routinely offered by modern Holter systems. Therefore, heart rate variability may be a new, important tool, for example, in the clinical assessment of congestive heart failure or in the early detection of diabetic autonomic neuropathy in children; the role of autonomic nervous system alterations in disease mechanisms could be explored and new therapeutic options could then be found.

It is expected that the analysis of heart rate variability, by providing noninvasive evaluation of autonomic neural balance, will find increasing popularity in many diverse areas of study in pediatrics. Our data, by providing normal ranges for pediatric patients, may contribute to that research in a number of physiological settings and in clinical and experimental protocols in children with disease or therapy supposed to affect the autonomic control of the heart.

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