Heart Rate Variability in Healthy Newborn Infants

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In adults and older children, heart rate variability (HRV) is frequently used to study autonomic function noninvasively. Normal values of HRV in newborn infants, however, are not widely available. This problem may be partially attributed to the lack of standardization of different methods. This study assessed HRV in normal newborn infants using 24-hour Holter monitoring. From 1997 to 2000, we prospectively evaluated frequency-(spectral analysis), geometric-, and time-domain indexes of HRV in normal term infants. Ninety-six asymptomatic infants who were <72 hours old were studied. Frequency-domain parameters (power in the high, low, very low, ultra low, and total frequency domains), a geometric parameter (HRV triangular index), and time-domain parameters (SDNN, SDANN, SDNNi, r-MSSD, s-NN50) are reported as means ± SD, medians, and 5th and 95th percentiles to establish the normative values for newborns. A high degree of correlation (r ≥0.85, p <0.0001) was noted among the 3 vagal tone dependent parameters, such as high-frequency power (frequency domain), r-MSSD, and s-NN50 (time domain). Our study supports the use of vagal dependent time-domain parameters like r-MSSD and sNN50 as surrogates for high-frequency power in newborns. Because the data are reported as means ± SD, medians, and 5th and 95th percentiles, their use facilitates the study of parasympathetic and sympathetic activity in comparable populations. ©2002 by Excerpta Medica, Inc.

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There are currently no data on heart rate variability (HRV) measures from a large cohort of normal newborns. In addition, there are methodologic differences among various studies reporting HRV. In most studies, HRV is measured either by long-term recordings, usually for 24 hours, or by short-term recordings of 2 to15 minutes. Short-term recordings of 2 to 15 minutes HRV measure high- and low-frequency components that correlate well with 24-hour high- and low-frequency data.[1] Recently, the European and North American Task Force Report[2] concluded that the very low-frequency component of the spectrum obtained from the short-term recordings is of questionable validity. In addition to the duration of the recording, differences exist in both the reported units and in the definition of frequency-domain variables. Among the various clinical applications, HRV measurements in newborns have the potential to predict future mental development.[3] The availability of normative data on HRV measured from a large sample of normal newborns would facilitate the evaluation and application of this modality in a variety of clinical settings. In this study, we used long-term heart rate recordings of normal newborns: (1) to establish normal values for frequency-, geometric-, and time-domain indexes, and (2) to validate correlations between similar frequency-, geometric-, and time-domain variables.

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METHODS

Selection criteria: All newborns were recruited from the level I normal newborn nursery at our primary institution from 1997 to 2000. This study included asymptomatic infants who were between 24 and 72 hours old, weighed >2,400 grams, and had a gestational period of between 36 and 42 weeks. A convenience sampling strategy was used. Infants were excluded from the study if they were: (1) born to mothers who used any medications during pregnancy known to affect the cardiovascular system (e.g., bronchodilators); (2) born to mothers with acute or chronic diseases, such as hypertension, hepatitis, diabetes, sepsis, or immune deficiency syndromes; (3) symptomatic or required administration of oxygen for >5 minutes, ventilatory support, or admission to the neonatal intensive care unit; or (4) born with associated congenital anomalies. All infants had 2-dimensional echocardiograms and Doppler examinations; if they were found to have significant cardiac defects (except patent ductus arteriosus, patent foramen ovale or physiologic mitral, tricuspid, or pulmonary regurgitation), they were excluded from the study. In addition, all infants had a negative history and laboratory values for in utero drug exposure, including smoking. At the time of enrollment, maternal urine as well as infant urine and meconium were tested for cocaine and its metabolites, barbiturates, benzodiazepines, cannabi-

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TABLE 1 Demographic Data of Normal Newborn Infants

Variable	Mean	SD	Minimum	5th Percentile	Median	95th Percentile	Maximum
Body surface area (m^2)	0.21	0.02	0.18	0.18	0.21	0.24	0.27
Birth weight (g)	3,250	414	2,445	2,600	3,238	3,875	4,608
Birth length (cm)	49.82	2.21	45.00	46.50	49.50	53.50	56.50
Gestational age (wks)	39.40	1.20	36.00	38.00	40.00	41.00	42.00
Head circumference (cm)	34.21	1.38	30.50	32.00	34.10	36.00	39.50
Apgar at 1 min	8.56	0.82	4.00	7.00	9.00	9.00	9.00
Apgar at 5 min	8.99	0.10	8.00	9.00	9.00	9.00	9.00
Maternal age	22.04	3.76	18.00	18.00	21.00	29.00	37.00
Prenatal visits	7.90	3.43	1.00	2.00	8.00	14.00	15.00
Gravida	2.78	1.63	1.00	1.00	2.00	6.00	10.00
Parity	2.19	1.13	1.00	1.00	2.00	4.00	8.00
Maternal education	11.70	1.58	7.00	9.00	12.00	15.00	16.00

noids, opiates, phencycladine, amphetamines, and cotinine.

Demographic and medical characteristics at the time of each infant's birth were abstracted from the hospital record. These included maternal race, age, gravidity, parity, number of prenatal care visits, infant Apgar scores, birth weight, length, head circumference, estimated gestational age, and maternal education (years of schooling). The study was approved by the Institutional Review Board for human investigation. Informed written consent was obtained from the legal guardians and/or parents of all participants.

Holter monitoring: Three-channel Holter monitors (Marquette M-8500, 3 channel recorders, Milwaukee, Wisconsin) were placed within the first 72 hours of life. Holter recordings were obtained for 24 hours. After skin preparation, electrodes were placed to record leads II, V_1, and V_5. A 1-mV calibration signal was recorded. A built-in clock started after electrode attachment.

A digital commercial Holter scanner (Pathfinder 700 Series, Reynolds Medical Ltd, Hertford, United Kingdom) was used to analyze rhythm and HRV (time-, frequency-, and geometric-domain indexes) from the Holter tapes. The system's electrocardiographic sampling rate, after analog-to-digital conversion, is 125 Hz. The method of QRS detection is by level detector, but it was manually overread by a physician. The analog-to-digital converter has 12-bit resolution, with a quantization level (step size) of 2.5 μV and a dynamic range of 10 mV. All tapes were edited to assure accuracy of QRS classification. Ectopic beats, noisy data, and artifacts were manually identified and then excluded from the HRV analysis. Nonstationarities were avoided by trigger adjustment. Average hourly heart rates were determined from the computerized Holter scanner. Maximum, minimum, and mean 24-hour heart rates with SDs were calculated for each subject.

The following 6 time-domain parameters were measured from the Holter tapes: (1) the average of all normal-to-normal beats (mean NN interval) (mean heart rate); (2) the sum of all pairs of adjacent NN intervals differing by $>$50 ms (s-NN50), standardized for the total of invalid intervals and the length of the recording; (3) the SD of all valid NN intervals (SDNN) in the recording with no adjustments for recording length; (4) SD of the average of valid NN intervals (SDANN) in 5-minute segments in the recording with no adjustments for recording length; (5) the average of the hourly means of SDs of all NN intervals (SDNNi) in 5-minute segments in the recording with no adjustments for recording length; and (6) the average of the hourly square root of the mean of the sum of the squares of differences between adjacent NN intervals (r-MSSD) with no adjustments for recording length.

We also measured the geometric index (HRV triangular index), which is the total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7.8125 ms, and with no adjustment for recording length.

Additionally, the following frequency-domain parameters (fast-Fourier transformation) were obtained (power is expressed as square milliseconds): high-frequency power (frequency range 0.15 to 0.40 Hz); low-frequency power (frequency range 0.04 to 0.15 Hz); very low-frequency power (frequency range 0.0033 to 0.04 Hz); ultra low-frequency power (frequency range $<$0.0033 Hz; and total frequency power (frequencies $<$0.4 Hz).[2]

Statistical analysis: A reliability analysis was performed by the 2 operators who participated in the study. Fourteen tapes (randomly selected) were assessed once by each of the operators and the intraclass correlations were considered to be fair to excellent (range 0.40 to 0.88). The correlations for the time-domain parameters ranged from 0.73 to 0.88, whereas the correlations for the frequency-domain parameters ranged from 0.40 to 0.62, with a high frequency of 0.62. Repeated assessments on 8 randomly selected tapes were performed by 1 of the operators. The intraclass correlations were all excellent (range 0.90 to 0.99), with 11 of 16 $\geq$0.98.

Data were analyzed using SAS V8.0 (SAS Inc., Chapel Hill, North Carolina). The data are descriptively presented as means $\pm$ SD, medians, and 5th and 95th percentiles in Tables 1 to 3. Spearman's rank correlation coefficients are used to quantify the relation between the HRV parameters. This is a nonparametric alternative to the product moment (Pearson's)

TABLE 2 Heart Rate Variability Data in 96 Newborns

Variable	Mean	SD	Minimum	5th Percentile	Median	95th Percentile	Maximum
Mean heart rate (beats/min)	130.28	8.22	109.00	114.00	132.00	143.00	145.00
Mean NN (ms)	456.78	30.77	408.00	414.00	450.00	522.00	545.00
HF	59.45	42.89	11.49	14.64	44.96	148.92	218.37
LF	139.22	79.57	40.81	45.68	117.16	277.18	506.78
LF/HF	2.69	0.93	1.21	1.57	2.44	4.68	5.91
Very LF	272.08	201.12	41.24	87.18	219.98	680.21	1,208.46
Ultra LF	654.63	570.36	66.31	211.25	495.45	1,320.12	4,713.78
Total frequency	1,125	760	221	396	933	2,675	5,549
HRV triangular index	14.05	4.12	7.00	8	13.00	22	27
SDNN (ms)	47.00	12.17	24.00	30.00	44.50	75.00	90.00
SDANN (ms)	34.73	9.08	17.00	21.00	33.00	51.00	61.00
SDNNi (ms)	30.54	9.37	11.00	19.00	29.00	50.00	64.00
r-MSSD (ms)	21.58	6.57	12.00	14.00	19.00	33.00	52.00
s-NN50 (total)	5,075	4,709	604	967	3,532	15,798	26,427

The power of the frequency = domain parameters is expressed as square milliseconds.
HF = high frequency; LF = low frequency.

TABLE 3 Spearman Correlation Coefficients in 96 Normal Newborns

Variable	Mean HR	SDNN	SDANN	SDNNi	r-MSSD	s-NN50
HF	−0.34*	0.54*	0.33*	0.61*	0.85*	0.87*
LF	−0.50*	0.72*	0.50*	0.79*	0.72*	0.73*
LF/HF	−0.04	−0.04	0.07	−0.08	−0.61*	−0.64*
Very LF	−0.48*	0.67*	0.61*	0.77*	0.59*	0.54*
Ultra LF	−0.49*	0.72*	0.80*	0.64*	0.42*	0.38*
Total frequency	−0.52*	0.77*	0.78*	0.77*	0.61*	0.57*
HRV triangular index	−0.59*	0.93*	0.71*	0.80*	0.46*	0.46*

*Correlation coefficients that are significant ($p < 0.05$).
In addition, the HRV triangular index correlated significantly ($p < 0.05$) with frequency-domain parameters, including high-frequency (HF) power ($r = 0.41$), low-frequency (LF) power ($r = 0.59$), very LF power ($r = 0.58$), ultra LF power ($r = 0.65$), and total power ($r = 0.67$).

correlation in that the assumption of bivariate normality can be relaxed. This was chosen because the Holter monitor data are not normally distributed. Each correlation coefficient is tested to determine if it significantly different from zero.

RESULTS

Ninety-six asymptomatic infants who were <72 hours old were studied. The racial distribution of neonates in this study was Caucasian (21%), African-American (66%), and others (13%). Fifty-two percent of the infants were males. All infants survived beyond 1 year of age; there were no sudden deaths or apparent life-threatening events. Other demographic and medical characteristics of these infants are listed in Table 1. The length of analyzable data was 18.5 ± 4.9 hours (median 20.28; range 2.37 to 23.76). Only 8 of 96 subjects had analyzable data for <12 hours.

The reported frequency-domain parameters include high, low, very low, ultra low, total frequency (square milliseconds), and the ratio of low- to high-frequency power. The time-domain parameters SDNN, SDANN, SDNNi, r-MSSD are reported in milliseconds, but s-NN50 represents the total count (Table 2).

Major frequency-domain measures correlated well with certain time-domain measures (Table 3). Variables that were dependent on vagal tone, such as high-frequency power, were significantly ($p < 0.001$) correlated with r-MSSD and s-NN50. There was no significant correlation ($p > 0.05$) between various HRV parameters and body surface area, birth weight, birth length, head circumference, Apgar score, or gestational age.

DISCUSSION

This is the first study to report long-term (24 hour) HRV parameters in a large cohort of normal newborns measured by time-, geometric-, and frequency-domain methods. In addition, vagal tone dependent parameters such as high-frequency power (frequency domain) and r-MSSD and s-NN50 (time domain) had a high degree of correlation. These findings are similar to those reported in adults[4] and in 200 healthy children and 200 children with congenital heart disease (aged 3 days to 14 years) who did or did not undergo surgery.[5]

There have been very few reports of HRV in healthy newborns. Additionally, because of the different methods used to obtain the data, a small number of subjects, and variations in the reported units, previous studies have failed to establish normal ranges. The reported data on 3-week old healthy infants ($n = 8$) were similar to the mean SDNN (45 vs 47), SDANN (36 vs 34.73), and the ratio of low- to high-frequency power (2.7 vs 2.69)[6] from the present study. However, data on low- and high-frequency power could not be compared due to differences in reported units. Four

additional reports of frequency domains on small samples (20, 24, 16, and 16, respectively) of healthy newborns also reported data in different units.[7–10] In another study, normal ranges of HRV in 3- to 7-day old infants (n = 10) were reported in graphic form only.[11] Data on vagal tone reported by Porges[12] are based on short-term recordings of 5 minutes and the HRV is represented as the natural logarithm in the frequency range of 0.24 to 1.04 Hz.

Vagal tone is the principal contributor to the high-frequency power of HRV, whereas vagal and sympathetic tones together influence the lower frequencies. Therefore, the ratio of low- to high-frequency power reflects sympathetic-parasympathetic balance and is an expression of sympathetic modulations on the heart rate.[2] Although spectral analysis has the advantage of identifying all frequency components of HRV, the precise physiologic correlates of the lower frequency parameters are unknown. Furthermore, spectral analysis provides a time-averaged estimate of power assuming stationarity of data, and is more prone to errors with artifacts, arrhythmias, and noisy data. As a result, manual editing is needed to identify and label the NN intervals, as was done in this study. Manual interference may result in a subjective bias. However, intraclass correlations were good between the 2 operators in this study. Time-domain analysis, in contrast, is less influenced by artifacts and ectopic beats, but provides limited information on HRV at lower frequencies. The intraclass correlations for time-domain parameters were excellent in the present study. The geometric method is also less likely to be influenced by the quality of the recording; however, it provides limited spectra of HRV, is not widely used, and is appropriate for long-term recordings only. Because most of our Holter monitor studies (88 of 96) included $\geq$12 hours of analyzable data, we recommend a similar duration of analyzable data if other studies are compared with our data.

HRV has a significant potential in evaluating the role of autonomic nervous system fluctuations in normal subjects and in patients with disorders characterized by autonomic dysfunction.[13,14] It can also aid in better understanding of disease mechanisms[15,16] and in the study of the action of certain drugs.[17] Vagal tone measurements in newborns and infants have been used to predict behavioral and psychological development and information processing.[18,19] These indexes may provide a marker for determining the likely outcome of fetal and neonatal disorders on behavior and development. Decreased HRV indicates a disturbance of autonomic function or decreased ability of the sinus node to respond to extrinsic signals. Decreased HRV, which may be a marker of "poor health," is seen in many conditions, e.g., diabetes with poor metabolic control,[20] congestive heart failure,[21] and major depression.[22] In contrast, "healthy" habits like physical training increase HRV, primarily through increased vagal tone.[23]

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