

Determinants of Heart Rate Variability

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Objectives. This study sought to examine clinical determinants of heart rate variability and to report normative reference values for eight heart rate variability measures.

Background. Although the clinical implications of heart rate variability have been described, clinical determinants and normative values of heart rate variability measures have not been studied systematically in a large community-based population.

Methods. The first 2 h of ambulatory electrocardiographic recordings obtained in Framingham Heart Study subjects attending a routine examination were reprocessed for heart rate variability. Recordings with transient or persistent nonsinus rhythm, premature beats >10% of total beats, <1-h recording time or processed time <50% of recorded time were excluded; subjects receiving antiarrhythmic medications also were excluded. Among five frequency domain and three time domain measures that were obtained, low frequency power (0.04 to 0.15 Hz), high frequency power (0.15 to 0.40 Hz) and the standard deviation of total normal RR intervals based on 2-h recordings were selected for the principal analyses. Variables with potential physiologic effects or possible technical influences on heart rate variability measures were chosen for multiple linear regression analysis. Normative

values, derived from a subset of healthy subjects, were adjusted for age and heart rate.

Results. There were 2,722 eligible subjects with a mean age ($\pm$ SD) of 55 ± 14 years. Three separate multiple linear regression analyses revealed that higher heart rate, older age, beta-adrenergic blocking agent use, history of myocardial infarction or congestive heart failure, diuretic use, diastolic blood pressure ≥ 90 mm Hg, diabetes mellitus, consumption of three or more cups of coffee per day and smoking were associated with lower values of one or more heart rate variability measures, whereas longer processed time, start time in the morning, frequent supraventricular and ventricular premature beats, female gender and systolic blood pressure ≥ 160 mm Hg were associated with higher values. Age and heart rate were the major determinants of all three selected heart rate variability measures (partial R^2 values 0.125 to 0.389). Normative reference values for all eight heart rate variability measures are presented.

Conclusions. Age and heart rate must be taken into account when assessing heart rate variability.

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Reduced beat to beat variability in RR intervals, commonly referred to as heart rate variability, is observed in patients with congestive heart failure (1), coronary heart disease (2,3) and diabetic neuropathy (4-6). Various physiologic factors also affect heart rate variability, including aging (7), postural changes (8) and time of day (9). Although prognostic (10-15) and other clinical implications (16-21) of altered heart rate variability have been described, the clinical determinants of heart rate variability have not been studied systematically. Few

previous studies have reported normative reference values for heart rate variability measures (22-24).

The objectives of the present study were to assess clinical determinants of heart rate variability and to provide normative values for several heart rate variability measures as a function of age and heart rate. This investigation was performed in a large population-based sample in which referral bias was inherently minimal.

Methods

Study sample. In 1948, 5,209 residents of Framingham, Massachusetts, who were between the ages of 28 and 62 years, were selected to undergo biennial examinations in a prospective epidemiologic study. In 1971, 5,124 additional subjects (offspring of the original cohort and spouses of these offspring) entered a similar prospective study. Selection criteria and study design have been previously reported (25,26). From 1983 to 1987, ambulatory electrocardiographic (ECG) recordings were obtained in surviving study subjects attending a routine, scheduled examination.

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Abbreviations and Acronyms

ECG	= electrocardiographic
LF/HF	= low frequency/high frequency power ratio
PNN50	= percentage of differences between adjacent normal RR intervals >50 ms
r-MSSD	= square root of the mean of the squared differences between adjacent normal RR intervals
SDNN	= standard deviation of normal RR intervals

Processing of ambulatory recordings. The first 2 h of ambulatory recordings were processed for heart rate variability using a Cardiodata/Mortara Mk5 Holter analysis system. The tape speed was 1 mm/s, and one channel was used to record a 32-Hz crystal-controlled timing track. For heart rate variability analysis, tapes were played back at 120 times real time on a Cardiodata/Mortara Mk5 Holter analysis system (Mortara Instrument Co.) that sampled each ECG channel at 180 samples/s. The playback incorporated a phase-locked loop using the recorded timing track to compensate for errors in recorder speed control. Beat to beat RR interval data were obtained from the "beat stream file." A linearly interpolated beat was substituted for intervals of ectopic beats or artifact less than or equal to two RR intervals (27). The fast Fourier transform was calculated on 100-s blocks of RR interval data. A continuous curve was formed by linear interpolation between RR intervals; this was subjected to a Hamming window and resampled at 1.28 times/s. If there was a run of arrhythmia or artifact >1 beat long, the 100-s block was terminated, the partial block was discarded, and a new block was started at the end of the unusable period. Power density spectrum was estimated by taking the sum of the squares of the magnitude of the fast Fourier transform performed on all usable 100-s blocks (27). The resulting 100-s power spectra were corrected for attenuation resulting from sampling and the Hamming window and were averaged. Although the resulting frequency range of the power spectra was 0.01 to 0.64 Hz, we restricted our analyses to frequencies ≤ 0.40 Hz to maintain comparability of the high frequency component of our data with previous reports (11,12). The 100-s method was intended to avoid any assumptions about sinus node activity in consecutive arrhythmias in which sinus node activity was unknown. When longer time blocks are used, larger amounts of data are discarded because of consecutive premature beats or artifact. In contrast, when shorter time blocks are used, the minimal frequency for which the power spectrum can be measured is >0.01 Hz. We computed the 2-h power spectral density and calculated five frequency domain measures: 1) very low frequency power (0.01 to 0.04 Hz); 2) low frequency power (0.04 to 0.15 Hz); 3) high frequency power (0.15 to 0.40 Hz); 4) total power (0.01 to 0.40 Hz); and 5) the ratio of low frequency to high frequency power (LF/HF). In addition, we computed three time domain measures: 1) standard deviation of normal RR intervals (SDNN); 2) the percentage of differences between adjacent normal RR intervals >50 ms (pNN50); and 3) the square root

of the mean of the squared differences between adjacent normal RR intervals (r-MSSD). Time domain variables were calculated from the 100-s segments used to calculate the frequency domain variables. Because SDNN theoretically increases as a function of recording time, the term 2-h SDNN is used hereafter.

We selected high and low frequency power as frequency domain measures for further analyses because the physiologic meaning of high frequency power has been delineated (28), and low frequency power was predictive of prognosis in the elderly population of the Framingham Heart Study (13). Also, both measures are compatible with those of previous reports and are not dependent on the 100-s block method (29). In addition to these two measures, 2-h SDNN was selected because it is conceptually a simpler measure of heart rate variability.

Normal QRS complexes and arrhythmias were diagnosed under constant visual monitoring. Supraventricular premature beats were differentiated from sinus arrhythmia on the basis of P wave configuration and cyclic changes in RR intervals. For a tape to be eligible for this study, we required that it have ≥ 60 min of analyzable data (11,12), at least 50% time processed and premature beats $<10\%$ of total beats (30).

Clinical covariates. Risk factors possibly predisposing to coronary heart disease were recorded at each examination (25). Variables that might be associated with autonomic function were also considered, including coffee and alcohol consumption, current cigarette smoking and use of cardioactive medications. Average reported alcohol consumption was converted to ounces of alcohol/week assuming that a 12-oz bottle or can of beer had 0.44 oz of alcohol, a glass of wine 0.40 oz and a measure of spirits 0.57 oz (31).

Systolic and diastolic blood pressures were obtained twice in the seated position by the examining physician using a mercury column sphygmomanometer positioned near eye level. The average of the two readings was used for each blood pressure variable. *Diabetes* was defined on the basis of a nonfasting blood glucose level ≥ 200 mg/dl (11.10 mmol/liter) or the use of insulin or an oral hypoglycemic agent. Heart rate was calculated as the mean value obtained on the same ambulatory monitoring recording that was processed for heart rate variability. The number of ventricular premature beats/hour was analyzed as a continuous variable, but supraventricular premature beats were recoded into three groups as follows: <120 /h, 120 to 240/h and >240 /h.

The Framingham definitions of myocardial infarction and congestive heart failure have been described elsewhere (32). At each follow-up examination, interim cardiovascular events were assessed with the help of medical history, physical examination and the 12-lead ECG. In addition, medical records were obtained for participants who did not attend an examination, and these were evaluated for evidence of interim heart disease. All suspected interim events were reviewed by a committee of three physicians who evaluated pertinent medical records, hospital records and pathology reports.

Table 1. Pearson Correlations Among Measures of Heart Rate Variability*

	ln VLF†	ln LF	ln HF	ln TP†	ln LF/HF Ratio	ln 2-h SDNN	ln pNN50	ln r-MSSD
Mean	7.37	6.44	5.31	7.82	1.12	4.41	1.50	3.36
SD	0.74	0.90	0.93	0.76	0.51	0.34	1.33	0.46
ln VLF†		0.88	0.76	0.98	0.38	0.89	0.70	0.68
ln LF			0.84	0.95	0.24	0.81	0.73	0.71
ln HF				0.85	-0.32	0.75	0.91	0.92
ln TP†					0.14	0.89	0.77	0.75
ln LF/HF ratio						0.07	-0.35	-0.41
ln 2-h SDNN							0.70	0.69
ln pNN50								0.93

*Although all correlations differ from zero with statistical significance at $p < 0.0001$, only those >0.80 are considered high correlations in this context. †Based on a 100-sampling method, which yields a minimal frequency of 0.01 Hz. HF = high frequency power; LF = low frequency power; pNN50 = percentage of differences between normal RR intervals >50 ms; r-MSSD = root-mean-square of successive differences; TP = total frequency power; VLF = very low frequency power; 2-h SDNN = standard deviation of normal RR intervals based on 2-h recordings.

Statistical methods. Measures of heart rate variability were natural log transformed because their distributions were highly skewed. Associations among transformed variables were assessed with Pearson's correlation coefficients. In preliminary analyses, mean values of heart rate variability measures were plotted against age (grouped in 10-year intervals) and heart rate (grouped in 10-beat/min intervals) to verify that the relations were linear with constant variance.

The principal analyses consisted of three forward stepwise multiple linear regression procedures (33) to select variables related to heart rate variability (i.e., ln 2-h SDNN, ln low frequency power, ln high frequency power) from among 16 candidate variables: age, gender, heart rate, starting time of monitoring (AM or PM), total processed time (≤ 90 vs. >90 min), systolic (<160 vs. ≥ 160 mm Hg) and diastolic (<90 vs. ≥ 90 mm Hg) blood pressure, number of ventricular premature beats/h, number of supraventricular premature beats/h (<120 vs. 120 to 240 vs. >240), history of myocardial infarction or congestive heart failure (no vs. yes), presence of diabetes mellitus (no vs. yes), use of beta-adrenergic blocking agents (no vs. yes), use of diuretic drugs (no vs. yes), smoking (no vs. yes), coffee consumption (0 vs. 1 to 2 vs. ≥ 3 cups/day) and alcohol intake (0 vs. 1 to 2 vs. ≥ 3 oz/week). These variables were chosen because of their potential physiologic effects on measures of heart rate variability or because of a possible technical influence on the measurement. The Statistical Analysis System procedure REG (34) was used, and each categorical variable was encoded by dummy indicators that were entered or removed as a group. Whereas it is common to define statistical significance with a Type I error rate of alpha 0.05, we adopted a more stringent alpha 0.001 for testing multiple variables across three outcomes; furthermore, we defined an "important" variable as one that contributed a partial R^2 statistic ≥ 0.005 .

Normative values of heart rate variability were generated from a subset of subjects who were free of coronary heart disease, cerebrovascular disease, congestive heart failure and

diabetes mellitus and who were not receiving cardioactive medications. We further restricted this reference sample to subjects 20 to 79 years old with heart rates between 40 and 99 beats/min. Linear regression was used with the log-transformed data to account for age and heart rate. Estimates were made of the 5th, 25th and 50th percentile values by applying normal theory to the natural log-transformed data before transforming back to the original units.

Results

Of the 10,333 original and offspring Framingham Heart Study subjects, 5,698 attended the index examination. There were 2,278 (40%) subjects in whom ambulatory recordings were not obtained. Ambulatory ECGs were obtained from June 1983 to September 1987. Subjects who attended corresponding examinations, but who did not have ambulatory ECGs, spanned a similar period (April 1983 to June 1987). Some basic statistics on subjects who had (vs. those who did not have) ambulatory ECG recordings are as follows: 52% (vs. 55%) women, mean age 56 (vs. 58) years, age range 21 to 93 (vs. 18 to 94) years, mean systolic/diastolic blood pressure 129/78 (vs. 130/78) mm Hg. Thus, the two groups were comparable; there was no evidence of selection bias. Among 3,420 subjects with tapes analyzed, 698 were excluded from analysis, mostly due to excessive artifact ($n = 500$). Compared with excluded subjects ($n = 698$), those who were analyzed were younger (age 55 vs. 62 years, analyzed vs. excluded) but had the same gender distribution (55% vs. 53% female) and had similar blood pressure (129/78 vs. 133/78 mm Hg) and mean heart rate (73 vs. 74 beats/min). The mean age of the 2,722 eligible subjects was 55 years (range 21 to 93), and 1,236 (45%) were men. The mean heart rate ($\pm$ SD) was 73 ± 11 beats/min. A history of myocardial infarction was present in 107 subjects (4%) and congestive heart failure in 17 (1%); diabetes was present in 127 subjects (5%).

Table 2. Clinical Variables and Mean Values for Heart Rate Variability Measures

	No. of Pts	ln 2-h SDNN*	ln LF*	ln HF*
Age (yr)				
<40	442	4.61 ± 0.27	7.16 ± 0.56	6.05 ± 0.81
40-49	660	4.53 ± 0.28	6.89 ± 0.63	5.62 ± 0.79
50-59	594	4.44 ± 0.33	6.48 ± 0.78	5.21 ± 0.81
60-69	561	4.31 ± 0.32	6.02 ± 0.74	4.91 ± 0.78
≥70	465	4.14 ± 0.33	5.54 ± 0.83	4.77 ± 0.90
Gender				
Male	1,236	4.44 ± 0.34	6.55 ± 0.96	5.30 ± 0.92
Female	1,486	4.39 ± 0.35	6.34 ± 0.90	5.32 ± 0.93
HR (beats/min)				
<60	229	4.66 ± 0.32	6.77 ± 0.87	5.88 ± 0.86
60-69	791	4.53 ± 0.31	6.65 ± 0.86	5.56 ± 0.90
70-79	997	4.42 ± 0.28	6.51 ± 0.78	5.32 ± 0.82
80-89	512	4.25 ± 0.31	6.12 ± 0.87	4.97 ± 0.85
≥90	193	4.02 ± 0.36	5.59 ± 1.07	4.52 ± 0.92
History of MI or CHF				
Yes	113	4.17 ± 0.38	5.13 ± 1.04	4.69 ± 0.66
No	2,609	4.42 ± 0.34	6.47 ± 0.88	5.34 ± 0.92
SBP (mm Hg)				
≥160	194	4.21 ± 0.37	5.77 ± 0.89	4.91 ± 0.90
<160	2,528	4.43 ± 0.34	6.49 ± 0.88	5.34 ± 0.92
DBP (mm Hg)				
≥90	342	4.33 ± 0.33	6.25 ± 0.83	5.06 ± 0.80
<90	2,379	4.42 ± 0.34	6.46 ± 0.91	5.35 ± 0.94
Diabetes mellitus				
Yes	127	4.15 ± 0.38	5.50 ± 0.97	4.71 ± 0.91
No	2,395	4.42 ± 0.34	6.48 ± 0.88	5.34 ± 0.92
Medications				
Beta-blockers				
Yes	277	4.33 ± 0.35	6.02 ± 0.87	5.17 ± 0.89
No	2,445	4.42 ± 0.34	6.48 ± 0.90	5.33 ± 0.93
Calcium antagonists				
Yes	31	4.27 ± 0.36	5.99 ± 0.95	5.03 ± 0.81
No	2,691	4.41 ± 0.34	6.44 ± 0.90	5.32 ± 0.93
Digitalis				
Yes	28	4.19 ± 0.30	5.58 ± 1.06	4.92 ± 0.91
No	2,691	4.41 ± 0.34	6.45 ± 0.90	5.32 ± 0.93
Diuretic drugs				
Yes	431	4.23 ± 0.37	5.76 ± 0.95	4.90 ± 0.97
No	2,291	4.45 ± 0.33	6.56 ± 0.84	5.39 ± 0.90
Smoking				
Yes	680	4.39 ± 0.33	6.42 ± 0.86	5.29 ± 0.92
No	2,040	4.42 ± 0.35	6.44 ± 0.92	5.32 ± 0.93
Coffee (cups/day)				
None	739	4.39 ± 0.36	6.37 ± 0.92	5.33 ± 0.94
1-2	1,035	4.40 ± 0.36	6.37 ± 0.96	5.28 ± 0.98
≥3	945	4.44 ± 0.32	6.56 ± 0.81	5.34 ± 0.86
Alcohol (oz/wk)				
None	900	4.34 ± 0.36	6.24 ± 0.95	5.14 ± 0.93
1-2	722	4.45 ± 0.33	6.52 ± 0.89	5.43 ± 0.95
≥3	1,090	4.44 ± 0.33	6.54 ± 0.86	5.37 ± 0.89
Start time				
AM	2,094	4.49 ± 0.31	6.68 ± 0.77	5.48 ± 0.88
PM	628	4.16 ± 0.33	5.63 ± 0.83	4.76 ± 0.86
Processed time (min)				
<60	201	4.33 ± 0.40	6.43 ± 1.01	5.42 ± 1.09
60-90	856	4.38 ± 0.35	6.43 ± 0.94	5.37 ± 0.95
>90	1,665	4.44 ± 0.33	6.44 ± 0.87	5.27 ± 0.89

(continued)

Table 2 (continued).

	No. of Pts	ln 2-h SDNN*	ln LF*	ln HF*
VPBs/h				
<70	2,571	4.42 ± 0.34	6.46 ± 0.89	5.33 ± 0.92
≥30	151	4.28 ± 0.39	6.06 ± 1.01	5.08 ± 0.98
SVPBs/h				
<120	2,606	4.42 ± 0.34	6.45 ± 0.90	5.31 ± 0.93
120-240	92	4.28 ± 0.37	5.93 ± 0.91	5.36 ± 0.84
>240	24	4.46 ± 0.29	6.43 ± 0.75	5.71 ± 0.74

*Values were natural log transformed and are expressed as mean value ± SD. CHF = congestive heart failure; DBP = diastolic blood pressure; HR = heart rate; MI = myocardial infarction; SBP = systolic blood pressure; SVPBs = supraventricular premature beats; VPBs = ventricular premature beats; other abbreviations as in Table 1.

Correlations between measures of heart rate variability. Correlations between measures of heart rate variability (natural-log transformed) are presented in Table 1. These split into two major groups: the first group comprised natural log-transformed (ln) total power, ln very low frequency power, ln low frequency power and ln 2-h SDNN; the second comprised ln high frequency power, ln pNN50 and ln r-MSSD. Average within-group correlations were 0.90 for the first group and 0.92 for the second, and the average between-group correlation was 0.74. Whereas many pairwise correlations exceeded 0.80, and all correlations not involving ln LF/HF exceeded 0.67, the variable ln LF/HF correlated poorly with other variables.

Determinants of heart rate variability. Mean values for low frequency power, high frequency power and 2-h SDNN according to categories of predictor variables are shown in Table 2. Taken individually, age, gender, heart rate, history of myocardial infarction or congestive heart failure, blood pressures, diabetes, medication use (beta-blocker, digoxin, diuretic drugs), coffee and alcohol intake, morning recording time and number of ventricular premature beats/hour were associated with significant ($p < 0.001$) differences in values of two or more heart rate variability measures.

Stepwise regression analysis identified several clinical variables that were significantly associated with heart rate variability in the presence of other clinical variables (Table 3). Age and heart rate were the two most important determinants for all three heart rate variability measures (partial R^2 values 0.125 to 0.389), and beta-blocker medication also affected all three heart rate variability measures (partial R^2 values 0.005 to 0.020). Each of the heart rate variability measures decreased with advancing age, increasing heart rate and beta-blocker use. Accounting for heart rate and age actually increased the strength of the association of beta-blocker use with heart rate variability because beta-blocker users were older but had a lower heart rate than nonusers.

Predicted values of 2-h SDNN and low and high frequency power for the entire sample are plotted as a function of heart rate and age in Figures 1 to 3. Basically, heart rate variability declined with advancing age and with increasing heart rate; the

Table 3. Regression Coefficients and Partial R² Values of Clinical Variables Related to Heart Rate Variability Measures*†

Variable	ln 2-h SDNN		ln LF		ln HF	
	Coeff	Partial R ²	Coeff	Partial R ²	Coeff	Partial R ²
Age (10 yr)	-0.11	0.218	-0.36	0.389	-0.33	0.222
HR (10 beats/min)	-0.17	0.226	-0.33	0.125	-0.38	0.152
Beta-blocker use	-0.17	0.019	-0.35	0.020	-0.24	0.005
Processed time >90 min	0.08	0.013	NS	NS	-	‡
Diuretic use	-	§	-0.26	0.009	-	‡
History of MI or CHF	-	§	-0.41	0.008	-	§
Smoking	-	§	-0.18	0.007	-	§
SVPBs 120-240/h	+		+		0.67	
SVPBs >240/h	+	§	+	§	0.87	0.022
Female gender	+	‡	-	‡	0.50	0.011
Listed model (no. of terms, R ²)	4	0.475	6	0.558	6	0.413
Final model (no. of terms, R ²)	14	0.501	13	0.572	16	0.429

*Only those clinical variables contributing partial R² >0.005 to one or more heart rate variability measures are included here; whenever the partial R² exceeded 0.005, the corresponding p value was <0.0001. †Other clinical variables associated with heart rate variability measures to a lesser extent were as follows (a minus sign indicates inverse association, whereas direct association is the default): for ln 2-h SDNN, there were VPBs/h (p < 0.001), morning start time (p < 0.001) and -diastolic blood pressure ≥90 mm Hg (p < 0.05); for ln LF power, there were VPBs/h (p < 0.001), -diabetes (p < 0.001), -diastolic blood pressure ≥90 mm Hg (p < 0.05) and morning start time (p < 0.05); and for ln HF power, there were VPBs/h (p < 0.001), -diastolic blood pressure ≥90 mm Hg (p < 0.001), systolic blood pressure ≥160 mm Hg (p < 0.05) and -coffee consumption (p < 0.05). Only alcohol consumption was not associated, at p < 0.05, with any of the three heart rate variability measures. ‡Variable was marginally significant with 0.001 ≤ p < 0.05, but partial R² was <0.005. §Variable was significant with p < 0.001, but partial R² was <0.005. ||Partial R² for SVPBs demonstrated contributions from all three categories: <120/h, 120 to 240/h, >240/h. NS = variable was not significant (p ≥ 0.05) in the stepwise model. - or + = sign of regression coefficient (coeff) in the final model; other abbreviations as in Tables 1 and 2.

effect of a 10-year age difference equaled the effect of a 7- to 11-beat/min heart rate difference.

Normative values of heart rate variability measures. A subset of 1,918 subjects (mean [± SD] age 50 ± 13 years, range 20 to 79 years; 865 [45%] men; heart rate 40 to 99 beats/min) were studied to assess heart rate variability in a healthy reference sample. These subjects were without clinically apparent heart disease and were not receiving cardioactive

medications. Percentile values for all heart rate variability measures were estimated by combining regression techniques and normal statistics theory; these are shown in Table 4 for three age groups and three heart rate categories. Note that as age or heart rate increases, heart rate variability decreases—the bottom 5th percentile limit is smaller at age 70 than at age 30. Agreement between these estimated percentiles and empiric data was excellent.

Figure 1. Fitted regression lines of 2-h SDNN as a function of age and heart rate for entire study sample. Data are shown for five specific ages (35, 45, 55, 65 and 75 years) at mean heart rates between 50 and 100 beats/min.

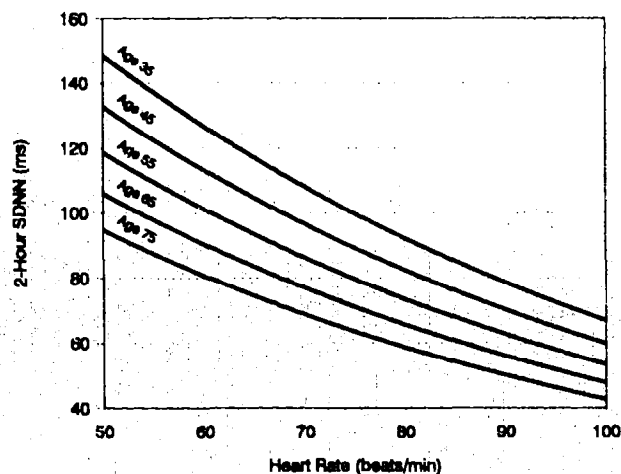
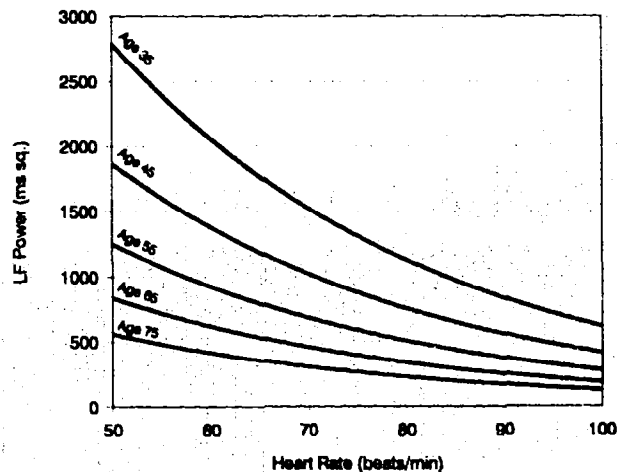


Figure 2. Fitted regression lines of low frequency (LF) power as a function of age and heart rate for entire study sample. Data are shown for five specific ages (35, 45, 55, 65 and 75 years) at mean heart rates between 50 and 100 beats/min.



Discussion

To our knowledge, this is the first report to quantitate the contributions of several determinants of heart rate variability in a large, community-based sample. Mean heart rate and age were the major determinants, together accounting for 37% to 51% of the variance of 2-h SDNN and low and high frequency power. These results confirm and supplement previous reports (7,22,35,36) that associated age and heart rate with heart rate variability.

Major determinants of heart rate variability. Heart rate was inversely associated with all eight measures of heart rate variability; this was true for all age strata and in both men and women. Heart rate accounted for 12.5% to 22.6% of the variance in 2-h SDNN and low and high frequency power. The role of heart rate should be considered when assessing interventions that affect heart rate, such as beta-blocker use (37) or exercise (38).

Consistent with previous reports (7,22,39), age was another major determinant of heart rate variability, accounting for 21.8% to 38.9% of the variance in 2-h SDNN and low and high frequency power. The impact of a 10-year increment in age was roughly that of a 10-beat/min increment in heart rate.

Other determinants of heart rate variability. After adjustment for heart rate and other covariates, beta-blocker use was significantly associated with reduced heart rate variability; it accounted for 1% to 2% of the observed variance. The impact of beta-blocker use was similar to that observed for a 10-beat/min increase in heart rate. Our data suggest, however, that if beta-blockers reduce heart rate by >10 beats/min, their use will result in a net increase in heart rate variability.

The effect of duration of recording on frequency domain measures has been reported by Bigger et al. (40). In their results, the heart rate variability values of 8-h daytime recording, computed from various short segments, were not meaningfully different from mean values obtained from a full 24-h period. In our 2-h analyses, duration of recording time had an association with high frequency power, but its contribution was very small, and no association was found with low frequency power. These data suggest that duration of recording contributes minimally to frequency domain measures of heart rate variability. In contrast, our data document that SDNN is affected by processed time: the longer the recording, the greater the fluctuations in heart rate and the larger the value of SDNN. The duration of available data should be considered in the interpretation of SDNN.

Diuretic use and smoking were associated with lower heart rate variability. Cigarette smoking has been reported (41) to reduce high frequency power. These associations might be due to biologic effects of diuretic drugs and cigarette smoking. It is also possible that left ventricular hypertrophy (42) or subclinical coronary artery disease confound these associations.

The presence of supraventricular and ventricular premature beats affected heart rate variability measures. To minimize the effect of premature complexes, we excluded subjects with premature beats >10% of total beats (30). Nevertheless,

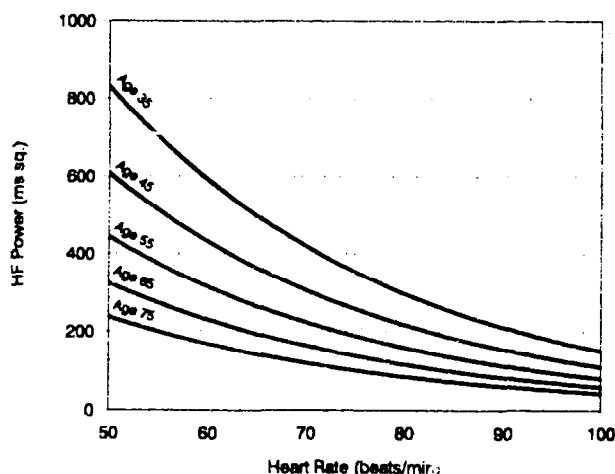


Figure 3. Fitted regression lines of high frequency (HF) power as a function of age and heart rate for entire study sample. Data are shown for five specific ages (35, 45, 55, 65 and 75 years) at mean heart rates between 50 and 100 beats/min.

frequent supraventricular premature beats substantially affected heart rate variability measures. The impact of single supraventricular premature beats was minimized by use of an interpolated correction method. Consecutive premature beats did not affect heart rate variability; when such arrhythmias occurred, the corresponding 100-s blocks were terminated and discarded. It is possible that the nonuniformity of compensatory pauses after ventricular premature beats resulted in imprecise interpolation of sinus node activity.

Heart rate variability has been reported (5) to be reduced in patients with diabetic neuropathy, but not in the presence of uncomplicated diabetes. In our study, diabetes was associated with reduced low frequency power, but not with high frequency power or SDNN. The lack of association of diabetes with high frequency power or SDNN may have been due to the small number of subjects with diabetes ($n = 127$), few of whom had diabetic neuropathy.

Minor differences in one or more heart rate variability measures were observed for gender, time of day of recording and presence of frequent ventricular premature beats.

Comparison with previous studies. A recent study by Bigger et al. (23) reported reference values for a variety of heart rate variability measures in 202 men and 72 women (40 to 69 years old, mean age 57; mean heart rate 73 beats/min). Mean values in that report were similar to those observed in our sample with a mean age of 55 years and a mean heart rate of 73 beats/min, except for total power and SDNN. The discrepancy in total power is explained by a different sampling method, whereas differences in SDNN are explained by the shorter duration of recordings in our sample. Smaller differences observed in high frequency power, LF/HF ratio and pNN50 may be due to differences in sample size and age range.

Limitations of the study. This study was based on intermediate-duration recordings, which yield different values for SDNN than shorter or longer recordings. The recordings

Table 4. Percentile Values of Heart Rate Variability Measures Predicted for Specified Ages and Heart Rates in "Healthy" Subjects*

HRV Measure	HR (beats/min)	Percentile								
		Age 30 yr			Age 50 yr			Age 70 yr		
		5th	25th	50th	5th	25th	50th	5th	25th	50th
VLF†	50	4,248	6,265	8,210	2,618	3,861	5,060	1,614	2,380	3,119
	70	1,848	2,726	3,572	1,139	1,680	2,202	702	1,035	1,357
	90	804	1,186	1,554	496	731	958	305	450	590
LF	50	1,488	2,480	3,537	718	1,196	1,705	346	576	822
	70	794	1,323	1,887	383	638	910	185	308	439
	90	424	706	1,007	204	340	485	98	164	234
HF	50	373	722	1,143	184	356	563	91	175	278
	70	181	351	556	89	173	274	44	85	135
	90	88	171	270	43	84	133	21	41	66
TP†	50	6,621	9,932	13,169	3,763	5,644	7,483	2,138	3,207	4,252
	70	3,074	4,611	6,114	1,747	2,620	3,474	993	1,489	1,974
	90	1,427	2,141	2,839	811	1,217	1,613	461	691	917
LF/HF	50	1.42	2.25	3.09	1.39	2.20	3.03	1.36	2.15	2.96
	70	1.56	2.47	3.40	1.53	2.42	3.32	1.50	2.26	3.25
	90	1.71	2.71	3.73	1.68	2.65	3.65	1.64	2.59	3.57
2-h SDNN	50	113	140	164	91	114	133	74	93	108
	70	80	99	116	65	81	94	53	66	77
	90	56	70	82	46	57	67	37	46	54
pNN50	50	13	32	61	5	14	26	2	6	11
	70	3	8	16	1	4	7	1	2	3
	90	1	2	4	<1	1	2	<1	<1	1
r-MSSD	50	40	56	70	31	43	54	24	33	42
	70	24	34	43	19	26	33	14	20	25
	90	15	21	26	11	16	20	9	12	16

*Values were generated from a subset of subjects who were free of clinically apparent coronary heart disease, cerebrovascular disease, congestive heart failure and diabetes, and who were not receiving cardioactive medications. Linear regression, adjusting for age and heart rate, was used with natural log-transformed data for heart rate variability (HRV) measures. Estimates of 5th, 25th and 50th percentile values were made by applying normal theory to the residuals of the natural log-transformed data before transforming back to the original units. †Based on a 100-s sampling method. Other abbreviations as in Table 1.

were obtained while subjects underwent an extensive clinic evaluation and are not representative of basal rest conditions. Frequency domain measures were obtained using a 100-s sampling method, which results in a lowest frequency response of 0.01 Hz. Last, the formulas for predicting normative reference values were obtained in subjects 20 to 79 years old with a heart rate of 40 to 99 beats/min and should not be extrapolated to values of age or heart rate outside these ranges.

Conclusions. There are many clinical variables associated with reduced or increased heart rate variability. The impact of age and heart rate must be taken into account when evaluating heart rate variability.

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