Increased total heart rate variability and enhanced cardiac vagal autonomic activity in healthy humans with sinus bradycardia

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Sinus bradycardia can be defined as a sinus rhythm with a resting heart rate of 60 beats per minute or less. While it is assumed that increased autonomic parasympathetic activity is associated with sinus bradycardia, such an association has yet to be proven. The aims of this study were to compute a number of heart rate variability (HRV) parameters in healthy individuals with sinus bradycardia and determine whether there was a significant vagal component to sinus bradycardia. Forty-three healthy adults with normal sinus rhythm and 25 healthy adults with sinus bradycardia had an electrocardiogram recorded for 20 minutes, from which HRV indices were calculated. Results showed significant increases in SDNN (standard deviation of NN intervals) ($P < 0.05$), RMSDD (square root of the mean squared differences of successive NN intervals) ($P < 0.05$), and DFA32 (detrended fluctuation analysis) ($P < 0.05$) in bradycardic subjects compared with subjects with normal sinus rhythm. There were no significant differences in sympathetic frequency domain indices between the two groups. In conclusion, there were significant increases in total heart variability and increased parasympathetic drive in subjects with bradycardia. Clinically, bradycardia is likely to be cardioprotective in aging populations based upon these HRV findings.

Sinus bradycardia can be defined as a sinus rhythm with a resting heart rate (HR) of 60 beats per minute (bpm) or less. However, few patients actually become symptomatic until their heart rate drops to <50 bpm (1). That is, even while resting HR tends to diminish with age (2), physiological regulatory mechanisms maintain normal cardiac output by increasing stroke output both at rest and during exercise (2).

Sinus bradycardia is not commonly included among relevant biomarkers precipitating overt cardiovascular disease (1); a low resting sinus rate even appears to be a protecting factor against heart failure, but a high sinus rate emerged as an independent predictor of mortality in prospective studies carried out in the general population (3) and in selected groups of patients with hypertension (4) or myocardial infarction (5).

Commonly, sinus bradycardia is an incidental finding in otherwise healthy individuals, particularly in adults or sleeping patients. However, it remains unknown whether the autonomic nervous system has a significant influence on the maintenance of sinus bradycardia. Although it is assumed that the vagal system is contributory toward sinus bradycardia (2), actual data relating to cardiac autonomic indices of asymptomatic patients with resting heart rates of <60 bpm are lacking. However, considerable effort has gone into describing resting HR being modulated by a balance between sympathetic and parasympathetic tone with a predominance of the latter (6, 7). On this basis, some reports state that an increased vagal tonus is the main mechanism for the bradycardia induced by aerobic and/or endurance physical training (8). However, several other studies have failed to demonstrate differences in vagal tone between trained and untrained subjects (9, 10). Thus, our aims were to study healthy asymptomatic subjects with sinus bradycardia, calculate their cardiac heart rate variability (HRV) indices, and contrast these results with those of a group of subjects with normal sinus HR.

METHODS

To be included in this study, human subjects had to be at least 45 years old with no known diabetes or other cardiovascular health problems. Participants were excluded from the analysis if any cardiovascular anomaly was reported or identified on the electrocardiogram (ECG) trace (apart from sinus bradycardia) as well as if the ECG trace contained excessive noise. A standard three-lead ECG was obtained from 43 subjects (15 men and 28 women; mean age 54 ± 11 years SD) who had normal sinus rhythm and from 25 subjects (8 men and 17 women; mean age 57 ± 11 years SD) with sinus bradycardia. ECG data were acquired using a Maclab system (AD Instruments) and Chart (version 5). The ECG sampling rate was 400 samples per second with filters set to recommended levels to minimize baseline noise. A 20-minute ECG was recorded while the subject was in a resting supine position.

HRV was analyzed using the program Soft-ECG (copyright Herbert Jelinek). Before the Macintosh ECG recording was

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Table 1. HRV definitions

Parameter	Units	Description
Frequency domain analysis		
Total power	ms^2	Variance of normal-to-normal (NN) intervals (i.e., from one QRS point of the ECG to the next) over the temporal segment. Used as a global index/measure of total HRV. (Frequency range: ~<0.4 Hz)
HF (high frequency)	ms^2	Power in high-frequency range. High power in this domain is associated with increased parasympathetic function/drive. (Frequency range: 0.15–0.04 Hz)
LF (low frequency)	ms^2	Power in low-frequency range. Usually consists of a parasympathetic and sympathetic component. High power in this domain is associated with increased sympathetic tone. (Frequency range: 0.04–0.15 Hz)
HF ln		HF power in logarithmic form. Can be used if distribution is skewed.
LF ln		LF power in logarithmic form. Can be used if distribution is skewed.
HF norm	nu	HF power in normalized units—to reduce the effects of noise/artifacts and to minimize the effects of changes in total power on LF and HF components.
LF norm	nu	LF power in normalized units—useful when evaluating subjects with varying differences in total power.
LF/HF		Ratio of low- to high-frequency power. An increase in the ratio suggests an increase in sympathetic modulation, a decrease in parasympathetic modulation, or both.
Time domain analysis: The heart rate at any point in time or the intervals between successive normal complexes. In a continuous ECG record, each QRS complex is detected, as well as the so-called normal-to-normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarizations).		
SDNN (standard deviation of NN intervals)	ms	Standard deviation of all NN intervals, reflecting all the cyclic components responsible for variability. A global marker of HRV, encompassing parasympathetic and sympathetic influences.
RMSSD (square root of the mean squared differences of successive NN intervals)	ms	The square root of the mean of the sum of the squares of differences between adjacent NN intervals. It evaluates components that have a short-term effect on HRV, corresponding to parasympathetic activity.
Nonlinear analysis		
DFA (detrended fluctuation analysis) $\alpha 1$ and $\alpha 2$		Reveals distinct fractal features of HRV. Scale invariance has been commonly observed with a characteristic break at segment sizes of 16 heartbeats. Consequently, two scaling exponents, termed $\alpha 1$ and $\alpha 2$, are computed in the ranges of 4 to 16 and 16 to 64 heart beats, respectively.
DFA32		Fluctuation seen within one time domain at 32 beats.
ApEN (approximate entropy)		An estimation of the overall regularity and complexity of time series data. A low ApEn value indicates more regular and less complex data, whereas a high value indicates a more irregular data set with high complexity.

ECG indicates electrocardiogram; HRV, heart rate variability.

converted into Soft-ECG format, the digital ECG trace was manually edited to remove any movement artifacts and ectopic beats (11). Soft-ECG then converts the raw ECG trace into an R-R interval graph for analysis. R-R intervals are determined by using the criteria for detecting the fiducial point of the QRS wave (12). Once converted into an R-R graph, further intervals greater and smaller than 200 ms from the mean interval length were removed, as these were deemed to reflect ectopic beats or noise. The HRV parameters calculated include frequency domain analysis, time domain analysis, and nonlinear analysis measures *(Table 1)*. The results were statistically analyzed using a *t* test or a Kruskal-Wallis test if the HRV data between sample comparisons were nonparametric. Results were considered significant if the *P* value was <0.05.

RESULTS

Statistically significant increases in time domain analysis HRV parameters (SDNN, RMSDD) were found in the sinus bradycardia group when compared with normal sinus rate subjects ($P < 0.05$) *(Table 2)*. SDNN reflects both sympathetic and parasympathetic activity and therefore provides an index of total HRV (6). RMSSD estimates the short-term components of HRV and provides an estimate of vagal nerve activity (6). Thus, in sinus bradycardia, total HRV is increased, and there is likely an increase in vagal activity that is also likely responsible for slowing the HR. It is difficult to interpret if sympathetic drive is changed using time domain analysis, although nonlinear analysis measures of HRV revealed no significant sympathetic differences between subjects with sinus bradycardia and normal sinus rate. Additionally, the nonlinear measure of HRV DFA32 was significantly increased in bradycardia subjects compared with normal sinus subjects, reflecting the increased complexity of the ECG and hence increased total HRV in bradycardia.

DISCUSSION

This study reflects two important findings. First, bradycardia is associated with increased total power, as measured in the frequency domain. Thus, a reduced nonpathological HR is

Table 2. Summary statistics for frequency domain, time domain, and nonlinear heart rate variability across the two heart rate groups

Parameter	Mean value ± standard deviation: Normal HR (n = 43)	Mean value ± standard deviation: Bradycardia HR (n = 25)	*P* value Kruskal-Wallis test	*P* value *t* test
Frequency domain analysis				
Total power	1817 ± 1460	2411 ± 1724	0.113	0.155
HF	367 ± 530	401 ± 290	0.038*	0.34
LF	448 ± 404	621 ± 572	0.135	0.19
HF ln	5.27 ± 1.09	5.720 ± 0.827	0.038*	0.06
LF ln	5.695 ± 0.960	6.086 ± 0.831	0.135	0.082
HF norm	47.7 ± 65.0	40.7 ± 12.6	0.488	0.498
LF norm	56.3 ± 19.0	56.8 ± 12.8	0.975	0.898
LF/HF	2.24 ± 2.10	1.75 ± 1.36	0.661	0.249
Time domain analysis				
SDNN	40.5 ± 15.4	48.7 ± 15.1	0.038*	0.038*
RMSSD	26.2 ± 14.5	33.6 ± 13.0	0.007*	0.034*
Nonlinear analysis				
DFA α1	1.013 ± 0.296	1.057 ± 0.247	0.537	0.513
DFA α2	0.938 ± 0.178	0.923 ± 0.132	0.642	0.688
DFA32	91.4 ± 42.2	129.0 ± 72.1	0.01*	0.023*
ApEN	1.112 ± 0.236	1.181 ± 0.199	0.242	0.203

*Significant at $P < 0.05$.

HR indicates heart rate; for other abbreviations, see Table 1.

likely to confer cardiac protection. Indeed, it has been shown that decreased HRV is associated with advancing age, which carries an increased risk of cardiac-related events in clinically disease-free patients (13); however, this is not likely to be the case in aging populations with reduced HR. Also, studies have demonstrated that a decreased HRV provides a poor prognosis for postinfarction patients and heart failure patients (14).

Second, we can confirm that "normal" sinus bradycardia in our study population is due to an increase in vagal drive, as revealed by time domain measures of HRV, i.e., an increase in RMSDD. It is incorrect to assume that increased vagal drive must be responsible for all cases of sinus bradycardia. For example, enhanced cardiac vagal efferent activity does not explain sports endurance training–induced bradycardia compared with age-matched controls. Finally, it has been shown that there is a decline in total HRV with aging mainly, but not exclusively, due to a decline in parasympathetic tonus (15). Thus, in an aging population, a slow heart rate is likely to confer cardioprotective benefits due to an associated increase in parasympathetic autonomic tone and also an associated increase in total HRV.

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