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# Relationship of Heart Rate Variability to Parasympathetic Effect

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**Background**—Baroreflex-mediated parasympathetic stimulation has variable effects on heart rate variability (HRV). We postulated that a quadratic function would describe the relationship between HRV and parasympathetic effect better than a linear function.

**Methods and Results**—Twenty-nine normal volunteers (15 women; mean age  $39 \pm 12$  years) were studied after  $\beta$ -adrenergic blockade with intravenous propranolol. Five-minute ECG recordings were made during graded infusions of phenylephrine and nitroprusside to achieve baroreflex-mediated increases and decreases in parasympathetic effect, respectively. Time- and frequency-domain measures of HRV were calculated from the R-R interval tachograms. The R-R interval and the vagal-sympathetic effect ( $VSE = R-R \text{ interval} / \text{intrinsic R-R interval}$ ) were used as indices of parasympathetic effect. The data were fit to both quadratic and linear models. In each case, the quadratic model (with a negative coefficient for the squared term) was superior to the linear model. There was some evidence that age influenced the responsiveness of the HRV parameters with changing parasympathetic effect, although the regression analysis was significant only in the models for MSSD ( $P < 0.03$ ) and pNN50 ( $P < 0.001$ ).

**Conclusions**—The relationship between HRV and parasympathetic effect is best described by a function in which there is an ascending limb where HRV increases as parasympathetic effect increases until it reaches a plateau level; HRV then decreases as parasympathetic effect increases. Because there is marked interindividual variation in this relationship, differences in HRV between individuals may reflect differences in this relationship and/or differences in autonomic effects. (*Circulation*. 2001;103:1977-1983.)

**Key Words:** heart rate ■ nervous system, autonomic

The relationship between heart rate variability (HRV) and parasympathetic effect on the sinus node is unclear. Some investigators<sup>1,2</sup> have demonstrated a direct relationship between HRV and parasympathetic effect. Others have cautioned that increased parasympathetic effect may saturate the HRV response,<sup>3-7</sup> which we have demonstrated.<sup>8</sup> This study was therefore designed to evaluate the relationship of HRV to parasympathetic effect by use of baroreflex-mediated parasympathetic stimulation and withdrawal. The importance of understanding this relationship is underscored by studies<sup>9-11</sup> that established that in normal individuals in the resting, supine state, the majority of HRV is related to parasympathetic effects.

There is substantial variance in HRV in normal individuals<sup>12,13</sup>; the source of this variability is unclear. It may reflect real differences in parasympathetic effects on the sinus node. In this case, defining the relationship between HRV and parasympathetic effect would be helpful in explaining the variance of HRV in normal individuals and relating these differences to specific differences in parasympathetic effect. Alternatively, there may be substantial interindividual variances in HRV even at equivalent levels of parasympathetic effect. In this case, each individual

may have his or her own curve relating HRV to parasympathetic effect. In this situation, it would be difficult to make inferences about interindividual differences in parasympathetic effect based on single HRV measurements.

To explore the intraindividual and interindividual relationships of HRV to parasympathetic effect, we studied normal subjects after  $\beta$ -adrenergic blockade, leaving heart rate control predominantly under parasympathetic influences. We previously showed that the change in HRV observed with baroreflex-mediated parasympathetic stimulation is inversely related to the baseline HRV.<sup>14</sup> This is consistent with a relationship between HRV and parasympathetic effect in which HRV initially increases with increasing parasympathetic effect and then decreases with further increases in parasympathetic effect. We therefore postulated that a concave-down quadratic function would better describe the relationship between HRV and parasympathetic effect than a linear function.

## Methods

### Subjects

Twenty-nine normal volunteers (14 men, 15 women; age 22 to 67 years, mean  $39 \pm 12$  years) were studied in the Clinical Research

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Center. All subjects had normal physical examinations, ECGs, hematocrits, and serum electrolytes. No subjects were taking medications. Written informed consent was obtained. The Northwestern University Institutional Review Board approved the study.

### Data Acquisition

After an overnight fast, an indwelling catheter was placed in the forearm, through which normal saline was infused at 30 mL/h. Subjects were attached to a cardiac monitor, and blood pressure was taken manually. In male subjects, chest hair was shaved as needed for proper electrode attachment. ECG data were recorded with Ag/AgCl electrodes positioned in the standard X, Y, and Z lead positions on a commercially available system (Predictor I, Arrhythmia Research Technology) as previously described.<sup>8,14-16</sup> During each condition, 5-minute ECG recordings were made at a 1000-Hz sampling frequency and stored on optical disk for subsequent analysis.

### Baseline

Subjects were allowed to rest comfortably in the supine position in a quiet room with dim lights. There was a  $\geq 15$ -minute rest period before the administration of any pharmacological agents. All subjects then underwent complete  $\beta$ -adrenergic blockade with intravenous propranolol (0.2 mg/kg), leaving R-R interval control solely under parasympathetic influences. A 5-minute ECG recording was then made.

### Baroreflex-Mediated Parasympathetic Stimulation

Graded doses of phenylephrine ranging from 0.2 to 1.8  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  were infused to raise the blood pressure. The phenylephrine dose was titrated upward in increments of 0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  until a 40 mm Hg increase in systolic blood pressure was achieved or a nonsinus rhythm was observed (ie, junctional rhythm). The mean maximal phenylephrine dose infused was  $1.2 \pm 0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The mean baseline systolic blood pressure was  $114 \pm 12$  mm Hg, and the mean maximal systolic blood pressure during phenylephrine infusion was  $152 \pm 19$  mm Hg. ECG data were acquired at each dose. After the phenylephrine had been discontinued, blood pressure and heart rate were allowed to return to baseline. An additional 0.07 mg/kg propranolol IV was administered to maintain  $\beta$ -adrenergic blockade, and another recording was obtained.

### Baroreflex-Mediated Parasympathetic Withdrawal

Graded doses of nitroprusside ranging from 0.4 to 7.0  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  were infused to lower the blood pressure. The nitroprusside dose was titrated upward in increments of 0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  until 1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  was reached and then by 1  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  until either a 30 mm Hg decrease in systolic blood pressure was achieved or the subject developed symptoms. The mean maximal nitroprusside dose infused was  $3.8 \pm 1.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The mean minimal systolic blood pressure during nitroprusside infusion was  $91 \pm 7$  mm Hg. ECG data were acquired at each dose.

### Intrinsic R-R Interval

Atropine 0.04 mg/kg was then given over 2 minutes to achieve double autonomic blockade and determine the intrinsic R-R interval.<sup>17</sup>

### Index of Parasympathetic Effect

In the setting of  $\beta$ -adrenergic blockade, R-R interval control is predominantly under parasympathetic influences. Because the R-R interval is directly related to vagal nerve activity,<sup>18</sup> for the purpose of this study, the R-R interval was used as the index of parasympathetic effect.

Although the R-R interval has been directly related to vagal nerve activity, interindividual differences in intrinsic R-R interval may limit the utility of the R-R interval as a measure of parasympathetic effect. In other words, an R-R interval of 750 ms may indicate different levels of parasympathetic effect in individuals with intrinsic

R-R intervals of 600 versus 700 ms. This limitation may be overcome by use of a normalization procedure to account for interindividual differences in intrinsic R-R interval.<sup>2,19,20</sup> In the setting of  $\beta$ -adrenergic blockade, the vagal-sympathetic effect ( $\text{VSE} = \text{R-R interval} / \text{intrinsic R-R interval}$ )<sup>19</sup> takes into account interindividual differences in the intrinsic R-R interval.

### HRV Analysis

By use of a template-matching algorithm, an interval tachogram was generated for each recording. All recordings were visually examined and manually overread to verify beat classification. Nonsinus beats were eliminated along with 1 R-R interval after the ectopic interval. Missing data were filled by use of a linear predictive model that incorporates the 20 preceding "good" data points. If there were not enough preceding good intervals, data after the missing interval were used instead. The R-R intervals resulting from the multiple recordings made in each patient were grouped into bins of 50-ms duration. If there were multiple data points in a bin, the results were averaged to provide a single data point in each 50-ms window. A minimum of 5 points was required for inclusion in the study.

The standard deviation of the R-R intervals (SD), root mean square of the successive R-R interval differences (MSSD), and percent of normal R-R intervals that differed by  $> 50$  ms (pNN50) were calculated for each recording. An autoregressive model (order 16) was used to generate heart rate spectra for each 5-minute recording as previously described.<sup>8</sup> The low-frequency (LF; 0.04 to 0.15 Hz) and high-frequency (HF; 0.15 to 0.40 Hz) powers (in  $\text{bpm}^2$ ) were measured. Because of the skewed distributions for LF and HF, these data were analyzed after natural logarithmic transformation. Although the LF/HF ratio is typically evaluated in HRV studies, this ratio is not used to characterize parasympathetic effect and therefore was not analyzed.

### Statistical Analysis

The relationships between HRV measures and parasympathetic effect were explored by linear regression methodology. Because we hypothesized that a quadratic function (concave-down) would describe the relationship between HRV and parasympathetic effect better than a linear function, the data were fit to both quadratic and linear models with S-PLUS4.5 software (Statistical Sciences) for linear mixed-effects models. The program takes into account multiple and different numbers of data points from each subject. The effects of age and sex were assessed with the same software. This program uses maximum-likelihood techniques to provide estimates for the coefficients in the models. Both linear and quadratic model coefficients are presented as mean  $\pm$  SEM. Comparisons between the likelihood ratios of the 2 models were made with  $\chi^2$  tests. All statistical tests were 2-tailed; a value of  $P < 0.05$  was considered significant.

Individual curves relating HRV measures to the R-R interval were classified according to whether the peak HRV was observed at the maximal R-R interval or whether the peak HRV was observed at an R-R interval that was less than the maximal achieved R-R interval. To evaluate whether the absence of a descending limb of the individual curve relating the HRV measures to the R-R interval in the former case was related to an absence of data at higher levels of parasympathetic effect, a 1-tailed unpaired *t* test was performed comparing the maximal achieved R-R interval in the 2 groups.

To evaluate interindividual variability of the HRV parameters, the coefficient of variation was measured for each parameter in each decile of R-R interval values. The coefficient of variation of the HRV parameter was divided by the coefficient of variation in the R-R interval in that decile to provide an index of the relative variation of the HRV parameters.

### Results

All subjects received multiple doses of phenylephrine and nitroprusside. After the results had been grouped into 50-ms bins and multiple determinations averaged within each bin,

TABLE 1. Ranges of Observed Minima and Maxima

	Range of Minimum Values	Range of Maximum Values
SD, ms	13.0–83.3	33.8–188.0
MSSD, ms	3.6–92.5	28.3–225.6
pNN50, %	0.00–54.63	8.10–86.3
lnLF, ln (bmp) <sup>2</sup>	–4.20–0.089	–1.056–3.019
lnHF, ln (bmp) <sup>2</sup>	–4.07–0.726	–1.162–1.993

there were  $\geq 5$  data points for each subject (range 5 to 11; mean  $8.0 \pm 1.6$ ). The R-R intervals observed ranged from a minimum of  $842 \pm 105$  to a maximum of  $1471 \pm 190$  ms. Table 1 shows ranges for the minima and maxima of the HRV parameters.

Table 2 provides results from the regression analyses. In all cases, the quadratic fit was better than the linear fit. The negative coefficient for the squared term implies a concave-down curve.

Figure 1 shows graphs of the HRV measurements for 3 subjects versus the R-R interval. The subjects demonstrate a pattern consistent with the findings of the regression analysis. The youngest subject, however, demonstrates more responsiveness of the HRV parameters with changes in parasympathetic effect than the older subjects. Figures 2 and 3 plot all the HRV measurements for all subjects versus the R-R interval or VSE. Although the data appear to be highly scattered, the regression analysis groups each subject's data together, allowing for detection of the overall quadratic versus linear pattern. Nevertheless, substantial variances in the data are apparent. Table 3 provides the relative variability in the HRV parameters for each R-R interval decile. In general, there was  $>10$ -fold relative variability in the HRV parameters compared with the R-R intervals.

Examination of the individual curves demonstrated that in some cases, the peak HRV was observed at the maximal R-R

interval (consistent with a monotonic relationship between HRV and parasympathetic effect). In other cases, the peak HRV was observed at an R-R interval that was less than the maximal achieved R-R interval (consistent with a nonmonotonic relationship between HRV and parasympathetic effect). Table 4 demonstrates the distribution of each type of response. In each case, the maximal achieved R-R interval was less in the group in which the peak HRV was observed at the maximal R-R interval, suggesting that these curves may have been incomplete because of the inability to attain longer R-R intervals. Neither age nor maximal achieved systolic blood pressure differed significantly between the groups.

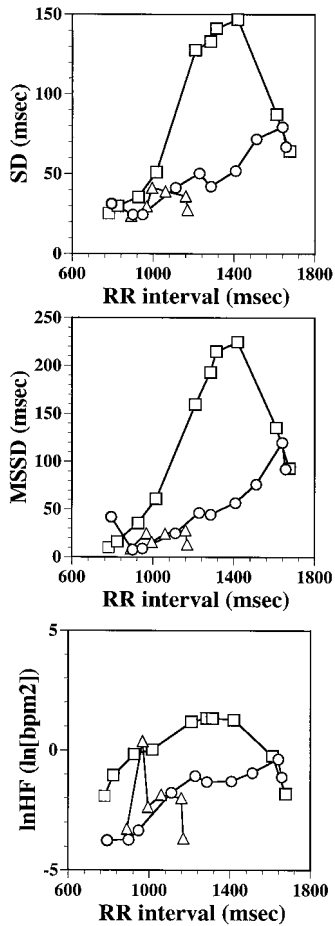
There was some evidence that age influenced the responsiveness of the HRV parameters with changing parasympathetic effect (Figure 1), although the regression analysis was significant only in the models for MSSD ( $P < 0.03$ ) and pNN50 ( $P < 0.001$ ). Figure 4 shows predicted curves from the regression analysis for ages 25, 40, and 55 years. With increasing age, there is decreasing responsiveness of the HRV parameters with changes in parasympathetic effect. A significant decline in maximum-achieved R-R interval with advancing age ( $P < 0.02$ ) was also noted (Figure 5). There was no significant sex effect.

## Discussion

Our findings support the notion that there is not a monotonic relationship between HRV and parasympathetic effect. As first observed in anesthetized dogs,<sup>21</sup> the relationship between HRV and parasympathetic effect in humans is also better described by a function in which there is an ascending limb where HRV increases as parasympathetic effect increases until it reaches a plateau level. Beyond this level, HRV actually decreases with further increases in parasympathetic effect. There is also marked interindividual variation in the relationship between HRV and parasympathetic effect; this makes it difficult to appreciate whether interindividual dif-

TABLE 2. Results of Regression Analyses (Shown as Estimate  $\pm$  SE)

	Linear Model		Quadratic Model			<i>P</i> , Quadratic Model Superior to Linear Model
	Intercept	RR Coefficient	Intercept	RR Coefficient	RR <sup>2</sup> Coefficient $\times 10^{-5}$	
SD	$-38.7 \pm 12.4$	$0.09 \pm 0.01$	$-103.7 \pm 55.3$	$0.20 \pm 0.10$	$-4.376 \pm 4.241$	$< 0.005$
MSSD	$-101.2 \pm 15.5$	$0.15 \pm 0.02$	$-206.1 \pm 74.8$	$0.34 \pm 0.14$	$-8.106 \pm 5.799$	$< 0.0001$
pNN50	$-64.3 \pm 7.4$	$0.09 \pm 0.01$	$-193.8 \pm 36.4$	$0.32 \pm 0.07$	$-9.896 \pm 3.008$	$< 0.0001$
lnLF	$0.3 \pm 0.4$	$-5.14 \times 10^{-4}$ $\pm 3.74 \times 10^{-4}$	$-2.5 \pm 1.2$	$4.58 \times 10^{-3}$ $\pm 2.03 \times 10^{-3}$	$-0.221 \pm 0.0861$	$< 0.0001$
lnHF	$-2.13 \pm 0.58$	$1.37 \times 10^{-3}$ $\pm 4.61 \times 10^{-4}$	$-11.2 \pm 1.9$	$1.76 \times 10^{-2}$ $\pm 3.23 \times 10^{-3}$	$-0.695 \pm 0.133$	$< 0.0001$
	VSE		VSE			<i>P</i> , Quadratic Model Superior to Linear Model
	Intercept	Coefficient	Intercept	Coefficient	VSE <sup>2</sup> Coefficient $\times 10^{-5}$	
SD	$-35.3 \pm 11.0$	$56.4 \pm 7.5$	$-160.2 \pm 42.7$	$203.6 \pm 48.4$	$-41.5 \pm 12.4$	$< 0.0001$
MSSD	$-99.2 \pm 14.0$	$94.4 \pm 9.7$	$-273.4 \pm 60.7$	$302.0 \pm 68.1$	$-59.4 \pm 17.5$	$< 0.0001$
pNN50	$-62.5 \pm 7.1$	$55.3 \pm 4.7$	$-224.4 \pm 31.3$	$241.4 \pm 36.8$	$-51.7 \pm 10.0$	$< 0.0001$
lnLF	$0.3 \pm 0.4$	$-0.27 \pm 0.21$	$-2.8 \pm 1.0$	$3.14 \pm 1.04$	$-0.89 \pm 0.26$	$< 0.04$
lnHF	$-2.15 \pm 0.53$	$0.91 \pm 0.26$	$-11.0 \pm 1.6$	$10.8 \pm 1.7$	$-2.65 \pm 0.46$	$< 0.0001$

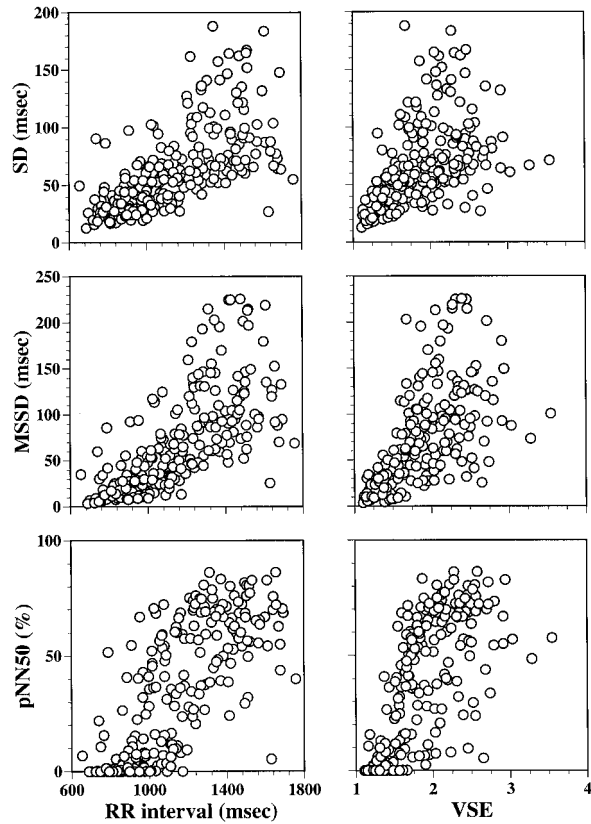


**Figure 1.** Plots of HRV vs R-R interval for a 24-year-old woman (squares), a 47-year-old woman (circles), and a 60-year-old man (triangles).

ferences in HRV reflect differences in autonomic effects or differences in the relationship between HRV and autonomic effects. Finally, an age-related effect on the relationship between HRV and parasympathetic effect was noted, but no sex effect. With increasing age, there was decreasing responsiveness of HRV with changes in parasympathetic effect. These findings are helpful in resolving the divergent findings of studies that have evaluated changes in HRV with increasing parasympathetic effect.

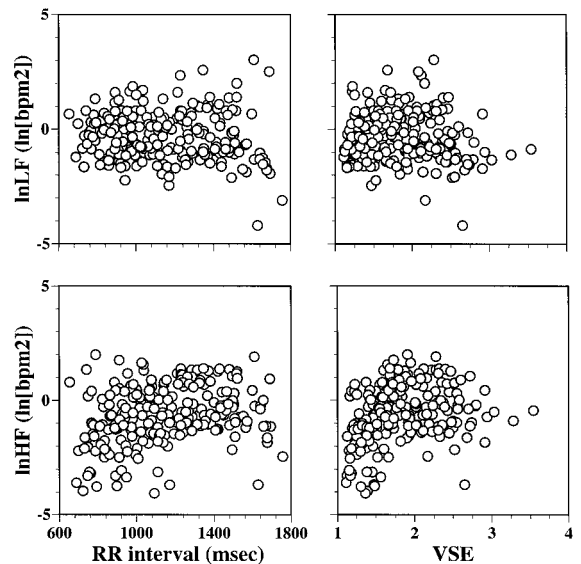
Some studies<sup>1,22</sup> demonstrated that baroreflex-mediated parasympathetic stimulation increases HRV. On the basis of these data and the reduction of HRV with parasympathetic blockade, one might presume a direct or monotonic relationship between HRV and parasympathetic effect. Bloomfield et al<sup>1</sup> recently concluded that “vagal measures of R-R variability track the increase in parasympathetic nervous system activity during baroreceptor activation.” Others, however, have demonstrated either a decrease<sup>8,21</sup> or no change<sup>3,14</sup> in HRV with baroreflex-mediated parasympathetic stimulation, challenging the notion that there is a direct relationship between HRV and parasympathetic effect.

Several publications<sup>4-7</sup> have highlighted that HRV measures modulation of heart rate. With enough autonomic stimulation, the HRV response may be saturated. The find-



**Figure 2.** Plots of time-domain parameters of HRV vs R-R interval and VSE for all subjects.

ings of our study support this notion. Specifically, the relationship between HRV and parasympathetic effect is not monotonic; it is better modeled with a quadratic equation. Statistically, the quadratic fit was superior to the linear fit for all parameters studied. For most individuals, the peak HRV value was not noted at the peak R-R interval value, suggesting that a descending limb was present. Furthermore, in



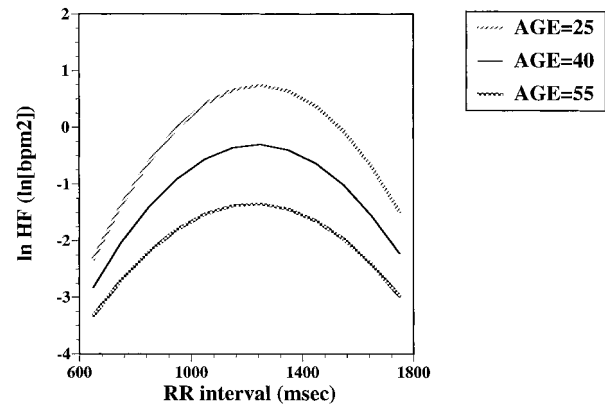
**Figure 3.** Plots of frequency-domain parameters of HRV vs R-R interval and VSE for all subjects.

**TABLE 3. Coefficient of Variation of HRV Parameters Divided by the Coefficient of Variation of the RR Interval for Each RR Interval Decile**

Decile	Relative Variability of				
	SD	MSSD	PNN50	LF	HF
1 (Lowest)	13	22	54	17	45
2	11	17	64	29	33
3	22	34	59	49	65
4	22	35	57	62	60
5	18	30	41	51	57
6	13	19	29	44	36
7	23	26	20	80	45
8	17	18	9	67	37
9	15	20	11	41	43
10 (Highest)	11	11	7	56	35

subjects in whom a descending limb was absent, the maximum-achieved R-R interval was smaller than in subjects in whom a descending limb was identified. The absence of a descending limb may therefore reflect an insufficient degree of baroreflex-mediated parasympathetic stimulation. These findings help reconcile the divergent findings in the literature regarding parasympathetic effects on HRV. The observed response depends on the baseline parasympathetic effect, the degree of baroreflex-mediated parasympathetic stimulation, and the intraindividual responses to baroreflex-mediated parasympathetic stimulation. Thus, Bloomfield et al,<sup>1</sup> who noted increased HRV with baroreflex-mediated parasympathetic stimulation, probably evaluated subjects predominantly on the ascending limb of their relationships between HRV and parasympathetic effect.

The first qualitative description of this relationship was made by Anrep et al<sup>21</sup> in 1936. "The rise of the arterial blood pressure [baroreflex-mediated parasympathetic stimulation] first affects the length of the 'deflation cardiac cycles' and has a considerably smaller effect on the 'inflation cycles' [resulting in increased HRV]. Ultimately, the difference between the length of the cardiac cycles during inflation of the lungs almost disappears and the heart beats at a nearly uniformly slow rate [representing decreased HRV at high levels of parasympathetic effect]. With low arterial blood pressure, and

**Figure 4.** Plots of predicted curves from regression analysis for ages 25, 40, and 55 years.

therefore absence of the vagus tone, the heart beats at an almost uniformly fast rate."

There are several potential explanations for the decrease in HRV with increasing parasympathetic effect. If with increasing blood pressure there is higher-frequency vagal discharge and inspiratory suppression is maintained,<sup>18,23</sup> then there must be persistent parasympathetic effect during inspiration despite the suppression of vagal nerve discharge. In *in vitro* preparations, the dose-response curve to acetylcholine has a rapidly rising portion and at higher concentrations is flat,<sup>24,25</sup> displaying a simple saturation relationship. High-intensity vagal nerve discharges during expiration may release enough acetylcholine to result in saturation of the parasympathetic effect during expiration. If acetylcholine concentrations during expiration are high enough, the expected decline in acetylcholine concentrations in the region of the sinus node during inspiration may not be enough to significantly diminish the parasympathetic effect. Alternatively, it is possible that with increasing blood pressure, there is loss of phasic respiratory changes in vagal nerve discharges,<sup>26</sup> resulting in a loss of phasic effect and a decrease in HRV. It is unclear which mechanism is operative in humans.

Age and sex may affect HRV.<sup>12,27-29</sup> Ryan et al<sup>27</sup> demonstrated that HF and overall complexity of heart rate dynamics are higher in women than men. This was not related to any specific level of autonomic effect, however. It is unclear whether the differences observed in that study represent sex differences in the relationship between HRV and autonomic

**TABLE 4. Individual Curves Relating HRV Measures to R-R Interval**

	Peak HRV Value at Maximal R-R Interval		Peak HRV Value Not at Maximal R-R Interval		<i>P</i>
	<i>n</i>	Maximal R-R Interval, ms	<i>n</i>	Maximal R-R Interval, ms	
SD	10	1397±181	19	1510±187	0.06
MSSD	13	1413±167	16	1518±199	0.07
PNN50	16	1407±198	13	1550±152	0.02
lnLF	5	1409±182	24	1484±193	0.22
lnHF	5	1311±187	24	1504±176	0.02

Curves demonstrated 1 of 2 patterns. For each pattern, the maximal achieved R-R interval in that group is shown (mean±SD) with the *P* value comparing the maximal achieved R-R intervals.

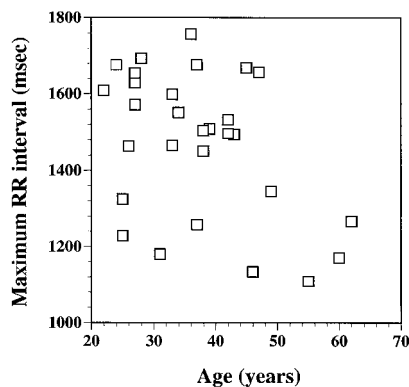


Figure 5. Plot of maximum achieved R-R interval vs age.

effect or represent actual sex differences in autonomic effects. Although sex-related differences in the relationship between HRV and parasympathetic effect were not identified in the present study, small differences cannot be excluded.

We identified marked interindividual variation in the relationship between HRV and parasympathetic effect. Although large variations in baseline HRV have been noted,<sup>12,13</sup> the source of this variability is unclear. Factors that could explain this variability include differences in autonomic effects among subjects, age-related differences, sex-related differences, or different curves relating autonomic effects to HRV for different subjects. Saul et al<sup>22</sup> evaluated individual relationships of muscle sympathetic nerve burst counts to LF and also found marked interindividual differences. Using an orthostatic stimulus, Furlan et al<sup>30</sup> evaluated the relationship between muscle sympathetic nerve activity and HRV. Of interest, the coherence between LF and muscle sympathetic nerve activity spectra increased with tilt, supporting the fact that there are dynamic changes in the relationship between HRV and sympathetic nerve activity. Singh et al<sup>31</sup> demonstrated that heritable factors might explain a substantial proportion of the variance in HRV noted in a population. Furthermore, alterations in expression of ion channel activity<sup>32</sup> or autonomic receptors<sup>33</sup> may also affect HRV. It is therefore plausible that each individual may have his or her own genetically determined curve relating autonomic effects to HRV. Other environmental factors (such as exercise) may also affect this relationship. Further work is necessary to understand the genetic/environmental determinants of HRV and the relationship between HRV and parasympathetic effect.

### Limitations

Although the quadratic model was superior to a linear model, it is likely that other models may provide better characterization of the relationship between HRV and parasympathetic effect. The quadratic relationship was chosen for analysis to most easily demonstrate the nonmonotonic relationship.

Respirations were not controlled in these studies. It is known that respiration has significant effects on HRV. In previous studies done under conditions similar to those in the present study, however, we demonstrated no significant differences in the HRV effects whether the respiratory rate

was fixed to a metronome at a physiological rate or not.<sup>14,16</sup> Although it is plausible that controlling respiration with a metronome at a physiological rate could have quantitative effects on the study results, it seems unlikely that the qualitative results would differ. Specifically, it is unlikely that a linear model would become superior to the quadratic model, and it is unlikely that the majority of the interindividual variability would be eliminated. Nevertheless, the present findings are for HRV measurements in the setting of natural breathing.

These data focused only on the relationship between HRV and parasympathetic effect, in the absence of sympathetic effects. In reality, there is a dynamic interaction between sympathetic and parasympathetic effects on heart rate regulation.<sup>34–37</sup> Further studies are necessary to explore these important interactions.

### Conclusions

Low HRV has negative prognostic implications in a variety of clinical situations. It is possible that a better understanding of the relationship between HRV and autonomic effect in an individual subject may provide even more prognostic information than a single HRV measurement. Furthermore, understanding this relationship will be necessary to understand the effects of interventions that either are designed to alter autonomic tone or that serendipitously affect autonomic tone and HRV.

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