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Gender- and Age-Related Differences in Heart Rate Dynamics: Are Women More Complex Than Men?

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Objectives. This study aimed to quantify the complex dynamics of beat-to-beat sinus rhythm heart rate fluctuations and to determine their differences as a function of gender and age.

Background. Recently, measures of heart rate variability and the nonlinear "complexity" of heart rate dynamics have been used as indicators of cardiovascular health. Because women have lower cardiovascular risk and greater longevity than men, we postulated that there are important gender-related differences in beat-to-beat heart rate dynamics.

Methods. We analyzed heart rate dynamics during 8-min segments of continuous electrocardiographic recording in healthy young (20 to 39 years old), middle-aged (40 to 64 years old) and elderly (65 to 90 years old) men (n = 40) and women (n = 37) while they performed spontaneous and metronomic (15 breaths/min) breathing. Relatively high (0.15 to 0.40 Hz) and low (0.01 to 0.15 Hz) frequency components of heart rate variability were computed using spectral analysis. The overall "complexity" of each heart rate time series was quantified by its approximate entropy, a measure of regularity derived from nonlinear dynamics ("chaos" theory).

Results. Mean heart rate did not differ between the age groups or genders. High frequency heart rate power and the high/low frequency power ratio decreased with age in both men and women ($p < 0.05$). The high/low frequency power ratio during spontaneous and metronomic breathing was greater in women than men ($p < 0.05$). Heart rate approximate entropy decreased with age and was higher in women than men ($p < 0.05$).

Conclusions. High frequency heart rate spectral power (associated with parasympathetic activity) and the overall complexity of heart rate dynamics are higher in women than men. These complementary findings indicate the need to account for gender- as well as age-related differences in heart rate dynamics. Whether these gender differences are related to lower cardiovascular disease risk and greater longevity in women requires further study.

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American women outlive men by an average of 7.5 years and consequently represent the largest segment of the elderly population (1). Multiple factors have been cited to account for this increased longevity, including the protective effect of estrogen against the development of coronary artery disease (2). Because they develop manifestations of cardiovascular disease at a later age than their male counterparts (2), women tend to have healthier cardiovascular function than similar-aged men throughout adult life.

Recently, a variety of measures of heart rate variability have been used as indicators of cardiovascular health. A reduction in beat-to-beat heart rate variability during sinus rhythm is associated with aging (3–12), congestive heart failure (13,14), coronary artery disease (15,16), postprandial hypotension (17) and sudden death syndromes (18,19). However, little attention has been paid to the effects of gender on heart rate dynamics.

Despite the widespread application of conventional measures of heart rate variability, traditional indexes based on mean and variance provide only limited information about the integrated dynamics of healthy or perturbed cardiac function. Additional information quantifying beat-to-beat fluctuations can be obtained by spectral analysis and by recently described measures derived from nonlinear dynamics ("chaos" theory). Approximate entropy is one such measure that provides an index of the "complexity" of the output of a dynamic process (20–25). Greater complexity (irregularity or unpredictability) of a process corresponds to larger approximate entropy values. Our previous work (24,26) has documented a decline in the

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complexity of sinus rhythm heart rate dynamics with healthy aging.

Because women live longer and develop cardiovascular illness at a later age than men, we postulated that women would have greater heart rate variability and greater "complexity" of heart rate dynamics than men across a wide adult age spectrum.

Methods

Subjects. Eighty-three healthy subjects 20 to 90 years old were recruited from the local community and screened with a detailed medical history, complete physical examination, including postural vital signs, and an electrocardiogram (ECG). Three young subjects were subsequently excluded (prominent atrial ectopic beats on the ECG [n = 1], development of syncope during participation in another study of head-up tilt testing [n = 1], technical problems with heart rate recording [n = 1]). Three middle-aged subjects were excluded (obesity and a history of an abnormal glucose tolerance test on a previous physician visit [n = 1], hypertension [defined as repeated supine blood pressure readings >140/90 mm Hg, n = 2]). Ten elderly subjects were excluded (technical problems during the heart rate recording [n = 4], abnormalities discovered during screening [n = 6], including an abnormal baseline ECG [n = 4], mild Parkinson's disease [n = 1] and an unexplained buccal mass [n = 1]).

All of the remaining 67 subjects were physically active and highly functional. None used tobacco products or took medications (including estrogen). No evidence of medical diseases was present on a careful review of the medical history, physical examination or ECG. No subject had prior surgical procedures of the head, neck or thorax that would affect autonomic innervation. The final sample was divided into three age groups: young (20 to 39 years, n = 21); middle-aged (40 to 64 years, n = 26); and elderly (>65 years, n = 20).

The study was approved by the Institutional Review Board of the Beth Israel Hospital, and all subjects provided written informed consent.

Data collection. All subjects were supine for a minimum of 10 min before the start of data collection. Subjects were studied between 11 AM and 6 PM, at least 2 h after meal ingestion and after abstaining from caffeine-containing beverages for a minimum of 12 h. There was no significant difference in the time that subjects from each age group were studied. Continuous ECG signals were recorded from bipolar precordial leads onto videotape (JVC video recorder interfaced to a Vetter Digital PCM recording adaptor) during 10 min of metronomic breathing, followed by 15 min of quiet (spontaneous) respiration while supine. Metronomic breathing was performed to standardize respiratory rate because differences in breathing frequency could influence differences in heart rate dynamics between age and gender groups. During metronomic breathing, subjects breathed in time to tape-recorded cues, at a rate of 15 breaths/min (0.25 Hz).

Data analysis: spectral and "complexity" measurements. Videotaped ECG signals were digitized at 250 Hz then each QRS complex was identified and annotated as a sinus or ectopic beat, using an automated arrhythmia detection algorithm. The annotations were verified by visual inspection. Eight-minute sections free of ectopic beats or artifacts were selected for analysis during metronomic and quiet breathing. Uniformly sampled "instantaneous" heart rates during these 8-min sections were obtained by resampling the RR intervals at 2 Hz.

Each 8-min heart rate time series was analyzed with a fast Fourier transform algorithm, yielding a 512-point power spectrum for the 0.0- to 1.0-Hz frequency band. Heart rate power (area under the curve, reported in arbitrary units) was then computed for three spectral bands: *total* (0.01 to 0.4 Hz), relatively *low frequency* (0.01 to 0.15 Hz) and *high frequency* (0.15 to 0.40 Hz) during quiet and metronomic breathing. In addition, the power in the narrow 0.23- to 0.27-Hz band was computed during metronomic breathing to provide a more specific measure of the magnitude of respiratory sinus arrhythmia during controlled breathing at 0.25 Hz. The high/low frequency power ratio during quiet and metronomic breathing was also measured. This provides an index of parasympathetic relative to sympathetic nervous system tone, which is an indicator of cardiovascular health, known to be decreased in patients with congestive heart failure (14) and coronary artery disease (15).

Approximate entropy is a "regularity statistic" that quantifies the predictability of fluctuations in a given variable such as heart rate (20). The methodologic details for computing approximate entropy have been published elsewhere (20–25). Approximate entropy is formally defined in the Appendix. Briefly, approximate entropy measures the (logarithmic) likelihood that a series of data points that are a certain distance apart (r) for a given number (m) of observations remain within the same distance on next incremental comparisons. A greater likelihood of remaining the same distance apart (i.e., greater regularity or predictability) produces smaller approximate entropy values. Conversely, the more complex (less regular or predictable) the process, the higher the approximate entropy value.

For this study, approximate entropy was calculated for n = 960 consecutive heart rate data points. Two input variables, m and r, must be fixed to compute approximate entropy. We chose m = 2 and r (effectively a "filter" factor) = 20% of the standard deviation of the data sets. These values were selected on the basis of previous studies indicating good statistical validity for approximate entropy within these variable ranges (20–25).

Statistical analysis. Statistical comparisons of heart rate spectral power data were performed after logarithmic transformation of the data, to normalize the distributions across the age ranges (9,27). Heart rate spectral data and approximate entropy values were compared between age and gender groups using a general linear models analysis of variance procedure, with tests for age and gender effects as well as their interaction. When statistical differences were identified across the age range, Bonferroni *t* tests were used to assess the differences between each age group. Differences between men and women within each age group were compared using standard *t* tests for

Table 1. Clinical Characteristics of the Study Subjects

	Young Subjects		Middle-Aged Subjects		Elderly Subjects	
	Men (n = 12)	Women (n = 9)	Men (n = 17)	Women (n = 9)	Men (n = 11)	Women (n = 9)
Age (yr)	29 (2)	27 (2)	48 (2)	44 (2)	78 (2)	73 (2)
BMI (kg/m²)	24 (1)	23 (1)	25 (1)	24 (1)	25 (1)	25 (1)
HR (beats/min)	65 (3)	60 (2)	65 (2)	66 (2)	65 (3)	67 (2)
HR-SD	3.6 (0.3)	3.9 (0.3)	3.9 (0.3)	3.6 (0.4)	3.0 (0.2)*	2.2 (0.2)*†
SBP (mm Hg)	119 (3)	103 (2)†	118 (3)	105 (3)†	132 (5)*	130 (7)*
DBP (mm Hg)	71 (3)	71 (2)	74 (2)	67 (1)†	73 (3)	69 (2)

*p < 0.05, elderly subjects have a higher supine systolic blood pressure (SBP) and a lower supine heart rate standard deviation (HR-SD) during 8 min of continuous recording (quiet breathing) than the other two groups. †p < 0.05, lower in women than in men. Data presented are mean value (SE). BMI = body mass index; DBP = supine diastolic blood pressure.

equal or unequal variances. Linear regression with gender as a covariate was used to examine the relation between approximate entropy and heart rate spectral indexes. Data were analyzed using the SAS (V6.06.01) system on a Microvax computer. All analyses were performed using an alpha level of 0.05 as the criterion for statistical significance.

Results

Clinical characteristics. Selected clinical characteristics of the subjects are summarized in Table 1. There were no differences in basal mean heart rate between men and women at any age. Heart rate variability, measured as the standard deviation of heart rate during 8 min of supine recording, was lower in elderly women than men ($p < 0.05$). Young and middle-aged men had significantly higher basal mean systolic blood pressure than in women of similar age ($p < 0.05$). Overall elderly subjects had a significantly higher basal systolic blood pressure and lower heart rate variability (standard deviation) than young and middle-aged subjects ($p < 0.05$).

Heart rate spectral power. The relations between age, gender and heart rate power spectrum during quiet and metronomic breathing are summarized in Tables 2 and 3, respectively. Figure 1 shows the relation between age and the high/low frequency power ratio for men and women during quiet breathing. All spectral power indexes (total, low and high and respiratory frequency power) during both quiet and metronomic breathing were significantly lower in elderly than in young or middle-aged subjects ($p < 0.05$). Overall, women had significantly greater "respiratory" (0.23 to 0.27 Hz) frequency power and high/low power ratios than men during both quiet and metronomic breathing ($p < 0.05$). Women also had significantly greater power in the total (0.01 to 0.4 Hz) and high (0.15 to 0.4 Hz) frequency bands than men during metronomic breathing ($p < 0.001$). Gender differences in the high/low power ratio were apparent during both quiet (Fig. 1) and metronomic breathing in all three age groups. These differences were statistically significant in all but middle-aged subjects during quiet breathing.

Although gender differences in the high/low power ratio could be attributable to reductions in low frequency power in women compared with men, this was observed only in the elderly group during quiet breathing. Most of the gender difference in heart rate spectral power occurred in the high frequency range, mediated by parasympathetic activity.

Table 2. Heart Rate Spectral Power and Complexity During Quiet Breathing

	Young Subjects		Middle-Aged Subjects		Elderly Subjects		All Subjects	
	Men (n = 12)	Women (n = 9)	Men (n = 17)	Women (n = 9)	Men (n = 11)	Women (n = 9)	Men (n = 40)	Women (n = 27)
Spectral power								
Total power* (0.01–0.40 Hz)	23.9 (5.2)	25.0 (3.6)	27.0 (3.7)	24.3 (5.0)	15.1 (2.5)	8.6 (2.2)	22.8 (2.4)	19.3 (2.6)
Low power* (0.01–0.15 Hz)	19.3 (4.3)	17.2 (2.5)	23.5 (3.4)	20.1 (4.1)	13.7 (2.2)	7.0 (1.9)†	19.5 (2.1)	14.8 (2.0)
High power* (0.15–0.40 Hz)	4.6 (1.2)	7.8 (1.5)	3.6 (0.5)	4.1 (1.1)	1.4 (0.5)	1.6 (0.4)	3.3 (0.5)	4.5 (0.8)
Respiratory† (0.23–0.27 Hz)	0.8 (0.2)	2.2 (0.6)‡	0.6 (0.1)	0.8 (0.3)	0.3 (0.1)	0.3 (0.1)	0.6 (0.1)	1.1 (0.3)‡
High/low ratio†	0.25 (0.04)	0.47 (0.07)§	0.19 (0.03)	0.22 (0.04)	0.10 (0.02)	0.25 (0.07)‡	0.18 (0.02)	0.32 (0.04)§
HR complexity (ApEn)†	0.89 (0.05)	1.0 (0.04)	0.78 (0.03)	0.86 (0.04)	0.66 (0.04)	0.86 (0.05)§	0.78 (0.03)	0.90 (0.03)§

*p < 0.05, less in the elderly than in the other two groups. †p < 0.05, less in the elderly than in young subjects and less in middle-aged than young subjects. ‡p < 0.05, §p < 0.01, men versus women. Data presented are mean value (SE). ApEn = approximate entropy; HR = heart rate.

Table 3. Heart Rate Spectral Power and Complexity During Metronomic Breathing

	Young Subjects		Middle-Aged Subjects		Elderly Subjects		All Subjects	
	Men (n = 12)	Women (n = 8)	Men (n = 17)	Women (n = 9)	Men (n = 10)	Women (n = 9)	Men (n = 39)	Women (n = 26)
Spectral power								
Total power* (0.01–0.40 Hz)	17.2 (3.0)	26.8 (5.0)	13.7 (1.9)	17.9 (4.1)	6.6 (1.2)	12.0 (5.0)	13.0 (1.4)	18.6 (2.9)†
Low power‡ (0.01–0.15 Hz)	12.3 (2.2)	15.5 (3.8)	9.6 (1.6)	9.5 (2.1)	5.2 (0.8)	8.8 (4.2)	9.3 (1.1)	11.1 (2.0)
High power* (0.15–0.40 Hz)	5.0 (1.1)	11.3 (2.4)†	4.1 (0.7)	3.5 (2.4)	1.4 (0.4)	3.3 (1.1)	3.7 (0.5)	7.5 (1.3)†
Respiratory* (0.23–0.27 Hz)	3.2 (0.8)	7.7 (1.9)†	2.7 (0.5)	6.4 (2.0)	0.6 (0.2)	2.0 (0.8)	2.3 (0.4)	5.3 (1.0)†
High/low ratio	0.4 (0.1)	1.2 (0.5)†	0.6 (0.2)	1.0 (0.2)†	0.3 (0.1)	0.5 (0.1)†	0.5 (0.1)	0.9 (0.2)†
HR complexity (ApEn)*	1.01 (0.03)	1.07 (0.03)	0.97 (0.03)	1.02 (0.04)	0.87 (0.04)	0.94 (0.04)	0.96 (0.02)	1.01 (0.02)†

One young woman and one elderly man were unable to perform metronomic breathing. *$p < 0.05$, less in the elderly than in the other two groups. †$p < 0.05$, greater in women than in men. ‡$p < 0.05$, less in the elderly than in the young group. Data presented are mean value (SE). Abbreviations as in Table 2.

Heart rate complexity (approximate entropy). Regression analysis revealed significant effects of age ($p < 0.002$) and gender ($p < 0.05$) on approximate entropy values during both quiet and metronomic breathing. Approximate entropy declined significantly with age (Tables 2 and 3, Figure 2). Overall, women had significantly higher approximate entropy values than men during both quiet and metronomic breathing ($p < 0.05$) (Tables 2 and 3). During quiet breathing conditions, there was a significant age-related decline in approximate entropy for men ($R^2 = 0.33$, $p = 0.0001$) but not for women ($R^2 = 0.09$, $p = 0.14$) (Fig. 2). However, during metronomic breathing, the age-related decline in approximate entropy was present for both men ($R^2 = 0.22$, $p = 0.003$) and women ($R^2 = 0.21$, $p = 0.02$). Despite the different age effects in men versus women during quiet breathing, there was no statistically significant age and gender interaction during either breathing condition.

As shown in Figure 2, nearly 75% (25 of 33) of the lowest approximate entropy values (i.e., those below the regression line) during quiet breathing were in male subjects. The gender difference was most apparent in the oldest group, where the seven lowest approximate entropy values were in men, and five of these values were far below any study values for women. Similar findings were observed during metronomic breathing.

For all subjects combined, there was a modest positive linear correlation between approximate entropy and the high/low frequency power ratio ($R^2 = 0.38$, $p = 0.0001$, after covariate adjustment for gender).

Discussion

The principal new findings of this investigation are that apparently healthy women have significantly greater high frequency heart rate fluctuations and greater overall "complexity" of heart rate dynamics than apparently healthy men. Consis-

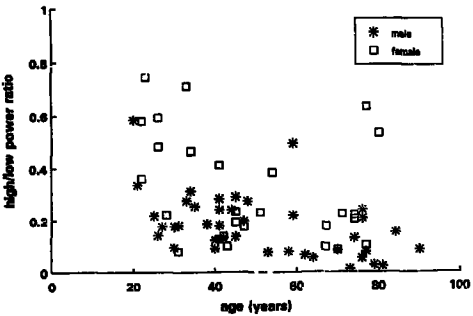

Figure 1. Effect of age on the high/low frequency power ratio for men and women during quiet breathing. There is a negative linear correlation between the high/low frequency power ratio and age ($R^2 = 0.32$, $p = 0.0007$). This relation is present for both men ($R^2 = 0.21$, $p = 0.01$) and women ($R^2 = 0.29$, $p = 0.02$).

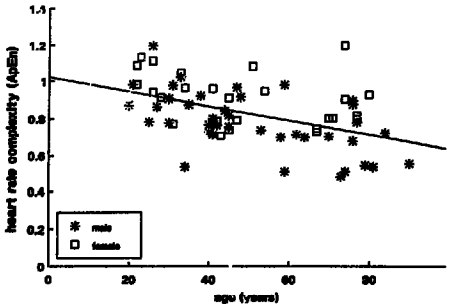

Figure 2. Effect of age on heart rate complexity (approximate entropy [ApEn]) for men and women during quiet breathing. There is a negative linear correlation between approximate entropy and age (R^2 = 0.36, p = 0.0001, adjusted for gender). For men alone, there is a negative linear correlation between heart rate approximate entropy and age (R^2 = 0.33, p = 0.0001), whereas this relation is not present for women (R^2 = 0.09, p = 0.14).

tent with previous reports, high frequency heart rate fluctuations and the overall complexity of heart rate dynamics were also found to decline with age (10,24).

Gender effects on heart rate variability. High frequency (0.15 to 0.40 Hz) heart rate fluctuations, which reflect vagally mediated respiratory sinus arrhythmia, are enhanced by metronomic breathing and are associated with healthy cardiovascular function (28–30). In contrast, heart rate fluctuations in this frequency band are attenuated with physiologic aging (10) and the development of coronary artery disease (15,31).

Although a number of studies (9–12) have reported age-related declines in spectral components of heart rate variability, these reports have either failed to describe gender differences or have provided only limited information. A previous report by Hayano et al. (31) includes a figure with data from control subjects that support our findings. In their study, female subjects had greater high frequency spectral power than healthy male subjects, across an age range of 40 to 70 years. However, Hayano et al. did not provide sufficient primary data for statistical comparisons.

Other studies that address the effect of gender on traditional measures of heart rate variability do not reveal prominent differences between men and women (7,8,32). However, these studies lack detailed analyses of beat-to-beat dynamics.

Nonlinear complexity of heart rate dynamics. Previous studies that failed to exhibit a gender distinction in heart rate variability (7,8,32) primarily applied *moment* statistical analysis (i.e., mean values and measures based on standard deviation) to the data. However, such measures of variability do not take into account dynamic variability. In contrast, spectral techniques and complexity measures, such as approximate entropy, provide information about the beat-to-beat dynamics of heart rate fluctuations (20–22). For example, the two heart rate time series shown in Figure 3 have similar mean values and variances but visually apparent differences in dynamic behavior. The dynamics are related to the *ordering* of the data points. As a more extreme illustration, one can take a perfectly periodic signal (sine wave) with a given mean value and variance and then randomize the data points to obtain a completely different signal but with the same first and second moments. To quantify such differences in dynamics requires measures other than mean value and variance, such as the power spectrum and newer complexity statistics. Spectral analysis and approximate entropy provide complementary information about the dynamics of a time series—the former quantifies the contribution of specific component frequencies, and the latter provides a single number that represents the overall regularity or predictability of the data.

Our finding that elderly women have a lower heart rate standard deviation but higher approximate entropy during 8 min of quiet breathing highlights the difference between variability and complexity. Conventional measures of heart rate variability reflect primarily the vagally mediated respiratory sinus arrhythmia. Therefore, they fail to describe the complex nonlinear interactions between multiple autonomic influences that regulate heart rate. By examining vagally mediated high frequency heart rate oscillations in relation to low frequency baroreflex-related oscillations, we found striking gender differences in all age groups that have previously not been evident with traditional techniques. Furthermore, mean approximate entropy values were generally higher in women than men in all age groups, although not always to a statistically significant extent. These preliminary findings suggest that there is an alteration in the balance of autonomic influences on heart rate in men compared with women and that this alteration may be reflected in measures of physiologic complexity, such as approximate entropy. Our results may motivate future studies with larger sample sizes to confirm the presence of gender-related differences in heart rate dynamics.

Recent reports (26,33) have suggested that a relatively high degree of "complexity" or unpredictability in physiologic signals, such as sinus rhythm heart rate, may be a marker of health, reflecting the multiple interacting physiologic control mechanisms that enable rapid adaptation to internal and

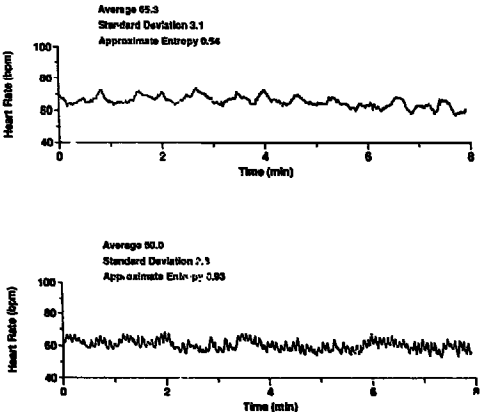

Figure 3. Illustration of heart rate complexity, which is different from heart rate standard deviation, a conventional measure of variability. Heart rate time series from a healthy 79-year old man (top) and a healthy 80-year old woman (bottom), both during quiet breathing in the supine position. Despite a slightly smaller standard deviation of the 8-min heart rate recording in the female than in the male subject, the elderly woman shows greater irregularity in beat-to-beat heart rate than the man. This irregularity or "complexity" is reflected in a higher approximate entropy value. In contrast, the more regular, less complex and more periodic features of the heart rate time series of the elderly man are reflected in a lower approximate entropy value. bpm = beats/min.

external perturbations. We showed in this and in previous work (24) that aging results in lower complexity of heart rate dynamics. Complexity measures such as approximate entropy may also provide novel markers of cardiovascular health that can be easily computed from relatively short data segments (20–25).

Mechanism of gender differences. The observed difference in heart rate dynamics between men and women could reflect a protective role of estrogen in women. In this case, one would anticipate a narrowing of the difference for men and women beyond menopause, which was not observed.

It is also possible that gender differences in systolic blood pressure and associated alterations in autonomic nervous system function could account for our findings. Hypertension is well known to impair baroreflex control of heart rate (34). However, this impairment would be manifest by differences in low frequency (baroreflex-mediated) heart rate oscillations rather than high frequency heart rate power (35). Only in elderly subjects during quiet breathing were there gender differences in low frequency power. However, in this age group gender differences in systolic blood pressure were the smallest (Table 1). Because low frequency power is enhanced by upright posture, blood pressure- or gender-related differences, or both, in baroreflex function may be evident only during orthostasis. In the present study, subjects were evaluated only while resting in the supine position.

Regardless of the mechanisms involved, the differences that we observed between men and women are important for interpreting past studies and devising new protocols that incorporate heart rate variability techniques, especially as more women are included in these investigations. Failure to analyze results in a gender-specific manner may yield misleading conclusions.

Limitations and future studies. There are several limitations to the present study. Because screening blood tests were not performed, some subjects may have had undetected diabetes, anemia or other diseases. There may also be unmeasured variables, such as individual levels of fitness, that influence the gender differences we observed in heart rate dynamics. Exercise stress tests and coronary angiography were not performed on our subjects; therefore, we cannot exclude with certainty the presence of subclinical coronary artery disease as a confounding variable, particularly in older men. However, gender differences in high frequency heart rate variability were also observed in young healthy subjects who are not likely to have occult heart disease. Studies in children and adolescents will be of interest to assess possible hormonal and developmental influences on heart rate dynamics.

Unfortunately, our sample size was small, with relatively few very elderly women. Because of subject exclusions and technical difficulties, there were disproportionate numbers of men and women in each age group. The relatively small sample size may be responsible for the lack of a statistically significant difference in approximate entropy values for men versus women in each age group. The finding of a significant gender difference in this complexity measure when all subjects were pooled may stimulate future studies with larger sample sizes.

Because tidal volume was not measured, we cannot directly assess the effects of respiratory mechanics on heart rate variability. However, it is not apparent how any such effects could account for gender differences in both spectral and

complexity measures observed during both spontaneous and metronomic breathing.

Finally, the influence of gender on heart rate responses to various perturbations other than metronomic breathing (e.g., autonomic blocking agents, cardiovascular diseases, posture change and other physiologic stresses), as well as on longer term basal heart rate dynamics, is also of interest. However, longer observation periods necessarily introduce nonstationarities, making controlled observations and statistical comparisons more difficult.

Conclusions. We find that women have relatively greater high frequency heart rate fluctuations and greater overall "complexity" of sinus rhythm heart rate variability than men. These complementary findings indicate the importance of gender- as well as age-related differences in heart rate dynamics. Whether these gender differences are related to the lower risk of cardiovascular disease and greater longevity in women requires further study.

Appendix: Approximate Entropy

Approximate entropy (ApEn) is calculated in the following way: Given N data points u(1), u(2), . . . , u(N), two input variables, m and r, must be fixed to compute ApEn (denoted precisely by ApEn(m, r, N)). To define ApEn, first form vector sequences x(1) to x(N − m + 1) from the {u(i)}, defined by x(i) = [u(i), . . ., u(i + m − 1)]. These vectors represent m consecutive u values, commencing with the ith point. Define the distance d[x(i), x(j)] between vectors x(i) and x(j) as the maximal difference in their respective scalar components. Use the sequence x(1), x(2), . . ., x(N − m + 1) to construct, for each i ≤ N − m + 1, $C_{im}(r)$ = (number of x(j) such that d[x(i), x(j)] ≤ r)/(N − m + 1). The $C_{im}(r)$'s measure *within a tolerance r* the regularity, or frequency, of patterns similar to a given pattern *of window length m*. Next, define $\Phi_m(r)$ as the average value of ln $C_{im}(r)$, where ln is the natural logarithm. We define approximate entropy by ApEn(m, r, N) = $\Phi_m(r) - \Phi_{m+1}(r)$, where ApEn measures the (logarithmic) likelihood that runs of patterns that are close for m observations remain close on next incremental comparisons. Greater likelihood of remaining close, regularity, produces smaller ApEn values, and conversely.

When m = 2, as previously shown, we interpret ApEn as a measure of the difference between the probability that runs of value of length 2 will recur within tolerance r, and the probability that runs of length 3 will recur (to the same tolerance). A high degree of regularity in the data would imply that a given run of length 2 would often continue with nearly the same third value, producing a low value of ApEn.

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