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Twenty-Four Hour Time Domain Heart Rate Variability and Heart Rate: Relations to Age and Gender Over Nine Decades

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Objectives. **This study sought to define the effects of age and gender effects on the normal range of time domain heart rate variability (HRV) over nine decades in healthy subjects.**

Background. **Low HRV is considered an independent marker of mortality risk. However, the age-related decline in HRV may limit its predictive value, particularly in the elderly. Delineation of the range of HRV in healthy subjects over the life span is needed. Gender-related differences in HRV also need clarification.**

Methods. **We determined, according to decade, 24-h heart rate (HR) and HRV of 260 healthy subjects (10 to 99 years old; 112 male, 148 female) by means of five standard time domain measures: standard deviation of all normal sinus RR intervals over 24 h (SDNN), standard deviation of the averaged normal sinus RR intervals for all 5-mm segments (SDANN), mean of the standard deviations of all normal sinus RR intervals for all 5-min segments (SDNN index), root-mean-square of successive normal sinus RR interval difference (rMSSD) and the percentage of successive normal sinus RR intervals >50 ms (pNN50).**

Results. **1) HRV decreased with aging, the pattern of change being measure dependent. HRV (SDNN and SDANN) decreased only very gradually, reaching 60% of baseline (second-decade values) by the tenth decade. With the SDNN index, HRV decreased linearly with aging, reaching 46% of baseline by the tenth decade. Using pNN50 and rMSSD, HRV decreased most rapidly, reaching 24% and 47% of baseline, respectively, by the sixth decade and then stabilized. 2) Using the SDNN index, rMSSD and pNN50, HRV of subjects >65 years old fell below published cutpoints for increased risk of mortality in 25%, 12% and 4%, respectively. 3) At age <30 years, HRV for all measures was lower in female than male subjects. Gender differences decreased at age >30 years and disappeared at age >50 years. 4) HR also declined with aging but much more slowly. HR at age <50 years was faster in female than in male subjects. Gender differences disappeared thereafter.**

Conclusions. **1) Using all measures, HRV of healthy subjects declines with aging, with measure-dependent patterns. 2) Using the SDNN index, rMSSD and pNN50, HRV of healthy subjects, particularly those >65 years old, may decrease to below levels associated with increased risk of mortality. 3) Gender influences HRV. Gender differences in HRV are age and measure dependent. 4) Age and gender also affect heart rate.**

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Low heart rate variability (HRV) has been proposed as a marker of a number of pathophysiologic conditions, including increased risk of mortality (1–6). Cutpoints for increased risk of mortality also have been proposed (2,3,7). However, the use of HRV for predictive purposes in the clinical setting must take into account the impact of a number of important physiologic factors. Of these, two stand out: age and gender.

With respect to age, HRV is known to decrease with normal aging (5,8–17). To the extent that this decline can lower HRV to levels associated with increased risk of mortality, it would limit the predictive value of HRV, particularly in the elderly, by making it difficult to distinguish low HRV due to disease from that due to normal aging (18).

Current concepts concerning the predictive utility of HRV are largely derived from 24-h Holter monitor–based time (1–3,7) and frequency (1,4) domain studies. Although a few recent studies of the effects of aging on HRV also have been based on 24-h Holter recordings (8,15–17,19), the available data are largely derived from studies over much shorter time periods that involved the use of a variety of autonomic function tests, including the tilt table, Valsalva maneuver and deep-breathing testing (9–14). There is little information concerning the changes in the normal range of 24-h HRV over a broad age span, particularly with respect to older subjects (1).

Gender also influences HRV. There are very few data concerning the effects of gender on HRV (9,15,19–23); most have been acquired incidentally in studies that focused on other concerns. In addition, available reports are controversial,

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with some reporting a higher HRV for female than for male subjects (19,20,22) and others reporting the converse (9,15,21,23). As a result, gender–HRV relations require clarification. Finally, because HRV is a function of heart rate (HR) in healthy subjects (21), and HR is influenced by gender (19,21), the effects of aging and gender on HR also require clarification.

Resolution of these concerns would help provide the improved standardization of HRV methodology requested by the Cardiovascular Technology Assessment Committee of the American College of Cardiology (24) and by doing so would enhance the predictive utility of HRV. Delineation of the effects of aging and gender on 24-h time domain HRV and HR over nine decades and establishment of age- and gender-adjusted norms could also enhance predictive utility. The rapid increase in the number of subjects living into the eighth and ninth decades of life and beyond underscores the need (25).

The present study therefore proposed to 1) assess, by decade, the effects of normal aging on 24-h HRV, defined in terms of five standard time domain measures (standard deviation of all normal sinus RR intervals over 24 h [SDNN], standard deviation of the averaged normal sinus RR intervals for all 5-min segments [SDANN], mean of the standard deviations of all normal sinus RR intervals for all 5-min segments [SDNN index], root-mean-square of the successive normal sinus RR interval difference [rMSSD] and the percentage of successive normal sinus RR intervals >50 ms [pNN50]); 2) establish age-adjusted normal ranges for each measure; 3) characterize the effect of gender on HRV at different ages; and 4) define the effects of age and gender on HR.

Methods

Subjects. Two hundred sixty healthy subjects 10 to 99 years old (112 male, 148 female) were recruited into the study (Table 1). Of the total, 137 were outpatients who had gone to the physician's office for a routine medical evaluation or minor symptoms. Twelve were healthy elderly subjects from assisted-living communities. One hundred eleven were healthy volunteers (30 from the Chicago and Elk Grove area, 81 from northern California). *Healthy subjects* were defined as those without clinical evidence of organic disease in terms of medical history, physical examination, rest 12-lead electrocardiogram, routine blood chemistry profiles and complete blood count. Oral contraceptives and nonsteroidal anti-inflammatory agents were the only medications allowed. Subjects who exhibited abnormalities in one or more of the aforementioned categories were excluded from study. Informed consent for the use of Holter information was obtained from each subject.

Data collection. All subjects underwent 24-h ambulatory Holter ECG monitoring. Of 179 subjects who were monitored with a Cardionostics Dura-Lite recorder (Cardionostics), 107 underwent HRV analyses with the Premier IV Holter program, version 1.10 Holter system (Cardiac Research) and 72 with the Epicardia 4000 53A-01 program (Medicomp). In the remaining 81 subjects, all from California, a Del Mar 459 recorder was used, and records were analyzed with the model 463 AccuPlus Holter Analyzer (Del Mar Avionics). Each beat was classified and labeled with respect to site of origin by means of template-matching techniques. All recordings were manually overread and corrected by an experienced Holter technician and a cardiologist (K.U., D.H.S.). The programs eliminate one RR interval before and two after each nonsinus beat. Recordings <20 h in duration, and those in which nonsinus beats comprised >10% of the total number of beats, were excluded. Three subjects were excluded from the study because of high frequency, high grade supraventricular ectopic beats. Randomly selected Holter tapes were cross-analyzed with the use of all three programs. HRV and HR determinations from identical tapes were within 10% of each other.

Measures of 24-h time domain HRV. HRV was computed for each subject by means of five standard 24-h time domain measures: SDNN, SDANN, SDNN index, rMSSD and pNN50. Relations between each HRV measure, HR and age were assessed with linear and quadratic regression methods. HRV and HR for different decades and two-decade groupings were compared. Gender effects on HRV and HR were analyzed on the basis of two-decade groupings to ensure an adequate number of subjects in each group.

The normal range of HRV for each measure was defined in

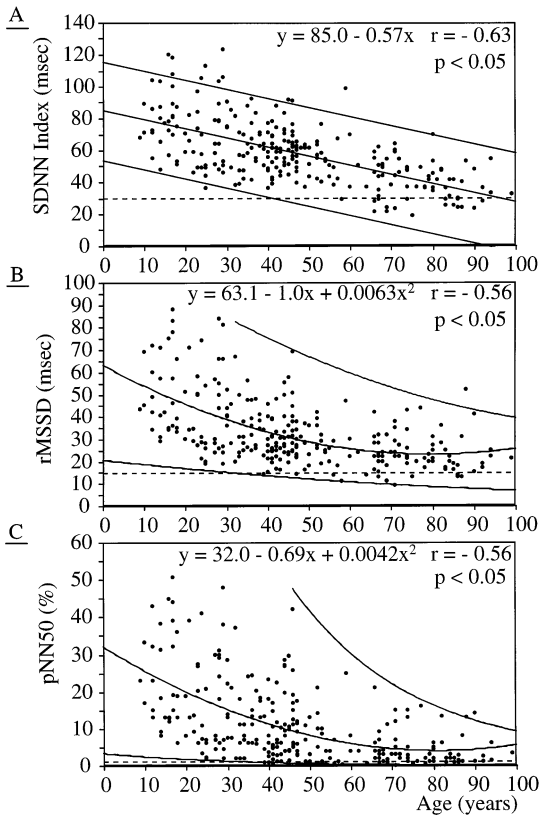


Figure 2. Relations between age and HRV determined by SDNN index **(A),** rMSSD **(B)** and pNN50 **(C)** in healthy subjects. **Solid lines** = fitted regression lines and upper and lower 95% confidence limits. **Dashed lines** = published cutpoints for increased risk of mortality (SDNN index 30 ms, rMSSD 15 ms, pNN50 0.75%). Only the SDNN index shows a linear regression pattern; rMSSD and pNN50 show quadratic regression. Note that HRV determined by these measures exhibits a much more pronounced decline with age than did that determined by SDNN and SDANN. The proportion of healthy subjects >65 years old for whom values extended below cutpoints was 25% for SDNN index, 12% for rMSSD and 14% for pNN50.

HRV: gender effects. Our data further confirm gender influences on HRV and show that these differences are age dependent (Fig. 3 and 4, Table 4). Table 4 provides a comparison of HRV for male and female subjects in two-decade groupings. HRV (for all measures) was significantly lower in "young" (10 to 29 years old) female subjects than in age-matched male subjects. Gender differences subsequently decreased and then disappeared with aging at varying measure-dependent rates. Using rMSSD and pNN50 measures, gender differences disappeared after age 30. However, using SDNN, SDANN and SDNN index measures, differences persisted until age 50. Beyond age 50, gender differences disappeared for all measures.

Figures 3 and 4 show the overall correlation between HRV and age for both male and female subjects. Only the SDNN index exhibited a linearly correlated pattern of decline with aging for both genders. Using SDNN, SDANN, rMSSD and pNN50, the relations between HRV and age were quadratic. The pattern of decrease with aging was steeper for male than for female subjects (all measures). Correlation coefficients (all measures) for female subjects were lower than those for male subjects.

In Table 4, the age-related decrease in HRV for male subjects was greater and more rapid than that for female subjects (all measures). Using SDNN, SDANN and the SDNN index, HRV for male subjects began to decrease significantly before age 30. Using SDNN and SDANN, HRV for female subjects exhibited a significant decrease with aging only with respect to the comparisons between the youngest (10 to 29 years) and oldest (70 to 99 years) groups. Using the SDNN index, HRV of female subjects >50 years old was significantly lower than that of young (10 to 29 years) female subjects. In contrast, using rMSSD and pNN50, HRV for both genders began to decline significantly at >30 years, although the rate of decline was still much slower in female subjects.

HR: age and gender effects. HR also declined significantly with aging but at a much slower rate (Fig. 5A). Decade comparisons did not show significant changes (Table 2). HR also was influenced by gender (Fig. 5B, Table 4). HR for female subjects was significantly higher than that for age-matched male subjects <50 years, and gender difference disappeared at >50 years. The rate of decline of HR with aging differed for male and female subjects (Fig. 5B). HR for female subjects declined significantly with aging. In contrast, HR for male subjects was not affected significantly by aging.

Discussion

Our results permit establishment of normal ranges of HRV (SDNN, SDANN, SDNN index, rMSSD and pNN50 measures) and of HR for healthy subjects over nine decades. The results show that 1) for all measures, HRV decreases with aging at a varying rate and to a different degree, depending on the measure; 2) aging can reduce HRV (SDNN index, rMSSD and pNN50) below published cutpoints for increased risk of mortality; 3) HRV (all measures) is gender dependent, with values for female subjects <30 years old being lower than those for age-matched male subjects (all measures); 4) gender HRV differences decrease with aging, disappearing at >50 years, the age of disappearance being measure dependent; and 5) HR also decreases with age and is influenced by gender: the HR for female subjects (<50 years) is higher than that for age-matched male subjects.

HRV: aging effects. With all measures, HRV declines with aging (Figs. 1 and 2, Table 2). Of the several measures, pNN50 exhibited the earliest and most rapid decline. This measure correlates closely with high frequency (HF) power (r = 0.88) (15), which is thought to reflect parasympathetic activity (1,26). The earlier and more rapid decline of HRV with pNN50 is in accordance with power spectrum studies by Shannon et al. (10) and Korkushko et al. (11) showing an early decline in the parasympathetic modulation of HR. HRV determined with rMSSD, which also correlates closely with HF power (r = 0.94) (15), declines more gradually. The differential rates of HRV decline determined by these measures may be more apparent

Table 2. Aging Effects on 24-h Heart Rate Variability and Heart Rate by Decade

Age (yr)	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	rMSSD (ms)	pNN50 (%)	HR (beats/min)
10–19	176 ± 38	159 ± 35	81 ± 20	53 ± 17	25 ± 13	80 ± 10
20–29	153 ± 44	137 ± 43	72 ± 22	43 ± 19	18 ± 13	79 ± 10
30–39	143 ± 32*	130 ± 33	64 ± 15*	35 ± 11*	13 ± 9*	78 ± 7
40–49	132 ± 30*	116 ± 31*	60 ± 13*†	31 ± 11*†	10 ± 9*	78 ± 7
50–59	121 ± 27*	106 ± 27*	52 ± 15*†	25 ± 9*†	6 ± 6*†	76 ± 9
60–69	121 ± 32*	111 ± 31*	42 ± 13*†‡§	22 ± 6*†	4 ± 5*†	77 ± 9
70–79	124 ± 22*	114 ± 20*	43 ± 11*†‡§	24 ± 7*†	4 ± 5*†	72 ± 9
80–99	106 ± 23*†‡	95 ± 24*†‡	37 ± 12*†‡§	21 ± 6*†‡	3 ± 3*†‡	73 ± 10

*$p < 0.05$, other age ranges versus 10 to 19 years. †$p < 0.05$, other age ranges versus 20 to 29 years. ‡$p < 0.05$, other age ranges versus 30 to 39 years. §$p < 0.05$, other age ranges versus 40 to 49 years. Data presented are mean value ± SD. HR = heart rate; pNN50 = percentage of successive normal sinus RR intervals >50 ms; rMSSD = root-mean-square of the successive normal sinus RR interval difference; SDANN = standard deviation of the averaged normal sinus RR intervals for all 5-min segments; SDNN = standard deviation of all normal sinus RR intervals over 24 h; SDNN index = mean of the standard deviations of all normal sinus RR intervals for all 5-min segments.

than real because by definition, the pNN50 measure cannot reflect variability in interbeat intervals that fall below its arbitrary limits of 50 ms. The rMSSD measure, which has no such limitation, would be expected to exhibit a more gradual decline.

Our data show that the decline in HRV determined using these measures stabilizes at age >60 years, which differs from the report by Shannon et al. (10), who showed that HF power decreases from 9 to 30 years and then stabilizes. The differences probably reflect the fact that the data of Shannon et al. were based on controlled short-term records rather than 24-h recordings. Unlike controlled short-term recordings, the 24-h record is influenced by environmental changes, including day/night differences, as well as by differences in emotional state and physical activity.

Using the SDNN and SDANN measures, HRV exhibits the weakest correlation with aging, declining only very slowly and very modestly over time (Fig. 1, Table 2), in accordance with findings by Bigger et al. (15) in healthy middle-aged (40 to 69 years old) subjects. Our study, which covers a much broader age range, shows only one exception to this pattern, namely that HRV determined with these measures exhibits an accelerated decline during the second, ninth and tenth decades. The mechanisms underlying the more rapid decline during the second compared with later decades are not known. Differences in activity levels represent one possible explanation (27).

The accelerated decline during the ninth and tenth decades also requires clarification. Kleiger et al. (3) and Bigger et al. (7) reported that SDNN and SDANN are good predictors of risk of death in patients with ischemic heart disease. It is tempting to speculate that deterioration in the underlying regulatory mechanisms during the ninth and tenth decades contributes to the probability of death in this population. It is of interest in this regard that the normal human life span only very rarely extends beyond the ninth decade (25). Resolution awaits further clarification of the physiologic basis of these measures.

HRV determined by the SDNN index most closely correlates with aging, exhibiting a linear decrease over the nine decades studied (Fig. 2). This accords with the findings of Ori et al. (8) over a more limited age range. Mechanistically, power

Table 3. Effects of Aging on Lower and Upper 95% Confidence Limits of 24-h Heart Rate Variability and Heart Rate*

	95% Confidence Limits					
Age (yr)	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	rMSSD (ms)	pNN50 (%)	HR (beats/min)
10	101–279	85–261	48–113	25–103	4–137	57–105
20	93–257	79–241	42–107	21–87	3–97	56–104
30	86–237	73–223	36–100	18–74	2–68	55–103
40	79–219	67–206	30–94	15–63	1–48	54–102
50	73–202	63–190	24–88	13–53	1–34	53–100
60	68–186	58–176	18–82	11–45	1–24	52–99
70	62–172	53–163	11–77	9–38	1–17	51–98
80	57–159	49–151	5–70	8–32	0–12	49–97
90	53–147	45–140	0–58	7–28	0–9	48–96

*Because use of rMSSD and pNN50 resulted in skewed data distribution, upper and lower 95% confidence limits provide a more reliable method for defining normal heart rate variability range with these measures than does mean value ± 2 SD. Abbreviations as in Table 2.

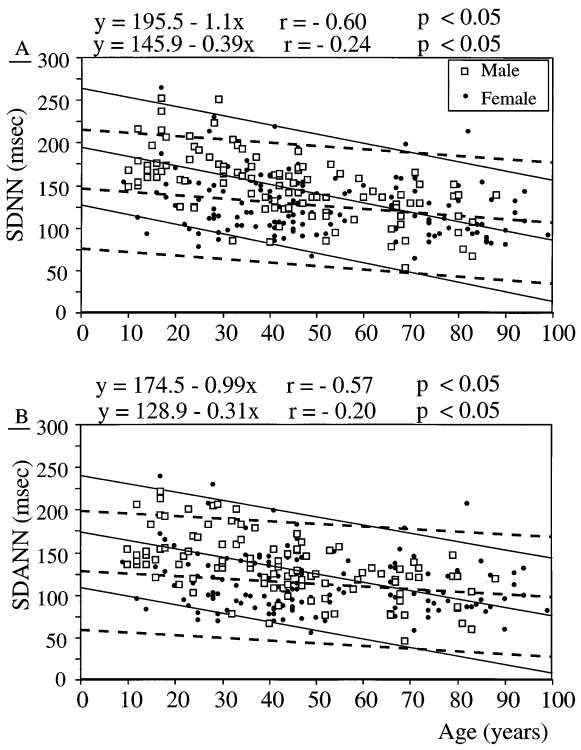


Figure 3. Relations between age and HRV determined by SDNN (**A**) and SDANN (**B**) for healthy male (**open squares**) and female (**solid circles**) subjects. The fitted regression line and upper and lower 95% confidence limits are depicted by **solid lines** for male subjects and **dashed lines** for female subjects.

spectral studies show that the SDNN index correlates with both low frequency (LF) (r = 0.86) and very low frequency (VLF) (r = 0.95) components of the power spectrum (15). The physiologic bases of LF and VLF power are still not well defined (1,6). LF power is generally thought to be modulated by both sympathetic and parasympathetic activity but predominantly by the latter through the baroreceptor mechanism (26). The gradual decline in the SDNN index over the life span could reflect the slower decline of sympathetic compared with parasympathetic activity.

HRV: normal range and aging effects. Given the age dependence of HRV, its use for predictive purpose requires an understanding of its normal range at different ages. In healthy populations, the range of HRV for all measures except the SDNN index (Table 3, Fig. 1 and 2), defined in terms of 95% confidence limits, is widest in young subjects and narrows with aging, reflecting a decrease in interindividual differences over time. Age-related narrowing is mainly due to a greater decrease in the upper, rather than the lower, 95% confidence limits.

Our HRV ranges are consistent with normal values reported by Ori et al. (8) for HRV determined by SDNN index in healthy 22- to 81-year old subjects and by Bigger et al. (15) for multiple HRV measures in healthy 40- to 69-year old subjects, but our mean HRV values determined by SDNN and SDANN were somewhat lower than their values for these measures. These differences reflect differences in the upper limits of the range of HRV values (i.e., 63 to 219 and 57 to 197 ms for SDNN and SDANN, respectively, for Bigger et al. [15] (age 57 ± 8 years, versus 68 to 186 and 58 to 176 ms for our own data [Table 3, age 60]). The reason for the differences in the upper limits between the two studies is not clear. In contrast, the lower limits of the normal HRV range for this age group are comparable for all measures. The comparability for the lower limits of the normal HRV range is important because it is the lower 95% confidence limit that defines cutpoints that separate normal from abnormal values.

Bigger et al. (15) reported that SDNN and SDANN are least affected by aging. Cutpoints (SDNN 50 ms, SDANN 40 ms) originally proposed by Kleiger et al. (3,7) might therefore be expected to hold throughout adult life. Our data, which show that the lower 95% confidence limits of HRV determined by these measures do not decline below published cutpoints for increased risk of mortality even at advanced ages,

Figure 4. Relations between age and HRV determined by SDNN index (**A**), rMSSD (**B**) and pNN50 (**C**) for healthy male (**open squares**) and female (**solid circles**) subjects. The fitted regression line and upper and lower 95% confidence limits are depicted by **solid lines** for male subjects and **dashed lines** for female subjects. Only the SDNN index exhibits a linear regression pattern for both genders. With rMSSD and pNN50, HRV declines in a quadratic regression pattern for both genders.

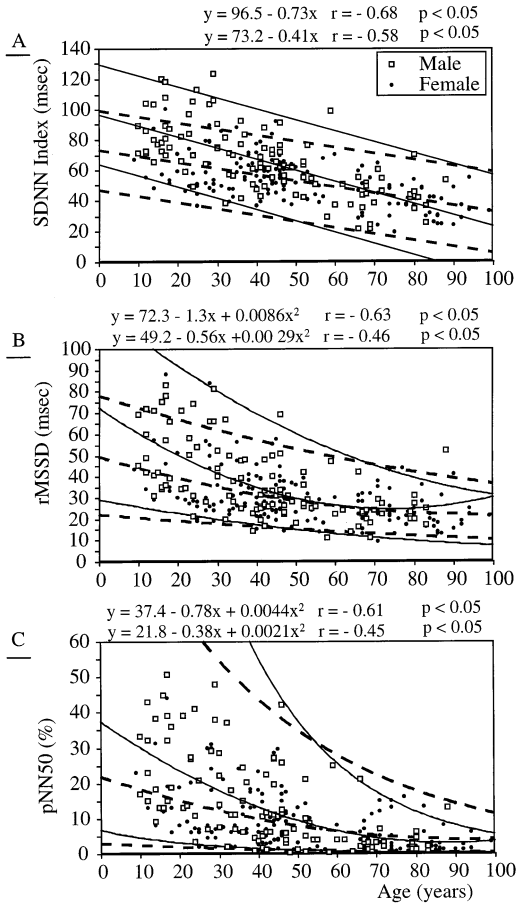


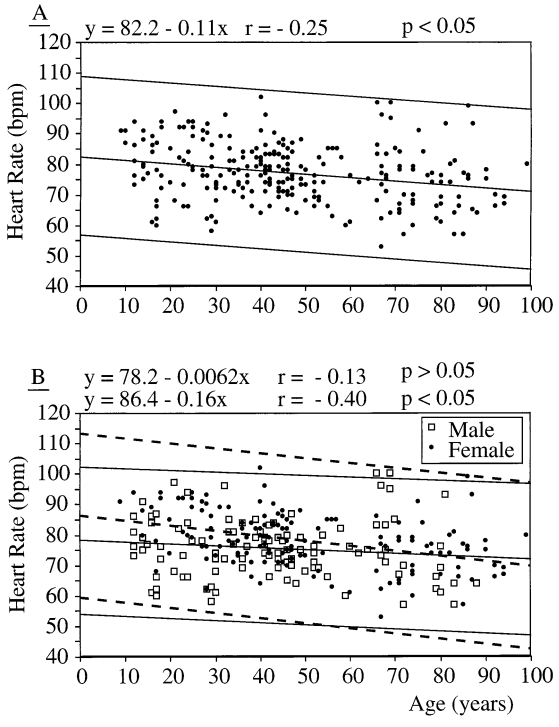
Table 4. Gender Effects on 24-h Heart Rate Variability and Heart Rate for Four Age Groups

Age (yr) and Gender	SDNN (ms)	SDANN (ms)	SDNN Index (ms)	rMSSD (ms)	pNN50 (%)	HR (beats/min)
10–29						
M	*182 ± 35	*162 ± 33	*88 ± 20	*53 ± 18	*26 ± 13	*76 ± 10
F	*147 ± 43	*133 ± 42	*66 ± 18	*43 ± 18	*17 ± 12	*83 ± 8
30–49						
M	*146 ± 30†	*131 ± 31†	*65 ± 14†	34 ± 13†	13 ± 10†	*76 ± 7
F	*129 ± 30	*114 ± 31	*58 ± 13	31 ± 10†	10 ± 7†	*79 ± 7
50–69						
M	117 ± 30†‡	104 ± 28†‡	46 ± 18†‡	22 ± 8†‡	4 ± 5†‡	78 ± 11
F	125 ± 29	114 ± 29	49 ± 11†	25 ± 7†	5 ± 4†	74 ± 10†
70–99						
M	123 ± 24†	109 ± 28†	43 ± 12†‡	22 ± 5†‡	3 ± 2†‡	72 ± 11
F	114 ± 23†	102 ± 22†	38 ± 10†‡	22 ± 8†‡	4 ± 4†‡	73 ± 8†‡

*$p < 0.05$, male (M) versus female (F) in same age range. †$p < 0.05$, other groups versus age range 10 to 29 years for same gender. ‡$p < 0.05$, other groups versus age range 30 to 49 years for same gender. Data presented are mean value ± SD. Other abbreviations as in Table 2.

are in accordance with the report of Bigger et al. That report also noted that LF and HF (which correspond to SDNN index, rMSSD and pNN50) are more sensitive to aging than SDNN and SDANN. Our data are in accordance with these findings. In addition, our findings that HRV falls below published cutpoints in 25% (SDNN index, cutpoint = 30 ms), 4% (SDNN index, cutpoint = 30 ms), 12% (rMSSD) and 14% (pNN50) of healthy subjects >65 years old (Table 5), suggest that cutpoints for these measures may be more sensitive to aging than are SDNN and SDANN. Findings that the lower 95% confidence limit of the normal range for HRV extend to below published cutpoints even in subjects <65 years old are supportive (Fig. 2). Comparisons between 24-h HRV of healthy subjects with those of patients with angiographically detected one-vessel and multivessel coronary disease in subjects >65 years old showing that HRV determined using rMSSD and pNN50 does not differ for the three groups (28) are pertinent in this regard, as are findings that HRV determined by SDNN index in healthy subjects and age-matched patients with one-vessel disease do not differ significantly. A strong age dependence of these measures may detract from their use for risk stratification in older populations.

Figure 5. Relations between age and HR for all subjects **(A)** and for male and female subjects **(B). A,** Linear regression line and upper and lower 95% confidence limits are depicted by **solid lines. B,** Linear regression line and upper and lower 95% confidence limits are depicted by **solid lines** for male subjects and **dashed lines** for female subjects. HR of the cohort as a whole declines gradually with aging **(A),** but this principally reflects a decline in female HR. Male HR does not decline significantly with aging **(B).**



HRV: gender differences. Previous investigations have found gender differences in 24-h HRV, with values for female subjects being significantly lower than those for age-matched male subjects (15,19,21). In this regard, Hoogenhuyze et al. (21) reported higher HRV in male subjects (age 24 to 54 years) with use of SDANN and SDNN index, an observation supported by findings by Bigger et al. (15) of higher levels of very LF and LF power in male than in female subjects (age 40 to 69 years). Bigger et al. did not report gender differences in HF power; however, subjects were not segregated by age.

Our data also show that gender differences are age and measure dependent, HRV of young female subjects being lower than that of age-matched male subjects (age 10 to 29 years) (Table 4). Gender differences decline with aging and disappear by age 50, the age at disappearance varying with the measure used. The most pronounced differences in young subjects occur with pNN50; HRV of young male subjects is 53% higher than that of age-matched female subjects. All the other measures result in smaller (22% to 33%), but still significant, gender differences.

The normal range of HRV (all measures) also differs for

Table 5. Low Heart Rate Variability With Age: Relation to Cutpoints for Risk of Mortality

HRV Measures	Published Cutpoints	% >65 Subjects With HRV Below Cutpoints
SDNN index	<30 ms	25%
	<20 ms	4%
rMSSD	<15 ms	12%
pNN50	<0.75%	14%
SDNN	<50 ms	0
SDANN	<40 ms	0

HRV = heart rate variability; other abbreviations as in Table 1.

male and female subjects (Fig. 3 and 4). Both the upper and lower limits of HRV appear to be higher in male than in female subjects, especially below age 50. Gender differences in the normal HRV range may be sufficiently pronounced to require the use of different HRV curves for male and female subjects.

The mechanisms underlying age-related gender differences in HRV are not clear. Because pNN50 and rMSSD correlate closely with parasympathetic function (1,26), the gender differences that we observed could reflect lower levels of parasympathetic activity in young female subjects. A higher HR in young female subjects supports this view. The early disappearance of gender differences with these measures (>30 years) probably reflects the earlier decline in parasympathetic, as compared with sympathetic, activity (10,11). The reason for the longer persistence (to age 50) of gender HRV differences with aging determined using SDNN index, SDNN and SDANN compared with rMSSD and pNN50, is not known. Because SDNN index reflects both sympathetic and parasympathetic activity (1,6,26), the slower reduction of gender difference in HRV determined by this measure could be attributed to the higher level of sympathetic activity in male subjects and the more gradual decline in sympathetic activity with aging. Furthermore, gender differences in physical fitness and activity levels also may affect gender HRV differences, particularly in young subjects (27). Although we did not standardize activity levels, none of our subjects engaged in competitive sports. Insofar as the SDNN and SDANN are concerned, further clarification of the physiologic bases of these measures is required to explain the effects of aging on gender HRV differences.

HR: age and gender effects. Our data show that HR decreases gradually with aging and at a different rate in male and female subjects. Gender differences disappear after age 50. Reported "intrinsic HR" (i.e., HR after pharmacologic blockade with atropine plus propranolol) also decreases with aging (29). In addition, intrinsic HR is higher than "real HR" at all ages, a finding that supports the conclusion that both genders exhibit parasympathetic predominance over the life span (29). The reported slopes of the decline in intrinsic HR with aging in both genders (approximation formulas: $y = 118 - 0.55\times$ for male subjects; $y = 119 - 0.61\times$ for female subjects) are steeper than the slopes of the decline in real HR (Fig. 5). Differences between intrinsic and real HR decrease with aging in both genders but more so in male than female subjects, underscoring evidence from HRV studies that parasympathetic activity is higher at younger ages, especially in young male subjects, and decreases more rapidly than sympathetic activity with normal aging.

Study limitations. A number of caveats deserve consideration. The first and most important of these concerns our definition of "healthy subject" and the nature of the selection process, particularly in elderly subjects (30). We defined "healthy subject" in terms of medical history, physical examination, rest 12-lead electrocardiography, routine blood chemistry profiles and complete blood count. In addition, it was required that subjects not take any medications except for nonsteroidal anti-inflammatory agents and oral contraceptives. We did not attempt to screen for occult cardiac disease. These criteria appear to be similar to those reported by other investigators (15,21). Although it would have been desirable to further refine the selection process by means of studies such as treadmill exercise testing, ultrasound examination and coronary angiography, this was rejected by a majority of the healthy subjects. As a result, the possibility that occasional subjects had occult heart disease that might contribute to the observed decline in HRV, as determined by SDNN index, rMSSD and pNN50, below published cutpoints cannot be entirely excluded. However, findings that SDNN and SDANN did not decrease to below the cutpoints detract from the possibility that apparent age-related decreases in HRV also could reflect the presence of occult heart disease. To the extent that occult heart disease influences HRV, it might be expected that HRV by SDNN and SDANN would exhibit a more pronounced decline (15). In addition, given that our study includes >20 subjects in each decade grouping, including 74 healthy subjects >60 years old, the inclusion of occasional subjects with occult heart disease would not be likely to significantly influence HRV.

Second, the number of subjects is not evenly distributed among the nine decades and different genders. Middle-aged subjects, particularly women 40 to 49 years old, are overrepresented, and elderly men >70 years old are underrepresented. To reduce the disproportion among male and female subjects, gender effects were analyzed on a two-decade basis to ensure an adequate number of subjects in each group. Although the disproportional distribution of subjects could affect the statistical analysis of decade-based data, the pattern of decrease in each HRV measure is virtually identical to the respective regression line. This suggests that the disproportional population distribution does not significantly affect decade by decade analysis of HRV. Additional large studies that include underrepresented groups are needed.

Third, 24-h HRV is known to be influenced by physical fitness and activity level (27). Aside from the exclusion of subjects who engage in competitive sports, we did not standardize activity levels. It therefore cannot be excluded that decreases in activity level with aging may have contributed to the observed age-related decline in HRV, particularly in the elderly. It is also possible that differences in activity contrib-

uted to the lower HRV of young female subjects compared with that in age-matched male subjects.

Conclusions. 1) Our results underscore the age dependence of 24-h time domain HRV of healthy subjects; that is, HRV (by all measures) decreases with aging. The results also facilitate the establishment of age-adjusted normal ranges for HRV across nine decades. The pattern of HRV decline is measure dependent. These phenomena presumably reflect age- and measure-dependent differences in underlying autonomic or other regulatory mechanisms. 2) Normal aging can lower HRV, as determined by SDNN index, rMSSD and pNN50, to below levels associated with increased risk of mortality, particularly at >65 years. 3) Gender also influences HRV. The differences are most pronounced in subjects <30 years, HRV of young male subjects being significantly greater than that of age-matched female subjects. Differences disappear by age 50. 4) Age and gender effects on HR are qualitatively similar to those defined for HRV. 5) Taking age and gender into account facilitates a more accurate delineation of the normal range of HRV and HR, which could help to improve the diagnostic and predictive usefulness of HRV in the clinical setting.

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