Relation of High Heart Rate Variability to Healthy Longevity

Usman Zulfiqar, MD[a,c], Donald A. Jurivich, DO[a], Weihua Gao, PhD[d], and Donald H. Singer, MD[b,e,*]

The population's aging underscores the need to understand the process and define the physiologic markers predictive of healthy longevity. The findings that aging is associated with a progressive decrease in heart rate variability (HRV), an index of autonomic function, suggests that longevity might depend on preservation of autonomic function. However, little is known about late life changes. We assessed the relation between autonomic function and longevity by a cross-sectional study of HRV of 344 healthy subjects, 10 to 99 years old. The HRV was determined from 24-hour Holter records, using 4 time domain measures of HRV (the root mean square of the successive normal sinus RR interval difference [rMSSD], percentage of successive normal sinus RR intervals >50 ms [pNN50], standard deviation of all normal sinus RR intervals during a 24-hour period [SDNN], and standard deviation of the averaged normal sinus RR intervals for all 5-minute segments [SDANN]). Autonomic modulation of the 4 measures differs, permitting distinctions between changes in HRV–parasympathetic function, using rMSSD and pNN50, and HRV–sympathetic function using SDNN and SDANN. Decade values were compared using analysis of variance and t-multiple comparison testing. The HRV of all measures decreases rapidly from the second to fifth decades. It then slows. The HRV–sympathetic function continues to decrease throughout life. In contrast, the decrease in HRV–parasympathetic function reaches its nadir in the eighth decade, followed by reversal and a progressive increase to higher levels ($p < 0.05$), more characteristic of a younger population. In conclusion, healthy longevity depends on preservation of autonomic function, in particular, HRV–parasympathetic function, despite the early age-related decrease. The eighth decade reversal of the decrease in HRV–parasympathetic function and its subsequent increase are key determinants of longevity. Persistently high HRV in the elderly represents a marker predictive of longevity. **(Am J Cardiol 2010;105:1181–1185)**

Little is known about the late age-related changes in autonomic function, in part, because very few studies[1–4] have included the "oldest" older subjects (>85 years). Moreover, few studies have fully used the 4 time domain measures of heart rate variability (HRV): the root mean square of the successive normal sinus RR interval difference (rMSSD), percentage of successive normal sinus RR intervals >50 ms (pNN50), standard deviation of all normal sinus RR intervals during a 24-hour period (SDNN), and standard deviation of the averaged normal sinus RR intervals for all 5-minute segments (SDANN). Restrictions to using SDNN and/or SDANN,[5] both of which are predominantly markers of HRV–sympathetic function[6] (HRV–SF), might detract from the analysis of HRV–parasympathetic function (HRV–PF). The present study sought to determine the relation between longevity and autonomic function (parasympathetic and sympathetic), through analyses of the HRV, determined from 24-hour Holter monitoring, using 4 standard time domain measures (rMSSD, pNN50, SDNN, and SDANN).

Methods

A total of 344 healthy subjects, aged 10 to 99 years (159 males and 185 females), were recruited to the present study. Of the 344 subjects, 221 were outpatients who had gone to the physician's office for a routine medical evaluation; 12 were healthy elderly subjects from assisted living communities; and 111 were healthy volunteers (30 from the Chicago and Elk Grove area and 81 from northern California).

Healthy subjects were defined as those without clinical evidence of organic disease. Oral contraceptives and low-dose aspirin were the only allowed medications. Their health status was established by a complete medical history, physical examination, and laboratory tests, including electrocardiography at rest, fasting blood chemistry panels, a complete blood cell count, and urinalysis. All subjects gave informed consent, with informed consent for minors (<18 years old) obtained from their parents or legal guardians.

All subjects underwent 24-hour ambulatory Holter monitoring. Of the 344 subjects, 263 were monitored using a Cardionostics Dura-Lite recorder (Cardionostics, Roche Biomedical, Tucker, Georgia). Of these, the records of 107 subjects were analyzed using the Premier IV Holter program, version 1.10, Holter system (Cardiac Research, Tampa, Florida) and 156 using the Epicardia 4000 53A-01 Program (Medicomp, Melbourne, Florida). The remaining 81 subjects from California were monitored using Del Mar 459 recorders, and the records were analyzed using the model 463 Accu-plus Holter Analyzer (Del Mar Avionics, Irvine, California).

Sections of [a]Geriatric Medicine and [b]Cardiology, University of Illinois at Chicago College of Medicine, Chicago, Illinois; [c]Department of Internal Medicine and [d]Division of Biostatistics, Mercy Catholic Medical Center, Darby, Pennsylvania; and [e]Department of Cardiology, Alexian Brothers Medical Center, Elk Grove Village, Illinois. Manuscript received October 26, 2009; revised manuscript received and accepted December 3, 2009.

*Corresponding author: Tel: (847) 328-9102; fax: (847) 864-2080.
E-mail address: dandrsinger@msn.com (D.H. Singer).

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Table 1
Effects of aging on 24-hour heart rate variability (HRV) of healthy subjects

Age (years)/Total Subjects	rMSSD (ms)	pNN50 (%)	SDNN (ms)	SDANN (ms)
10–19/n = 22	53 ± 16	26 ± 13	173 ± 33	151 ± 33
20–29/n = 47	41 ± 16*	17 ± 12*	151 ± 37	134 ± 36
30–39/n = 54	36 ± 15*	14 ± 11*	145 ± 41*	129 ± 40
40–49/n = 96	27 ± 10*†‡	8 ± 7*†‡	125 ± 33*†‡	112 ± 35*†
50–59/n = 43	24 ± 11*†‡	6 ± 7*†‡	120 ± 37*†‡	108 ± 38*†
60–69/n = 38	20 ± 10*†‡	4 ± 6*†‡	114 ± 33*†‡	106 ± 34*†‡
70–79/n = 24	19 ± 7*†‡	3 ± 3*†‡	116 ± 29*†‡	107 ± 30*
80–99/n = 20	30 ± 21*†§	10 ± 14*†§	109 ± 30*†‡	99 ± 29*†‡

* Other age ranges versus 10–19 years ($p < 0.05$); † other age ranges versus 20–29 years ($p < 0.05$); ‡ other age ranges versus 30–39 years ($p < 0.05$); § Age range 80–99 years versus 70–79 years ($p < 0.05$).

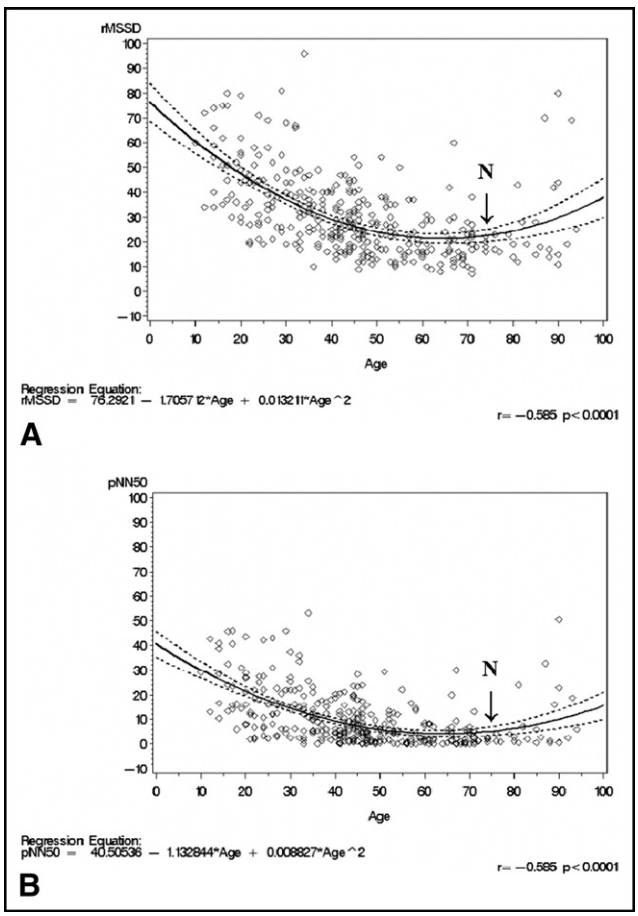

Figure 1. Scatter plots showing best fit line depiction of age-related changes in HRV–PF determined using rMSSD *(A)* and pNN50 *(B). Solid lines* indicate fitted regression lines; and *dashed lines,* upper and lower 95% confidence intervals. Note, 2 HRV curves exhibited U-shaped pattern (quadratic regression), with a trough in their mid-section, at which point HRV had reached its low point or nadir. Postnadir upswing reflected reversal of decrease in HRV–PF associated with longevity. The period between the age at which HRV (both rMSSD and pNN50) reached nadir (eighth decade) and the age at which it began to increase (ninth decade) has been designated the "critical threshold."

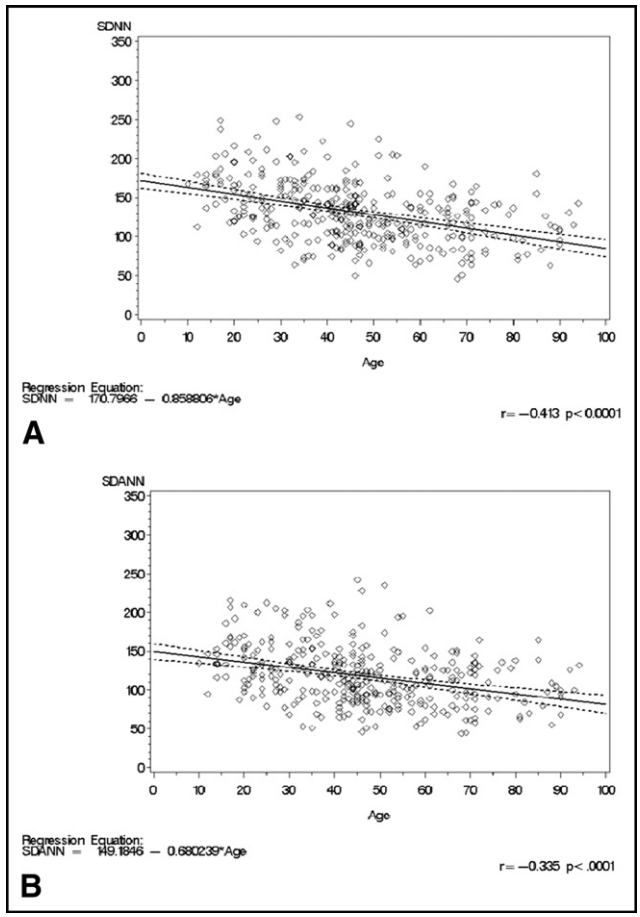

Figure 2. Scatter plots showing best fit line depictions of age-related changes in HRV–SF, determined using SDNN *(A)* and SDANN *(B). Solid lines* indicate fitted regression lines; and *dashed lines,* upper and lower 95% confidence intervals. Both SDNN and SDANN showed a linear regression pattern. In contrast to HRV determined using rMSSD and pNN50, curves for sympathetically modulated SDNN and SDANN did not undergo reversal with aging.

The recordings were manually analyzed and interpreted by an experienced cardiologist and a research fellow (DHS, UZ). Each beat was classified and labeled with respect to origin, using template matching techniques. The analysis programs eliminated 1 RR interval before, and 2 after, each nonsinus beat. The recordings that were <20 hours in duration and those with ectopic activity >10% of the total heart beats and/or with paced rhythms were excluded. To ascertain intersystem variability, randomly selected Holter tapes were cross-analyzed using all 3 programs. Records exhibiting >10% HRV differences among the 3 programs were excluded.

The HRV was computed for each subject using the 4 standard 24-hour time domain measures: rMSSD, pNN50, SDNN, and SDANN.

These measures exhibit different autonomic modulation; rMSSD and pNN50 exhibit parasympathetic modulation[6,7] and SDNN and SDANN mostly sympathetic modulation.[6] The HRV determinations were averaged on a single-decade (ages 10 to 79 years) and 2-decade (ages 80 to 99 years) basis. To define the age-related changes in HRV–PF relative to HRV–SF, the PF/SF ratio was determined for each decade.

Table 2
Aging effects on ratio of heart rate variability (HRV)/parasympathetic function (PF)/sympathetic function (SF)*

Age (years)	rMSSD/SDNN	rMSSD/SDANN	pNN50/SDNN	pNN50/SDANN	rMSSD + pNN50/SDNN + SDANN
10–19	0.31 ± 0.08	0.37 ± 0.14	0.15 ± 0.07	0.18 ± 0.10	0.25 ± 0.09
20–29	0.27 ± 0.06	0.31 ± 0.09	0.10 ± 0.06	0.12 ± 0.07†	0.20 ± 0.07
30–39	0.25 ± 0.08	0.29 ± 0.12	0.09 ± 0.06†	0.10 ± 0.08†	0.18 ± 0.08†
40–49	0.22 ± 0.07†‡§	0.25 ± 0.10†	0.06 ± 0.05†‡¶	0.07 ± 0.06†‡	0.15 ± 0.07†‡§
50–59	0.21 ± 0.08†‡§	0.24 ± 0.10†§	0.04 ± 0.04†‡§¶	0.05 ± 0.05†‡§¶	0.13 ± 0.07†‡§
60–69	0.18 ± 0.08†‡§¶	0.20 ± 0.10†‡§¶	0.03 ± 0.05†‡§¶	0.04 ± 0.06†‡§¶	0.11 ± 0.07†‡§¶
70–79	0.17 ± 0.06†‡§¶	0.19 ± 0.07†‡§¶	0.02 ± 0.02†‡§¶	0.03 ± 0.03†‡§¶	0.10 ± 0.04†‡§¶
80–99	0.29 ± 0.21	0.34 ± 0.28	0.10 ± 0.14	0.12 ± 0.18	0.21 ± 0.20

* Data show that all measured ratios decreased progressively from second to eighth decades, a finding consistent with a decrease in both HRV–PF and HRV–SF; beginning with ninth decade, pattern of HRV change reversed and HRV PF/SF ratios increased, as evidenced by ninth decade ratios, a finding consistent with a late increase in HRV–PF.

† Other age ranges versus 10–19 years ($p < 0.05$); ‡ other age ranges versus 20–29 years ($p < 0.05$); § other age ranges versus 30–39 years ($p < 0.05$); ¶ other age ranges versus 80–99 years ($p < 0.05$).

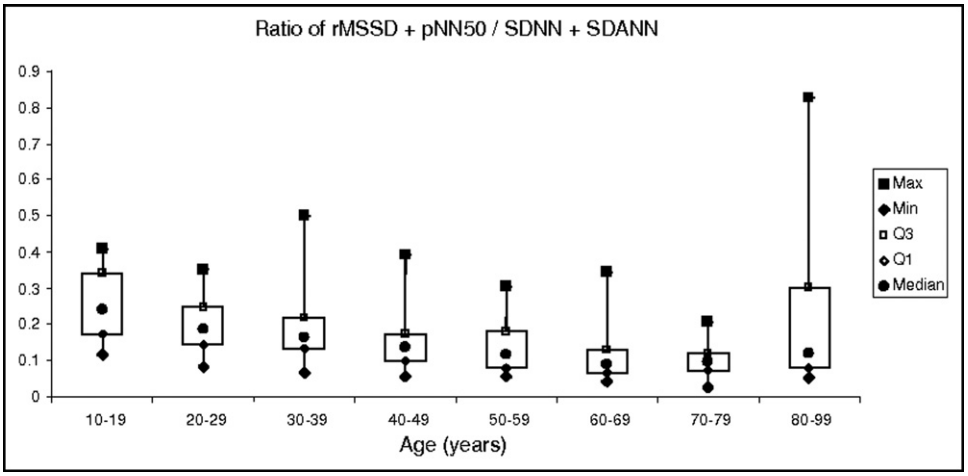

Figure 3. Whisker plot of age-related changes in ratio of rMSSD plus pNN50/SDNN plus SDANN. Note, rMSSD plus pNN50/SDNN plus SDANN ratio showed continuous age-related decrease in quartile values of ratio of HRV–PF to HRV–SF from age 10 to 79 years. Maximum and minimum values also show age-related decrease. Values subsequently increased with subsequent aging in 80- to 99-year-old group.

The results are expressed as the mean ± SD. Analysis of variance and Tukey's multiple comparison tests were used to determine the interdecade differences in HRV. A linear regression model was applied to test the relations between HRV and aging. The linear and quadratic equations were compared for all 4 HRV measures, and the best fit approximation was chosen. Fitted regression lines and upper and lower 95% confidence intervals for the predicted mean response were drawn. Differences were considered significant at $p < 0.05$. The analyses were performed using Statistical Analysis Systems (PROC ANOVA and PROC REG, version 9.1, SAS Institute, Cary, North Carolina). The PF/SF ratios were compared using Tukey's honest significant difference post hoc test.

Results

Table 1 lists the mean values for the HRV ± SD of healthy subjects across 9 decades determined using the 4 time domain measures. The patterns of age-related changes in HRV were measure dependant.

The HRV–PF, determined using rMSSD and pNN50, exhibited a rapid and precipitous decrease, in a quadratic regression pattern with aging, particularly from the second to fifth decades (correlation coefficient, $r = -0.58$ for rMSSD and pNN50; Figure 1 and Table 1). However, the decrease in HRV–PF slowed, beginning in the sixth decade, and continued at increasingly slow rates until the mid- to late eighth decade, at which point it reached its nadir. At the nadir, rMSSD had decreased 64% and pNN50 88% from the second-decade baseline values. The nadir then continued until the early ninth decade, at which point the pattern of decrease abruptly reversed itself and HRV–PF began a progressive increase. By the tenth decade, rMSSD and pNN50 had increased 58% and 233%, respectively, from their nadir levels ($p < 0.05$) to the levels characteristic of the fifth decade.

HRV determined using the sympathetically modulated SDNN and SDANN measures decreased uninterruptedly with aging (correlation coefficient $r = -0.41$ and $r = -0.33$, respectively; Figure 2 and Table 1). The rate and magnitude of the decrease were most pronounced from the second to fifth decades (28% and 26%, respectively, from the second-decade baseline values). The rate of the HRV decrease using SDNN and SDANN measures then slowed

and continued at lower rates through the tenth decade, at which point it had reached its lowest levels, with a decrease of 37% and 34%, respectively, from the second-decade baseline values ($p < 0.05$). This sharply contrasted with the decrease in rMSSD and pNN50, which had essentially stopped by the end of eighth decade.

HRV determined using SDNN and SDANN demonstrated a less steep, linear regression pattern of decrease than the steeper, quadratic regression pattern using rMSSD and pNN50.

Given the divergent patterns of age-related changes in HRV–PF and HRV–SF, the ratios of the 2 were also calculated to compare the changes in PF and SF. Table 2 lists the effects of aging on the ratios of HRV–PF/SF using rMSSD/SDNN, rMSSD/SDANN, pNN50/SDNN, pNN50/SDANN, and rMSSD plus pNN50/SDNN plus SDANN. Figure 3 shows a whisker plot of the age-related changes in the ratio of pNN50 plus rMSSD/SDNN plus SDANN. Figure 3 also shows the data distribution and indicates the degrees of dispersion and skewing.

All ratios decreased progressively from the second to eighth decades, suggestive of a decrease in both HRV–PF and HRV–SF. Beginning with the ninth decade, the pattern of HRV change reversed itself and the HRV–PF/SF ratios began to increase, consistent with the ninth-decade increase in HRV–PF.

Discussion

The findings of the present cross-sectional study have revealed a new pattern of age-related changes in autonomic function, defined in terms of the 4 time domain measures of HRV,[1,8] in a healthy elderly population, supporting the hypothesis that longevity depends on maintenance of good autonomic function, particularly HRV–PF, in the face of age-related decreases.

Differences in autonomic modulation of the HRV measures[6,7] facilitate distinctions between the changes in HRV–PF and HRV–SF. The differences using rMSSD and PNN50 (parasympathetic-modulated measures) and SDNN and SDANN (sympathetic-modulated measures) were particularly striking and underscore the importance of using all 4 measures in population analyses. Also, the findings from the present study and other studies[3,4] that critical changes in both HRV–PF and HRV–SF occur into the tenth decade underscore the need to incorporate the "oldest" older subjects (>85 years) in longevity studies.

Although both HRV–PF and HRV–SF decreased progressively between adolescence and the sixth decade, they differed strikingly in that the decrease in HRV–PF did not persist throughout life (Figure 1), but the decrease in HRV–SF continued unchecked (Figure 2). The initial decrease in HRV–PF was also more rapid and precipitous than that of HRV–SF, resulting in a transient hyperadrenergic excitatory state.[9,10] By mid-life, the decrease has slowed, and HRV–PF has reached its nadir in the late eighth decade, a point coinciding with the end of the average United States lifespan.[11] Subsequently, in the early ninth decade, the pattern has reversed itself, and HRV–PF undergoes a progressive increase (Figure 1), often reaching high HRV levels, more typical of younger (fifth decade) subjects. These findings, together with the findings that centenarians exhibit high HRV–PF,[3,4] demonstrate the tight connection between high levels of HRV–PF and longevity.

The mechanisms of the "reversal" are uncertain. One possibility is that the "reversal" reflects the existence of populations with high and low levels of HRV–PF, and that the former outlive the latter, with a resultant increase in the average HRV–PF. A high HRV–PF could have also resulted from lifestyle modifications (eg, increased exercise and caloric restriction programs), modalities reported to increase HRV–PF and enhance longevity.[12,13] Population differences in HRV–PF aside, the phenomenon could represent a true reversal resulting from genetically mediated changes in receptor-membrane function and signal transduction[14,15] in the autonomic connections to the heart. However, irrespective of the mechanisms of the reversal, these findings underscore the association between the maintenance of good HRV–PF and longevity.

HRV–SF also decreased with aging, but at a slower rate than HRV–PF.[1,10] Of critical importance with respect to longevity, HRV–SF does not undergo a reversal. Instead, the decrease continues at a more or less constant rate (Figure 2), a trend that serves to accentuate parasympathetic influence in late life and underscores the association between optimum sympathovagal balance (high HRV–PF and reduced HRV–SF) and longevity.[2] This is in accordance with the findings from power spectral studies[3,4] showing that ultracentenarians exhibit a lesser low-frequency power (sympathetic modulation) and greater high-frequency power (parasympathetic modulation) than do even modestly younger subjects (85 to 100 years old). The findings[3,4] that centenarians exhibit low SF/PF ratios are also supportive of, and consistent with, our own findings (Figure 3 and Table 2).

The period between when the HRV–PF has reached its nadir (eighth decade) and when it undergoes a reversal and subsequent increase (ninth decade) can be considered a "critical threshold" for long-term survival, because the failure of these events to occur could be expected to decrease longevity. The finding that the "critical threshold" coincides with the end of the average United States lifespan[11] underscores its significance.

Although the present study focused on the elderly, autonomic function influences mortality throughout life. For example, the more rapid and precipitous decrease in HRV–PF compared to HRV–SF between adolescence and the sixth decade, which results in a transient hyperadrenergic state, could potentially trigger ventricular tachycardia and arrhythmic death. It represents one possible explanation for sudden death in healthy young adults without structural heart disease.[16] The ninth decade reversal of the decrease in HRV–PF, combined with the continuing decrease in HRV–SF, is an example at the other end of life. Because a high HRV–PF protects against ventricular tachycardia and arrhythmic death,[17,18] the reversal provides an explanation for the late life reduction in arrhythmic, in contrast to other modes of death.[19]

The age-related changes in HRV and their implications for mortality suggest that periodic HRV monitoring of the elderly and other populations at increased risk could help predict and promote longevity. It could also help identify elderly subjects with a persistently low HRV–PF and a

putative increased risk of mortality, who might stand to benefit from interventions that could increase HRV–PF and improve the PF/SF ratio. Modalities reputed to enhance longevity, including exercise,[12] caloric restriction,[13] weight reduction,[20] ascorbic acid,[21] and ω-3 polyunsaturated[22] and fatty acids in fish oils[23] are also supportive.

One limitation of our study was the paucity of the "oldest" older (>85 years) population. To minimize this problem, we combined the subjects in their ninth and tenth decades into a single, larger and statistically more powerful group. Second, our study was cross-sectional in character. Definitive analysis of age-related changes in HRV requires a prospective, longitudinal study, which, by its very nature, would be extremely difficult to achieve.

Our criteria for the selection of healthy subjects constituted a third possible limitation. In-depth screening for the presence of covert medical conditions, using treadmill exercise testing, echocardiographic examination, and coronary angiography, could have provided additional information about the health status of our cohort. However, subject reluctance to undergo these diagnostic measures, their cost, and ethical considerations limited their use. Thus, the possibility of occult cardiovascular-related co-morbidities could not be entirely excluded.

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