Phase-rectified signal averaging as a sensitive index of autonomic changes with aging

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Abstract

Standard heart rate variability (HRV) techniques have been questioned in the sleep and autonomic fields as imprecise measures of sympathetic and parasympathetic activity. A new technique has emerged, known as phase-rectified signal averaging (PRSA). PRSA is used to quantify the quasi-periodic accelerations and decelerations in short-term heart rate, an effect that is normally masked by artifacts and noise. When applied to a signal of peak-to-peak (RR) time intervals, these quasiperiodicities can be used to estimate overall vagal activity, quantified as deceleration capacity (DC) and acceleration capacity (AC). We applied the PRSA analysis to a healthy cohort (ages 21–60 yr) enrolled in a clinical sleep trial, in which ECG data during wakefulness and sleep were available. We found that DC and AC were significantly attenuated with increasing age: a 0.27 ms/yr decrease in DC and a 0.29 ms/yr increase in AC ($P < 0.001$). However, even in the older subjects, DC values were higher then previously found in people post-myocardial infarction. We also found a drop in percentage of normal-to-normal intervals where the current interval deviated >50 ms from the previous interval with age, with a decrease of 0.84%/yr. We did not find any differences between younger and older subjects with traditional HRV techniques, such as low-frequency or high-frequency power. Overall, the study provides normative PRSA data and suggests that PRSA is more sensitive than other HRV measurements. We propose that the decrease in DC and AC may be a sensitive marker for autonomic changes with aging. Further work will be required to determine whether the observed changes predict poorer cardiac health prognosis.

Keywords: deceleration capacity, heart rate variability, sleep, lung, autonomic

FOR UNCLEAR REASONS, AGING is a risk factor for cardiovascular morbidity and mortality ([23](#)). Considerable research has been performed in elderly populations to define underlying mechanisms; however, such individuals often have multiple comorbidities and medication requirements. Thus clear conclusions are difficult to draw from various observed abnormalities. On the other hand, the investigation of the "super" healthy elderly is problematic due to selection bias among the enrolled participants. Because epidemiological data suggest important increases in cardiovascular risk in the middle aged ([18](#)), we sought to determine the effects of aging in a relatively young cohort to avoid the potential issues with studying the elderly.

Standard heart rate (HR) variability (HRV) metrics have been extensively investigated as markers for cardiovascular morbidity and mortality ([6](#), [15](#), [16](#), [20](#), [27](#)). However, such techniques have been criticized, since their underlying biological basis is essentially unknown. Several studies have suggested that the low-frequency (LF) and high-frequency (HF) power in the electrocardiogram (ECG) are not simply sympathetic and parasympathetic surrogates, respectively ([1](#), [8](#), [29](#)). Most HRV metrics are nonspecific ([9](#)), and, therefore, their utility may be limited. Furthermore, many HRV metrics require long temporal analysis windows (of several hours) and are susceptible to nonstationarities in the cardiovascular time series. As a result, many investigators have sought newer, more robust methods to assess autonomic activity using noninvasive means ([2](#), [4](#), [17](#), [26](#)).

Phase-rectified signal averaging (PRSA) is a recently developed technique used to identify subtle short-term repeated patterns (i.e., quasiperiodicities) in a time signal that are normally masked by nonstationarities (such as ectopic beats and changes in activity), noise, and artifacts ([14](#)). When PRSA is applied to a heartbeat time series derived from the ECG, the quasiperiodicities that are extracted can be used to estimate overall vagal activity. PRSA characterizes how the heart behaves around points of deceleration [deceleration capacity (DC)] and acceleration [acceleration capacity (AC)] under a given recording condition. An abrupt deceleration is characteristic of enhanced vagal tone (vagotonic), while an attenuated DC would indicate a withdrawal in vagal activity (vagolytic).

Recently, PRSA techniques have been used to predict mortality in survivors of myocardial infarction (MI) ([3](#)). Bauer et al. ([3](#)) found that a low DC was a stronger predictor of mortality following a MI than left ventricular ejection fraction and traditional HRV techniques. Furthermore, Kantelhardt et al. ([14](#)) found that survivors of an MI exhibited a strong linear decrease of DC with age. However, to our knowledge, the PRSA technique has not been reported on a healthy cohort. We, therefore, sought to assess its utility on a healthy cohort with a variable age range. Because behaviors during wakefulness can also vary with aging, we used the period of relaxed wakefulness before sleep onset to standardize the level of activity and the behavioral state (which may well vary with aging).

We sought to determine whether DC or AC was influenced by aging within a healthy subject population, and if differences could be detected with traditional HRV techniques. This aim would allow us to test the hypothesis that healthy aging may lead to changes in PRSA, indicative of deleterious autonomic changes, which could theoretically explain some of the cardiovascular risk associated with aging.

METHODS

Subjects were prospectively enrolled from the general population in an overnight sleep study to record a digital polysomnogram (PSG). Subjects were enrolled at six sites in the United States, with each site receiving approval of the protocol by their local Institutional Review Board or a central Institutional Review Board. All subjects gave written, informed consent before participation in the study. All subjects underwent a thorough history and physical examination by a licensed physician to exclude all relevant comorbidities. Subjects were healthy adults (ages 21–60 yr) without any sleep disorders, cardiovascular problems, or diabetes, as indicated by the medical history. Subjects did not have insomnia, as assessed by self-reporting at least 6.5–8.5 h sleep/night and confirmed with 7–14 days of actigraphy. PSGs included a single-lead ECG acquired at 500 Hz with 16-bit resolution. The PSG data were used to detect and stage sleep using standard criteria by experienced technologists registered in polysomnography ([1], [19]). Two 5-min ECG data sets were analyzed using the PRSA technique described below: the 5 min before sleep onset and the 5 min after sleep onset. Sleep onset was defined as the time from lights out to the beginning of the first epoch of 10 min of continuous sleep.

PRSA methods. The PRSA technique has been described in detail elsewhere ([2], [14]). The PRSA algorithm and analysis of the results were performed using Matlab. The PRSA software was benchmarked against the freely available download from the Technical University of Munich ([25]) on artificial data to ensure accuracy. The PRSA algorithm begins with the detection of the RR intervals in an ECG signal, using a standard peak detection program ([13]). The next step is to identify each of the remaining data points as either a deceleration or acceleration "anchor." If an RR interval is increased (slower HR) relative to the previous interval, it is identified as a deceleration anchor, while, if the interval is shorter then the previous interval (faster HR), it is identified as an acceleration anchor ([Fig. 1]). Any RR intervals that exhibited more then a 20% change from the previous RR interval were eliminated as anchors in the analysis, as they are likely to be related to measurement noise or ectopic beats ([10]).

After the deceleration and acceleration anchors are determined, a window surrounding each anchor is created. The window is defined by the two intervals immediately preceding and following the anchor interval. Note that many of these windows will overlap, as the anchor points are usually close to one another. All of the deceleration (or acceleration) windows are then aligned at the anchor point (phase rectified). Once aligned, the respective intervals are averaged together ([Fig. 2]). Once averaged, the DC and AC are calculated using *Eq. 1*.

$$\text{DC or AC} = [RR(0) + RR(1) - RR(-1) - RR(-2)]/4 \tag{1}$$

where RR(0) is defined as the RR interval at the anchor (*interval 0*, the current interval), while RR([1]) is the next RR interval, and so on.

HRV methods. In addition to PRSA, traditional HRV metrics were calculated. The power spectral density of the linearly detrended RR intervals was calculated using the Lomb periodogram ([17], [22]). LF power was defined as the total power in the spectra from 0.015 to 0.15 Hz. HF power was defined as the total power in the spectra from 0.15 to 0.4 Hz ([19]). We normalized LF and HF by the total power in the spectra from 0.0 to 0.5 Hz. The percentage of normal-to-normal intervals where the current interval deviated >50 ms from

the previous interval (pNN50), another possible marker of parasympathetic tone ([7], [12]), was calculated. HR was calculated by averaging the intrabeat intervals in the 5-min segment, and the standard deviation of the intrabeat intervals was calculated as well. All variables were analyzed in the 5-min period of wakefulness and the 5-min period of sleep and stratified by age.

Statistics. Linear regression was performed to evaluate how AC, DC, and pNN50 change with age. F-test was performed on the R^2 value to evaluate significance. Furthermore, ages were segregated into four groups (20–29, 30–39, 40–49, and 50–60 yr), and the Kruskal-Wallis one-way ANOVA was performed on DC and AC during wakefulness. A Wilcoxon (nonparametric) rank-sum test was used to determine whether PRSA and HRV metrics (LF, HF, and LF-to-HF ratio) were significantly different between each older (>31 yr, based on median) and younger (≤31 yr) subjects and between sleep and wakefulness. Values are means ± SD.

RESULTS

Subject demographics. A total of 166 subjects were analyzed with a mean age of 33. 9 ± 10.9 yr (median age 31 yr) and were 64.3% female.

PRSA. During wakefulness, anchor points were identified, and, on average, 140 ± 32 windows were used to determine DC and 139 ± 27 windows were used to determine AC in the 5-min period directly preceding sleep for each subject. During NREM sleep, 144 ± 28 anchors were used to determine DC and 145 ± 22 for AC. There was no statistically significant difference in either DC or AC between the 5-min period of wakefulness and the 5-min period of sleep. During wakefulness, there was a significant decrease in DC with increasing age ($R^2 = 0.12$, $P < 0.001$) (Fig. 3A). For every additional decade, DC decreases by ~3 ms. Furthermore, DC was significantly higher in the 20- to 29-yr-old group ($N = 79$) compared with the 40- to 49-yr-old ($N = 28$) and 50- to 60-yr-old group ($N = 20$) (Fig. 3B). A similar slope and regression fit was found when comparing AC with age during wakefulness ($R^2 = 0.12$, $P < 0.001$) (Fig. 4A), and AC was significantly different in the 20- to 29- and 30- to 39-yr-old ($N = 39$) groups compared with the 50- to 60-yr-old group (Fig. 4B).

HRV measurements. pNN50 was also decreased with age ($P < 0.001$) during the 5-min period of wake before sleep onset (Fig. 5A). Furthermore, subjects in their 20's had significantly higher pNN50 then those in their 40's and 50's, and subjects in their 30's had significantly higher pNN50 then those in their 50's (Fig. 5B). No statistically significant differences were seen between the two groups of older (>31 yr) and younger (≤31 yr) patients in LF power, HF power, LF-to-HF ratio, or HR during wakefulness; however, there was a larger standard deviation of HR found in the younger group (Table 1).

DISCUSSION

We show that PRSA measurements, even in a healthy cohort, vary by age. DC and AC show clear decrements with increasing age in otherwise healthy individuals. We hypothesize that the decrement in DC with age is a result of decreased vagal tone in older people, which may be a marker for future cardiovascular dis-

ease. While AC is most likely modulated by vagal tone as well, due to the short time scale on which changes occur, we cannot rule out other inputs, and, therefore, the corresponding decline in AC with age is difficult to interpret.

Our results are similar to those from Kandelhart et al. (14), who also found an effect of age on PRSA metrics among people with disease. The authors found a linear relationship between DC and age in a cohort of middle-aged (ages 33–77 yr) post-MI subjects (DC = 12.2–0.10 age/yr). Our work adds to the generalizability of the prior research by including people who were ostensibly normal over a wider age range than the existing literature. Interestingly, our healthy subjects had a higher DC than those subjects in the same age range who had a history of coronary artery disease, furthermore the slope of the decrement in DC with age was steeper in our population compared with the Kandelhart study (−0.27 vs. −0.10 ms/age in years, respectively). One potential issue is that, in the Kandelhart study, 24-h ECG recordings were used, while, in this study, short 5-min recordings were used. Previous studies have shown that mental and physical activity alters HRV measurements (5, 11, 24) and creates motion artifacts. By using a small section of data with little physical or mental activation (i.e., relaxed wakefulness), the measurement does not have to account for various levels of activity that subjects may have throughout the day in a 24-h recording (which may well be influenced by aging as well). This comparison supports the idea that PRSA metrics can be used to estimate cardiovascular health.

Other correlates of decreased vagal tone are HF power and pNN50. Previous studies have shown decreases in HF power with increasing age (28, 30); however, we found no such decrement in our sample. We believe that, since our population was screened for clinical cardiovascular disease and did not contain any subjects over the age of 60 yr, HF power was not sensitive enough to measure the resultant vagal decrement in this subject pool. We did see a trend of increasing LF-to-HF ratio with increasing age; however, it was not statistically significant. pNN50 has also been shown to be depressed in the elderly (21), and a reduced level of pNN50 correlates with an increased risk of incident hypertension (27). Our results follow those of Mietus et al. (21), yet our study was not designed to assess incident cardiac events in our cohort. We hypothesize that the subjects with very low values of pNN50 and DC will be at the highest risk of disease.

One surprising result is that no changes were seen from wake to sleep in either AC, DC, or pNN50. If AC, DC, and pNN50 characterize the level of vagal activity, one might expect to see increases in both DC and pNN50 and decreases in AC upon sleep onset. One possible explanation is that the period of wakefulness we examined is a highly relaxed state just before sleep onset, and, therefore, large changes are not seen when persistent sleep does occur. However, we anticipate that our results would be different, if we examined active wakefulness rather than relaxed wakefulness before sleep onset. Similarly, once asleep, subjects were recorded during stage I or II non-rapid eye movement (REM) sleep; greater differences might be seen during slow-wave or REM sleep. Alternatively, these particular HRV measurements might reflect the intrinsic properties of the vagal nerve (which likely do not change from wakefulness to sleep) rather than its level of activity, which is modulated by changing levels in activity and wakefulness.

Limitations. Our paper had a number of strengths, including its novelty, our relatively large sample size, our exclusion of comorbidities, and our use of relaxed wakefulness before sleep onset to characterize intrinsic biological properties (rather than behaviors) of our participants. However, we acknowledge the following weaknesses. First, we studied a limited age range, and, therefore, we are unable to draw conclusions about elderly participants (e.g., we studied only 20 individuals above the age of 50 yr). Similarly, we excluded comorbidities based on rigorous history and physical examination, but may have missed subclinical

or occult disease based on our study design. Therefore, we accept that our conclusions are not generalizable beyond the study participants. Second, based on our study design, we only examined a 5-min window of ECG activity. We made this decision to assess a stable period of relaxed wakefulness before sleep onset to minimize the influences of activity and behavioral state. We also accept that subsequent research examining longer periods of recording will be of interest. Third, as our ultimate aim is to understand the mechanisms underlying cardiovascular morbidity and mortality, one could argue that we are simply measuring autonomic surrogates rather than true events, such as MI, fatal arrhythmias, or cerebrovascular events. However, we would argue that such large-scale epidemiological studies would be premature before more straightforward, well-controlled physiological assessments have been performed. We would ultimately support further research into the utility of PRSA in predicting hard outcomes. Despite our acknowledged limitations, we believe that our findings are robust and represent an important addition to the existing literature.

Conclusions. We performed PRSA analysis in a young, healthy cohort and found *1*) DC values higher than those previously reported, and *2*) a decrease in PRSA metrics with aging in a healthy and relatively young population. We did not see an effect of aging in other HRV metrics, suggesting that PRSA is a more sensitive marker of age-related changes in autonomic activity. Future studies must be performed to determine whether this decrement of vagal tone with age is just a natural aging phenomenon, or if it can be used to predict future cardiac events.

GRANTS

DISCLOSURES

A. Malhotra has consulting and/or research income from Philips, Ethicon, Medtonic, SHC, SGS, Pfizer, Novartis, Sepracor, Cephalon, Apnex, and Itamar. S. D. Pittman is employed by Philips.

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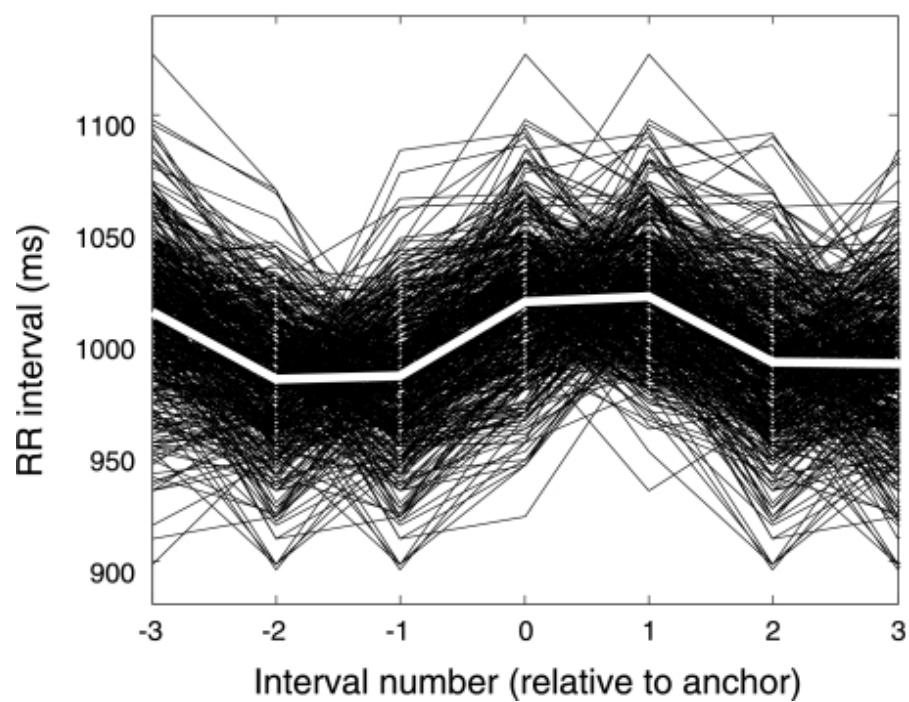
## Figures and Tables

Fig. 1.
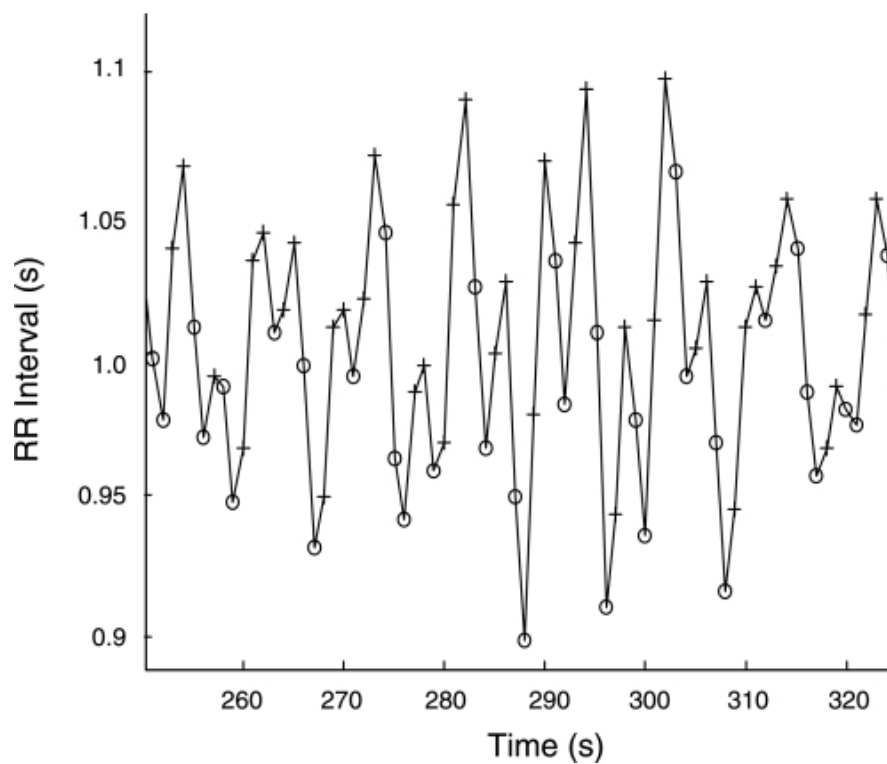
Example sample data, showing RR intervals over time derived from an artificial ECG recording. RR intervals are identified as either deceleration anchors (+) or acceleration anchors (O).

Fig. 2.

Deceleration windows, aligned (phase rectified) to the anchor interval. Each interval in each window is averaged (white line) and then used to calculate the deceleration capacity (DC).

Fig. 3.
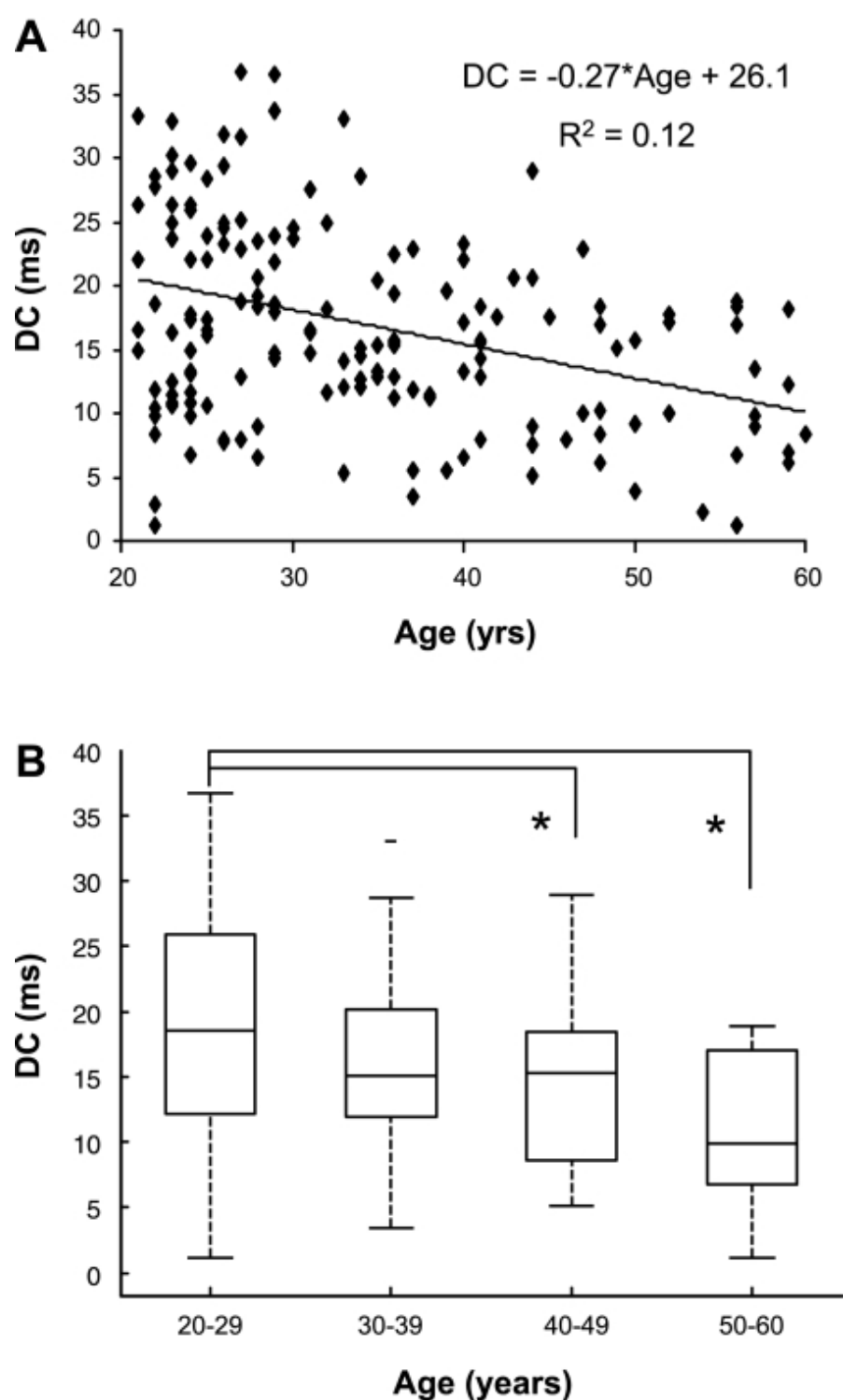
A: DC during wakefulness as a function of age in years with regression line plotted. $R^2 = 0.12$. B: box plot of DC for various age groups: 20–29 ($N = 79$), 30–39 ($N = 39$), 40–49 ($N = 28$), and 50–60 ($N = 20$). In both plots, the data from one subject are not plotted due to visual purposes, although included in the analysis (age = 29 yr, DC = 58.3 ms). *$P < 0.05$.

Fig. 4.
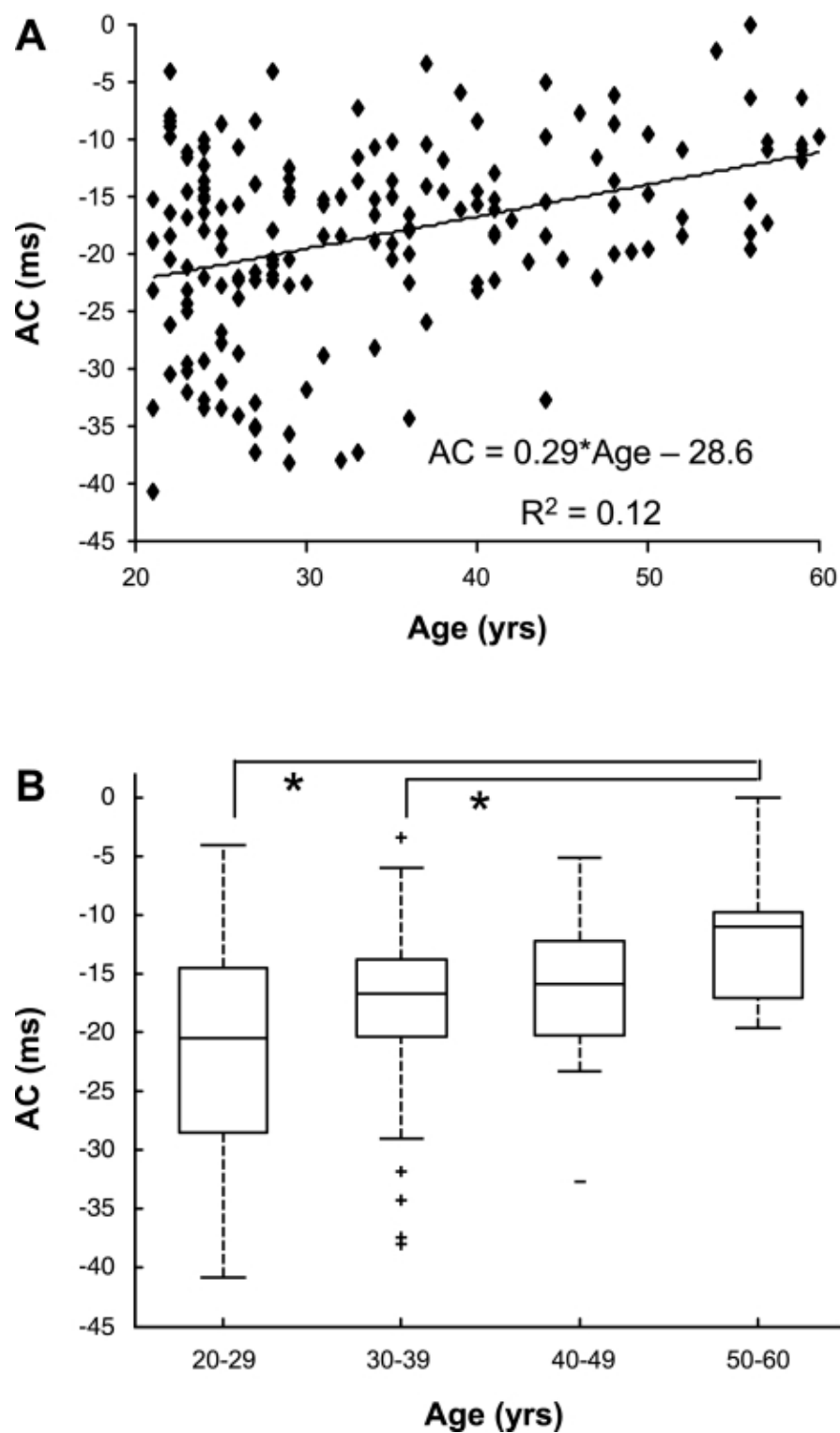
A: acceleration capacity (AC) during wakefulness as a function of age in years with regression line also plotted. $R^2 = 0.12$. B: box plot of AC for various age groups. In both plots, the data from one subject are not plotted due to visual purposes, although included in the analysis (age $= 29$ yr, AC $= -69.7$ ms). $*P < 0.05$.

Fig. 5.
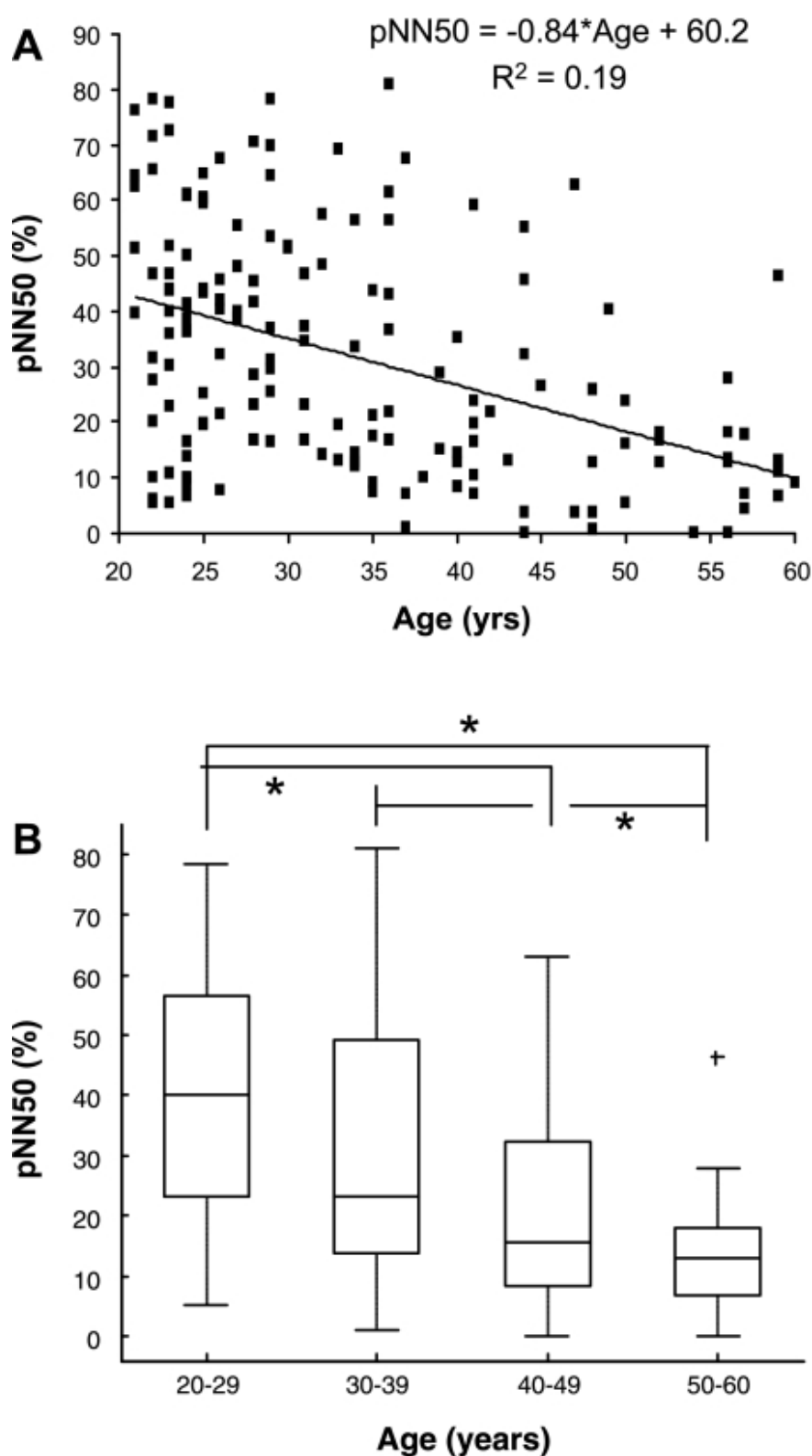
A: percentage of normal-to-normal intervals where the current interval deviated >50 ms from the previous interval (pNN50) as a function of age. Regression line is also plotted. $R^2 = 0.19$. *B*: box plot of pNN50 for various age groups. *P < 0.05.

Table 1.

Average phase-rectified signal averaging and heart rate variability during wakefulness for younger and older subjects

	n	DC, ms	AC, ms	LF	HF	LF/HF	HR, beats/min	SD
Older (age >31 yr)	81	14.02 ± 6.36	−15.68 ± 7.11	0.18 ± 0.07	0.23 ± 0.10	1.05 ± 1.19	65.34 ± 9.24	0.13 ± 0.07
Younger (age ≤ 31 yr)	85	19.43 ± 9.68	−21.52 ± 10.13	0.17 ± 0.08	0.25 ± 0.09	0.81 ± 0.53	64.56 ± 9.40	0.16 ± 0.81
P value		0.0001[*]	0.0001[*]	0.71	0.32	0.20	0.63	0.03[*]

Values are means ± SD; n, no. of subjects. Phase-rectified signal averaging and traditional heart rate variability metrics in older and younger groups are shown. DC, deceleration capacity; AC, acceleration capacity; LF, low-frequency power; HF, high-frequency power; LF/HF, LF-to-HF ratio; HR, heart rate; SD, standard deviation of HR.

[*]Statistically significant difference between the two age groups.