Phase Rectified Signal Averaging as a Sensitive Index of Autonomic Changes with Aging

Campana LM, Owens RL, Clifford GD, Pittman SD, Malhotra A. Boston University, Massachusetts Institute of Technology, Philips-Home Healthcare Solutions, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA USA

PRSA as an Index of Autonomic Changes with Aging

Lisa Campana
lcampana@bu.edu
Phone: 617-732-8450
Fax: 617-732-7337
Department of Biomedical Engineering
44 Cummington St.
Boston, MA 02215

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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 quasi-periodicities 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 21-60yrs) 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/year decrease in DC and a 0.29 ms/year increase in AC (p<0.001). However, even in the older subjects DC values were higher than previously found in people post myocardial infarction. We also found a drop in pNN50 with age, with a decrease of 0.84% per year. 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.

Key Words: deceleration capacity, heart rate variability, sleep, lung, autonomic
Introduction

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 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 are not simply sympathetic and parasympathetic surrogates respectively (1, 8, 29). Moreover, most HRV metrics are non-specific (9) and therefore their utility may be limited. Furthermore, many HRV metrics require long temporal analysis windows (of several hours) and are susceptible to non-stationarities in the cardiovascular time series. As a result, many investigators have sought newer, more robust methods, to assess autonomic activity using non-invasive 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. quasi-periodicities) in a time signal that are normally masked by non-stationarities, (such as ectopic beats and changes in activity), noise and artifacts (14). When PRSA is applied to a heart beat time series derived from the electrocardiogram (ECG), the quasi-periodicities that are extracted can be used to estimate overall vagal activity. PRSA characterizes how the heart behaves around points of deceleration (deceleration capacity) and acceleration (acceleration capacity) under a given recording condition. An abrupt deceleration is characteristic of enhanced vagal tone (vagotonic), while an attenuated deceleration capacity would indicate a withdrawal in vagal activity (vagolytic).

Recently, PRSA techniques have been used to predict mortality in survivors of myocardial infarction (3). Bauer et al. found that a low deceleration capacity (DC) was a stronger predictor of mortality following a myocardial infarction (MI) than left ventricle ejection fraction and traditional heart rate variability techniques. Furthermore, Kantelhardt et al. found that survivors of an MI exhibited a strong linear decrease of DC with age (14). 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 prior to sleep onset to standardize the level of activity and the behavioral state (which may well vary with aging).

We sought to determine whether deceleration or acceleration capacity 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 6 sites in the
United States with each site receiving approval of the protocol by their local Institutional
Review Board (IRB) or a central IRB. 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 years) 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 hours sleep/night and
confirmed with 7-14 days of actigraphy. PSGs included a single lead ECG acquired at
500Hz 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 minute ECG data sets were analyzed using the PRSA technique described below,
the 5 minutes before sleep onset and the 5 minutes after sleep onset. Sleep onset was
defined as the time from lights out to the beginning of the first epoch of 10 minutes 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 heart rate) relative to the previous interval it is identified as a deceleration anchor, while if the interval is shorter then the previous interval (faster heart rate) it is identified as an acceleration anchor (Figure 1). Any RR intervals that exhibited more than 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 the deceleration (or acceleration) windows are then aligned at the anchor point (phase rectified). Once aligned, the respective intervals are averaged together (Figure 2). Once averaged, the deceleration and acceleration capacity are calculated using equation 1.

\[
\text{DC or AC} = \frac{(RR(0) + RR(1) - RR(-1) - RR(-2))}{4}
\] (1)
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). Low frequency (LF) power was defined as the total power in the spectra from 0.015-0.15 Hz. High frequency (HF) power was defined as the total power in the spectra from 0.15Hz – 0.4Hz (19). We normalized LF and HF by the total power in the spectra from 0.0-0.5 Hz. The percent of normal to normal intervals where the current interval deviated more then 50 ms from the previous interval (pNN50), another possible marker of parasympathetic tone (7, 12), was calculated. Heart rate was calculated by averaging the intra-beat intervals in the five minute segment and the standard deviation of the intra-beat intervals was calculated as well. All variables were analyzed in the five minute period of wakefulness and the five minute 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 R² value to evaluate significance. Furthermore, ages were segregated into four groups (20-29, 30-39, 40-49, and 50-60 years) and the Kruskal-Wallis one way ANOVA was performed on DC and AC during wakefulness. A Wilcoxon (non-parametric) rank-sum test was used to determine whether PRSA and
HRV metrics (LF, HF and LF/HF-ratio) were significantly different between each older (≥31 years – based on median) and younger (≤31 years) subjects and between sleep and wakefulness.

Results

Subject Demographics

A total of 166 subjects were analyzed with a mean age of 33.9 ± 10.9 years (median age 31 years), and 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 five minute 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 five minute period of wakefulness and the five minute period of sleep. During wakefulness, there was a significant decrease in DC with increasing age ($R^2 = 0.12$, $p<0.001$) (Figure 3A). For every additional decade DC decreases by approximately 3ms. Furthermore, DC was significantly higher in the 20-29 year old group (N = 79) as compared to the 40-49 year old (N= 28) and 50-60 year old group (N=20) (Figure 3B). A similar slope and regression fit was found when comparing AC with age during wakefulness ($R^2 = 0.12$, $p<0.001$) (Figure 4A) and AC was significantly different in the 20-29 and 30-39 year old (N = 39) group as compared to the 50-60 year old group (Figure 4B).
HRV Measurements

pNN50 was also decreased with age (p<0.001) during the 5 minute period of wake before sleep onset (Figure 5A). Furthermore subjects in their 20s had significantly higher pNN50 then those in their 40s and 50s and subjects in their 30s had significantly higher pNN50 then those in their 50s (Figure 5B). No statistically significant differences were seen between the two groups of older (>31 years) and younger (≤31 years) patients in LF power, HF power, LF/HF-ratio, or heart rate (HR) during wakefulness; however there was a larger standard deviation of heart rate 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 disease. 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 Bauer and Kandelhart (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 years) post-myocardial infarction 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 as compared to the Kandelhart study (-0.27 vs. -0.10 ms/age in years respectively). One potential issue is that in the Kandelhart study 24 hour ECG recordings were used, while in this study short five minute 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 hour 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 60yrs, that HF power was not sensitive enough to measure the resultant vagal decrement in this subject pool. We did see a trend of increasing LF/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 prior to 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 prior to
sleep onset. Similarly, once asleep, subjects were recorded during stage I or II non-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 prior to
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 50yrs). Similarly, we
excluded comorbidities based on rigorous history and physical examination, but may
have missed sub-clinical 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 minute window of ECG activity. We made this decision to assess a stable period of relaxed wakefulness prior to sleep onset in order 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 myocardial infarction, 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.
Acknowledgements

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References


Figure Legends

Figure 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).

Figure 2. Deceleration windows, aligned (phase rectified) to the anchor interval. Each interval in each window is averaged (white line), then used to calculate the deceleration capacity.

Figure 3. A) Deceleration Capacity (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, though included in the analysis (Age = 29 years, DC = 58.3 ms). (*p<.05)

Figure 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, though included in the analysis (Age = 29 years, AC = -69.7 ms). (*p<.05)

Figure 5. A) pNN50 as a function of age. Regression line also plotted. \( R^2 = 0.19 \). B) Box plot of pNN50 for various age groups. (*p<.05)
Table 1. PRSA and traditional HRV metrics in older and younger groups. Decelerations capacity (DC), acceleration capacity (AC), low frequency power (LF), high frequency power (HF), LF/HF ratio, Heart Rate (HR), and standard deviation of heart rate (SD). † Indicates statistically significant difference between the two age groups.
Table 1. Average PRSA and HRV during wakefulness for younger and older subjects.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>DC ±</th>
<th>AC ±</th>
<th>LF ±</th>
<th>HF ±</th>
<th>LF/HF</th>
<th>HR ±</th>
<th>SD ±</th>
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<td>Older (age&gt;31yrs)</td>
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<td>0.23</td>
<td>1.05</td>
<td>65.34</td>
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<tr>
<td>Younger (age&lt;=31yrs)</td>
<td>85</td>
<td>19.43</td>
<td>-21.52</td>
<td>0.17</td>
<td>0.25</td>
<td>0.81</td>
<td>64.56</td>
<td>0.16</td>
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<tr>
<td>p-value</td>
<td></td>
<td>0.0001†</td>
<td>0.0001†</td>
<td>0.71</td>
<td>0.32</td>
<td>0.20</td>
<td>0.63</td>
<td>0.03†</td>
</tr>
</tbody>
</table>
Figure 1
Figure 2
Figure 3

A. Scatter plot showing the relationship between DC (ms) and Age (yrs) with a linear regression line. The equation is DC = -0.27*Age + 26.1, and R² = 0.12.

B. Box plots showing the distribution of DC (ms) across different age groups (20-29, 30-39, 40-49, 50-60). The asterisks (*) indicate statistically significant differences.
Figure 4

A

AC (ms)

Age (yrs)

AC = 0.29*Age – 28.6

R² = 0.12

B

AC (ms)

Age (yrs)

20-29

30-39

40-49

50-60

AC

*
pNN50 = -0.84*Age + 60.2

$R^2 = 0.19$

Figure 5

A

B

pNN50 (%)

Age (yrs)

20-29 30-39 40-49 50-60

Age (years)

20-29 30-39 40-49 50-60