Frailty and Impaired Cardiac Autonomic Control: New Insights From Principal Components Aggregation of Traditional Heart Rate Variability Indices

Ravi Varadhan,1,2 Paulo H. M. Chaves,1,2 Lewis A. Lipsitz,3 Phyllis K. Stein,4 Jing Tian,2 B. Gwen Windham,5 Ronald D. Berger,6 and Linda P. Fried1,2

1Division of Geriatric Medicine and Gerontology, School of Medicine, and 2the Center on Aging and Health, Johns Hopkins University, Baltimore, Maryland. 3Beth Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. 4Washington University School of Medicine, St. Louis, Missouri. 5Clinical Research Branch, National Institute on Aging, Baltimore, Maryland. 6Division of Cardiology, School of Medicine, Johns Hopkins University, Baltimore, Maryland.

Background. Age-related deterioration in homeostatic regulatory mechanisms leads to decreased complexity in their output. For example, the degradation of cardiac autonomic control results in loss of complexity in the heart rate signal. Frailty is a state of critically impaired homeostasis that results in heightened vulnerability to stressors. We propose a new measure of heart rate variability (HRV) to capture the impairment in cardiac autonomic control associated with frailty.

Methods. Traditional time and frequency domain indices of HRV were obtained from 2-hour ambulatory electrocardiograms (ECGs) of 276 women (65–101 years old) in the Women’s Health and Aging Study-I. Principal components analysis was conducted on the correlation matrix of HRV indices. Frailty was defined using a validated instrument. Regression models were used to evaluate associations of HRV measures with age, frailty, and 5-year mortality.

Results. The first two principal components (PCs), PC1 and PC2, explained 90% of the variance in HRV indices. PC1 is the mean of log-transformed HRV indices. PC2 is a linear combination of log-transformed indices, with positive weights for very low frequency (VLF), low frequency (LF), and standard deviation of N-N intervals (SDNN), and negative weights for high frequency (HF), root-mean-squared differences of successive N-N intervals (RMSSD), and proportion of all N-N intervals that are larger than 50 ms (pNN50). Decreases in SDNN, VLF, LF, and LF/HF were associated with an increased risk of frailty. PC2 was more strongly associated with age ($\beta = -0.23$, $p < 0.001$) and frailty ($\beta = -0.73$, $p < 10^{-5}$) than were the individual HRV indices and LF/HF. PC2 was also the best predictor of 5-year mortality ($\beta = -0.60$, $p < 10^{-4}$).

Conclusions. Cardiac autonomic control, as reflected by HRV, is impaired in frailty. A new measure derived from PC aggregation of traditional HRV indices provides a compact summary of this impairment.

Key Words: Frailty—Mortality—Homeostatic impairment—Frequency domain indices—Time-domain indices—Principal components analysis.
in the time between successive heartbeats. Methods to quanti-
fy heart rate variability (HRV) can be broadly classified into
two categories: (a) traditional time and frequency domain mea-
sures and (b) measures based on nonlinear dynamics (11).

This article has two objectives: (1) to demonstrate that the
heart rate fluctuations due to parasympathetically mediated
cardiac autonomic function, as reflected by HRV, is impaired
in frail older adults and (2) to develop a novel, integrative
index of HRV that aggregates the traditional time and fre-
quency domain measures. The aggregate index is a linear
combination of the log-transformed indices obtained using a
principal components analysis (PCA), a powerful and versa-
tile tool for multivariate analysis (12). We test whether (a)
the structure of dominant PCs is consistent across multiple
studies (Women’s Health and Aging Study-I [WHAS-I] and Framingham), (b) PC2 is correlated with age (independently
of diseases), (c) PC2 is associated with frailty (independ-
ently of age and diseases), and (d) PC2 is a predictor of
5-year mortality (independently of age and diseases).

METHODS

Study Design

All the analyses used baseline data from a subset of older
women in the WHAS-I, Baltimore, Maryland, during 1992–
1995. WHAS-I was designed as an observational study to
investigate the epidemiology of disability progression in
community-dwelling women 65 years and older, with mod-
erate-to-severe physical disability at enrollment (N = 1,002)
(13). Ambulatory ECG Holter recordings over a 2-to 3-hour
period were obtained on 812 participants during standardized
evaluations. Of these, a random sample of 389 recordings
was processed as part of a previous pilot study (14). Our ana-
lytic sample includes 276 recordings, which had complete
data on the traditional time and frequency domain indices
of HRV. There were no significant differences between the
participants in our analytic sample, and the entire WHAS-I
cohort at baseline, with regard to key covariates including
age, race, smoking, cardiovascular disease (CVD) preva-
lence, and beta-blocker use (Table 1). Therefore, our analytic
sample may be viewed as a random subset of the WHAS-I
cohort. The study procedures were approved by the institu-
tional review boards of Johns Hopkins Medical Institutions.

Outcomes

Frailty was defined according to a previously validated
instrument (8) as the presence of three or more of the five
clinical characteristics: (a) shrinking—losing >10% of body
weight since age 60; (b) slowness—being in the bottom
20th percentile of 4-m usual walking speed, stratified by
gender and height; (c) weakness—being in the bottom 20th
percentile of maximal grip strength measured using a Jamar
hand-held dynamometer, stratified by gender and height;
(d) exhaustion—self-report of feeling unusually tired or
weak most or all of the time in the previous month or scor-
ing ≤3 on a visual analog scale assessing usual energy level
(0 = no energy to 10 = most energy); and (e) low-energy
expenditure—being in the bottom 20th percentile of total
physical activity in the past 2 weeks (self-report).

The date of death for those who had died during a 5-year
follow-up since baseline was obtained from death certifi-
cates. There were 72 deaths (26%) in our analytic sample.

Holter Monitoring

Two-channel continuous ECG recordings were obtained
using a calibrated analog Holter device with a temporal
resolution of 120 Hz (SpaceLabs 90205, Redmond, WA)
over a period of 2–3 hours, during which the study partici-
pants underwent standardized assessments (ie, interviews,
physical examination, performance-based tests). Analog
tape recordings were digitized and processed using a com-
puterized analysis system (SpaceLabs FT2000). After the
scanner automatically detected and labeled all QRS com-
plexes, files were reviewed manually and edited to ensure
that only normal-to-normal (N-N) intervals were included
for HRV analyses. Linear interpolation was used to fill-in
for deleted ectopic beats. ECG recordings with more than
20% ectopic beats were excluded from analyses.

The following traditional HRV indices were obtained using
standard methods (11): standard deviation of N-N intervals
(SDNN), root-mean-squared differences of successive N-N
intervals (RMSSD), and the proportion of all N-N intervals
that are larger than 50 ms (pNN50). Frequency domain HRV
indices were derived from spectral analysis using the fast Fou-
rier transform, by partitioning the overall variability into three
frequency bands: (a) very low frequency (VLF, <0.04 Hz),
which primarily reflects parasympathetic modulation of heart
rate but is also influenced by the renin–angiotensin system
(15); (b) low frequency (LF, 0.04–0.15 Hz), which reflects
both sympathetic and parasympathetic modulation; and (c)
high frequency (HF, 0.15–0.4 Hz), which primarily reflects
heart rate fluctuations due to parasympathetically mediated
respiratory sinus arrhythmia, although it can also be influ-
benced by erratic rhythms from nonrespiratory sinus arrhythmia (16).
Additionally, the LF/HF ratio, which has been proposed as a
marker of sympathetic–parasympathetic balance, was also
calculated. HRV indices were log-transformed and then stan-
dardized in the statistical analyses described below.
Table 2. Pearson Correlations Among the Traditional HRV Indices in the WHAS-I and Framingham

<table>
<thead>
<tr>
<th></th>
<th>VLF</th>
<th>LF</th>
<th>HF</th>
<th>SDNN</th>
<th>pNN50</th>
<th>RMSSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>.69 (.85)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>.48 (.61)</td>
<td>.84 (.77)</td>
<td></td>
<td>.75 (.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN</td>
<td>.76 (.86)</td>
<td>.80 (.75)</td>
<td>.75 (.71)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pNN50</td>
<td>.49 (.47)</td>
<td>.64 (.57)</td>
<td>.77 (.87)</td>
<td>.78 (.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMSSD</td>
<td>.39 (.48)</td>
<td>.72 (.60)</td>
<td>.91 (.93)</td>
<td>.79 (.54)</td>
<td>.84 (.94)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Correlations for Framingham [reported in Tsuji (19)] are given in parentheses. HRV = heart rate variability; WHAS-I = Women’s Health and Aging Study-I; VLF = very low frequency; LF = low frequency; HF = high frequency; SDNN = standard deviation of N-N intervals; pNN50 = proportion of all N-N intervals that are larger than 50 ms; RMSSD = root-mean-squared differences of successive N-N intervals.

Statistical Methods

Principal components analysis.—PCA is a technique to reduce the dimensionality of data consisting of correlated variables while capturing the bulk of variation present in the data (14). There are as many principal components (PCs) as there are original variables. Each PC is a linear combination of the original variables with a set of weights called “loadings,” which reflect the correlations between PCs and original variables. PC1 is the directional vector representing the best fit to data cloud. PC2 is the directional vector orthogonal to PC1 that provides the best fit to residual variability in the data, and so on. PCs are mutually uncorrelated. Effective dimensionality reduction is achieved when the first few (dominant) PCs capture most of the variation present in the data. Useful insights on the interrelationship between original variables can be obtained when the dominant PCs have substantive interpretations.

Regression analyses.—Separate linear regression models for age were constructed to evaluate its association with each HRV measure (six traditional HRV indices and two aggregate measures: LF/HF, and PC1 and PC2), adjusting for disease status as confounders. Separate logistic regression models of frailty status (yes/no) were constructed to evaluate its association with each HRV measure, adjusting for age, race, and diseases. Separate Cox regression models, under proportional hazards assumption, were constructed to test whether each HRV index predicted time-to-death, adjusting for age, race, diseases, and beta-blocker use. Proportional hazards assumption was evaluated by visually examining whether cumulative hazard plots of dichotomized covariates crossed each other, and via significance testing of the time–covariate interaction term.

Strength of association.—We used $p$ values, Akaike information criterion (AIC), area under the receiver operating characteristic (AU-ROC) curve (for logistic regression models) (17), and partial predictive score (PPS) for Cox regression models (18) to obtain a comparison of the strength of association between the dependent variables and each HRV measure. Smaller $p$ value and AIC suggest stronger associations; larger AU-ROC values (>0.5) suggest better predictive ability; and larger (less negative) PPS values indicate better prediction of timing of events.

RESULTS

Pearson correlations among HRV indices are reported in Table 2. Correlations for Framingham study population reported in (19) are shown in parentheses. We note that the

Table 4. Associations of Age With HRV Indices in Unadjusted and Adjusted (for race, CVD status, diabetes, and beta-blocker use) Linear Regression Models

<table>
<thead>
<tr>
<th></th>
<th>WHAS-I</th>
<th>Framingham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC1</td>
<td>PC2</td>
</tr>
<tr>
<td>VLF</td>
<td>.33</td>
<td>.76</td>
</tr>
<tr>
<td>LF</td>
<td>.42</td>
<td>.17</td>
</tr>
<tr>
<td>HF</td>
<td>.43</td>
<td>-.29</td>
</tr>
<tr>
<td>SDNN</td>
<td>.44</td>
<td>.21</td>
</tr>
<tr>
<td>pNN50</td>
<td>.41</td>
<td>-.27</td>
</tr>
<tr>
<td>RMSSD</td>
<td>.42</td>
<td>-.43</td>
</tr>
</tbody>
</table>

% Variation explained 76.3 13.3 74.6 17.4

Note: HRV = heart rate variability; WHAS-I = Women’s Health and Aging Study-I; PC = principal components; VLF = very low frequency; LF = low frequency; HF = high frequency; SDNN = standard deviation of N-N intervals; pNN50 = proportion of all N-N intervals that are larger than 50 ms; RMSSD = root-mean-squared differences of successive N-N intervals.
WHAS-I population comprises one-third most disabled women, with an average age of 78.4 years, whereas the Framingham group consists of both sexes and is younger and healthier. The correlations are qualitatively similar for these two studies, although there are some quantitative differences. In WHAS-I, the correlations between VLF and other indices are weaker, in particular, that between VLF and SDNN. Also, the correlation between SDNN and LF and that between SDNN and high-frequency components (HF, pNN50 and RMSSD) are stronger. Because SDNN is a measure of overall variability, these patterns suggest that the contribution of VLF variations to total variability is diminished, whereas the relative contribution of high-frequency variations is increased in WHAS-I compared with the Framingham population.

Table 3 presents the results of the PCA. The first two PCs explained 90% of the covariance between HRV indices. This is not surprising given the large positive correlations between the HRV indices. PC1 is essentially the average of the (log-transformed) indices. For WHAS-I, PC2 assigns largest positive weight to VLF; smaller positive weights for LF and SDNN; and negative weights for HF, pNN50, and RMSSD. Whereas PC1 provides a composite measure of variability, PC2 captures the correlation in heartbeat intervals across a broad frequency spectrum ranging from VLF to HF. A qualitatively similar pattern of loadings for PC2 is also seen in the Framingham study. In fact, we can expect to see this same pattern universally because it is a typical characteristic of PCA involving large positive correlations.

Table 4 presents the results of unadjusted and adjusted linear regression models evaluating the association between age and HRV indices. Among the individual indices VLF, pNN50, RMSSD, and LF/HF ratio were weakly associated (p values between .05 and .1) with age in the adjusted models. PC1 was not associated with age. PC2 was most strongly associated with age in both unadjusted (p value < .01) and adjusted (p value < .001) models.

Table 5 presents the results of unadjusted and adjusted logistic regression models evaluating the association between frailty and HRV measures. VLF, LF, SDNN, LF/HF ratio, and PC2 were significantly (p < .05) and negatively associated with frailty. Interestingly, increased LF/HF ratio was associated with a decreased risk of frailty. PC2 was the best predictor in both unadjusted and adjusted models. The adjusted model with PC2 had the smallest p value, smallest AIC, and the largest AU-ROC curve. However, PC1 was only weakly associated with frailty. Among the individual indices, VLF was the strongest predictor of frailty.

Table 6 shows the results of Cox regression models for predicting 5-year mortality. Proportionality of hazards was found to hold for all the Cox models (results not shown). Decreased VLF and LF/HF ratio were associated with an increased risk of mortality, whereas decreased RMSSD, pNN50, and HF were associated with a decreased risk of mortality. Decreased PC2 was positively associated with an increased risk of mortality. PC2 was the best predictor of all-cause mortality in both unadjusted and adjusted models. The adjusted model with PC2 had the smallest p value, smallest AIC, and largest PPS. Among the individual indices, RMSSD was the strongest predictor of mortality.

Figure 1 shows the unadjusted Kaplan–Meier curves for mortality, comparing VLF and PC2 in terms of their ability to predict 5-year mortality. Survival curves are drawn for four groups: low VLF (VLF < 6) versus high VLF, and low PC2 (PC2 < −0.6) versus high PC2, where “low” was defined as being in the lowest sample tertile. Although both low VLF and low PC2 are associated with a significantly increased risk of mortality, low PC2 is a stronger predictor of mortality than VLF.

**Discussion**

PC aggregation provides a compact summary of multivariate HRV data while discarding any redundancies in the highly correlated HRV indices. PC regression also avoids the thorny statistical issue of multiple testing, that is, the inflation of Type I error rates when testing for significance of association between a health outcome and the various individual HRV indices. The second PC, PC2, was most
strongly associated with age and was the best predictor of frailty and mortality in older, disabled women. This suggests that PC2 can be a useful, compact measure not only of impaired cardiac autonomic regulation but also of reduction in multisystem physiological complexity associated with frailty and increased risk of mortality. Weak association between age and the traditional HRV indices could be due to the combination of a relatively small sample size and a high prevalence of disability.

We interpret PC2 as capturing the long-range correlation in heartbeat fluctuations across frequencies ranging from VLF to HF. Decrease in PC2 suggests decay in these long-range correlations. In this regard, PC2 is similar to the power-law exponent (PLE), which is the slope of regression line fitted to log(power) versus log(frequency), over frequencies less than 0.02 Hz (20), that is, ultra-low frequency (ULF) and VLF oscillations. PLE becomes increasingly negative with age. PLE $<-1$ is associated with increased mortality risk (21,22). Interestingly, no changes in ULF power but a linear decline in VLF power has been observed with aging, explaining the increasing steepness of PLE (23). A decline in VLF will also result in a decrease in PC2. There are important differences, however, between PLE and PC2. PLE is limited to ULF and VLF oscillations, whereas PC2 incorporates LF and HF oscillations, in addition to VLF. Furthermore, PC2, being a linear combination of traditional HRV indices, can be readily determined from standard Holter summaries, whereas PLE estimation requires more sophisticated analytic procedures applied to raw spectrum. Because our Holter ECG recordings were only 2–3 hours long, the PLE, which is estimated from a 24-hour recording, could not be computed in our study. Therefore, we were unable to perform a rigorous comparative evaluation of PC2 and PLE.

Limitations of our study are (a) women-only sample, (b) sample consists of severely disabled older women, (c) cross-sectional assessment of association between frailty and HRV, (d) possibility of confounding due to measurement error in ascertainment of cardiovascular diseases and diabetes status and severity, and (e) possibility of residual confounding in the association between frailty and PC2 due to unascertained diseases and medications. We cannot infer a causal relationship between HRV and frailty due to these limitations. They also threaten the generalizability of our findings. Our findings on the associations between PC2 and outcomes, including frailty and mortality, must be replicated in clinical trials and/or in large epidemiological studies, using the loadings presented in Table 3, which are quite similar between WHAS-I and Framingham. The only major difference is in the loading of VLF on PC2. Comparing the correlation matrices (Table 2) for WHAS-I and Framingham, it can be seen that the correlation between VLF and the other indices, especially LF and HF, is weaker in WHAS-I. Also, the contribution of VLF oscillations to overall variability is lesser (as indicated by a weaker correlation between VLF and SDNN). This results in VLF loading weakly on PC1 and strongly on PC2. Physiologically, this is
suggestive of a breakdown in long-range correlations in heart rate time series, which might be related to the high prevalence of disability among WHAS-I participants.

There are encouraging signs that our results are potentially generalizable. Sensitivity analyses (results not shown) demonstrate that the associations of PC2 with outcomes are robust to reasonable changes in PC1 and PC2 loadings. Regression analyses reported in Tables 4–6 were repeated with PC1 and PC2 scores recomputed using Framingham loadings. Strong associations of PC2 with age, frailty, and mortality persisted. We also conducted a “homogeneous” PCA involving only the frequency domain measures, VLF, LF, and HF. Homogeneous PC2 was similar to “full” PC2 in that it assigned positive weights to VLF and LF and a negative weight to HF. It was as strongly associated with age, frailty, and mortality as full PC2, demonstrating the robustness of our conclusions.

Summary
Cardiac autonomic control is impaired in frailty. PC aggregation of traditional HRV indices provided a compact summary of this impairment and also revealed a new index (PC2), which was the better predictor of frailty and mortality in older, disabled women.

Funding
This research was supported by the National Institute on Aging, Claude D. Pepper Older Americans Independence Centers, grant P30 AG021334, and National Institutes of Health-National Center for Research Resources grant R37 AG19905 at the Johns Hopkins University School of Medicine.

Correspondence
Address correspondence to Ravi Varadhan, PhD, Johns Hopkins University Center on Aging and Health, 2024 E Monument Street, Suite 2-700, Baltimore, MD 21205. Email: rvaradhan@jhmi.edu

References

Received April 4, 2008
Accepted October 16, 2008
Decision Editor: Luigi Ferrucci, MD, PhD