The many metrics of cardiac chronotropy: A pragmatic primer and a brief comparison of metrics

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Abstract

This paper focuses on pragmatic issues in obtaining measures of cardiac vagal control, and overviews a set of freely available software tools for obtaining several widely used metrics that putatively reflect sympathetic and/or parasympathetic contributions to cardiac chronotropy. After an overview of those metrics, and a discussion of potential confounds and extraneous influences, an empirical examination of the relationships amongst these metrics is provided. This study examined 10 metrics in 96 unselected college students under conditions of resting baseline and serial paced arithmetic. Intercorrelations between metrics were very high. Factor analyses were conducted on the metrics reflecting variability in cardiac rate, once at baseline and again during mental arithmetic. Factor structure was highly stable across tasks, and included a factor that had high loadings of all variables except Toichi’s “cardiac sympathetic index” (CSI), and a second factor that was defined predominantly by the CSI. Although generally highly correlated, the various metrics responded differently under challenge.

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1. Introduction

Measures of heart rate variability (HRV) and respiratory sinus arrhythmia (RSA) in particular have been used to index autonomic nervous function and reactivity in relation to diverse phenomena, such as diabetes (Ewing et al., 1981), hypertension and other cardiovascular disease (Masi et al., 2007; Thayer and Lane, 2007), attentional capacity (Porges, 1992), emotion regulation (Calkins and Johnson, 1998), coronary artery disease (Carney et al., 1988), daily stressors (Fabes and Eisenberg, 1997), major depression (Chambers and Allen, 2002; Rottenberg, 2007), anxiety (Friedman, 2007), and children’s levels of empathy (Eisenberg et al., 1996), among many others. Numerous metrics have been used to summarize variability in cardiac chronotropy in the literature, but the selection of particular metrics is highly variable across studies, and metrics are often used interchangeably, or with little justification. Rarely have the various metrics been compared to assess the degree to which they assess similar constructs. This article will provide a pragmatic overview of obtaining measures of heart rate variability, followed by an empirical comparison of some of the more popular and easily obtained metrics of cardiac chronotropy. Finally, a suite of freely available software tools is introduced for converting EKG signals to metrics that may be used as indices of cardiac vagal control, in the hope that more researchers may incorporate such indices into their experimental protocols.

1.1. The physiological basis of heart rate variability

Heart rate variability results from a dynamic relationship between sympathetic and parasympathetic nervous system influences. HRV can occur from a co-activation, coinhibition, or activation of one with an inhibition of the other division of the autonomic nervous system (Bernston et al., 1991). Studies suggest that the vagus nerve is responsible for heart rate variability within the respiratory frequency band, as pharmacological blockades of vagal synapses at the sino-atrial node of the heart nearly abolish this coupling of heart rate and respiration, whereas interruption of the cardiac sympathetic inputs via beta-adrenergic blockade do not (Japundzic et al., 1990; McCabe et al., 1985; Pagani et al., 1986), although there

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is some evidence that high levels of sympathetic activity may attenuate RSA by inhibiting phasic vagal driving (see Berntson et al., 1993). This association of respiratory-linked heart rate variability, often termed respiratory sinus arrhythmia (RSA), with vagal influence as its putative mechanism, has led to the use of RSA as an approximation of vagal efferent activity to the sino-atrial node, since no direct noninvasive assessment of vagal cardiac efferent activity exists (e.g. Grossman and Taylor, 2007). The present manuscript will focus on how to obtain a variety of metrics of respiratory-linked variability, presenting a pragmatic overview and a description of tools available for use by researchers wishing to assess cardiac vagal control.

1.2. From the electrocardiogram to metrics

1.2.1. The EKG

Assessing cardiac vagal control begins with a simple digitized time series of the electrocardiogram (EKG), typically recorded from bipolar recordings between pairs of limbs according to Einthoven’s triangle (Einthoven et al., 1913), although any placement that permits a reliable identification of the R-spike in the EKG is acceptable. The EKG reflects voltage changes associated with phases of the cardiac cycle, with peaks and valleys in the waveform associated with the timing of atrial and ventricular depolarization and repolarization. Accurate identification of the QRS complex of the EKG, associated with ventricular depolarization, provides an easy-to-identify and reliable index of cardiac timing. Data should be digitized at a rate of 500 Hz or faster (Bernston et al., 1991), and the distance in milliseconds between each R-spike (the most prominent feature of the EKG waveform) will form the basis of an interbeat interval (IBI) series (see Fig. 1). This IBI series will form the input data for most algorithms that compute metrics of heart rate variability.

1.2.2. Artifacts in the detection of R–R intervals

Instead of the laborious task of detecting each IBI by hand, beat detection algorithms can automate this process, but such algorithms are seldom perfect, either skipping R-spikes (indicated by an unusually large IBI value, e.g. 1800 ms) or detecting a spurious beat (indicated by an unusually small IBI value, e.g. 150 ms). Even one artifact can result in an invalid index of HRV or RSA, regardless of whether the metric was derived from spectral analysis or time series analysis (Berntson and Stowell, 1998). It is thus important that the IBI series created from the beat detection program be hand-corrected for artifacts, a process that is facilitated by one of the two software tools (QRSTool) discussed in Appendix A.

1.3. The many metrics of HRV and RSA

1.3.1. Time domain metrics of variability

Time-domain metrics are plentiful and easily obtained (see Stein and Kleiger, 1999, for an accessible review). Several metrics summarize overall variability, but are not necessarily specific to respiration-linked changes in heart rate. Such metrics provide crude estimates of HRV and as such they are more appropriate for clinical trials than for use in most psychophysiological studies (Bernston et al., 1997). Other metrics are better indices of respiratory linked changes, and thus may serve as better indices of cardiac vagal control.

Measures of overall variability include the variance of the IBI series, with greater beat-to-beat variability reflected in greater variance. This metric is often log-transformed to make it more suitable to parametric statistical analyses. Similarly, the standard deviation of the interbeat intervals (SDNN; Murray et al., 1975) has been recommended as a measure for overall variability (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Because the variance and SDNN measures will potentially be larger as recording length increases, as slow changes in overall heart rate will influence these measures in addition to the beat-to-beat changes (Ewing et al., 1981), the Task Force (1996) recommends standardizing the recording length to 5 min to aid comparisons across studies.

Several other time-domain measures may more closely reflect respiratory-linked changes in heart rate, and thus provide better indices of the parasympathetic nervous system’s contribution to heart rate variability (respiratory sinus arrhythmia). These include: the percentage of the absolute differences between consecutive IBIs that are greater than 50 ms (pnn50; Ewing et al., 1984); the mean of the absolute value of the difference between successive interbeat intervals (MSD); the mean square successive difference (MSSD); the square root of the mean of squared successive differences between interbeat intervals (root mean square of successive differences, or RMSSD; Von Neumann et al., 1941); the peak to valley method (Grossman and Svebak, 1987; Grossman et al., 1990; Katona and Jih, 1975); the Porges adaptive polynomial filter method (also known as $V_{HAT}$ and $V_{NA}$), a method that is closely approximated using one of the software tools (CMetX) described in Appendix A; Toichi’s cardiac vagal index (Toichi et al., 1997).

MSD and MSSD provide nearly identical values (Ewing et al., 1981). These metrics primarily index parasympathetic influences to HRV, because slow changes to HR that are not due to respiration produce little change from one successive beat to
the next, and thus do not appreciably influence the metrics (Berntson et al., 2005; Porges and Bohrer, 1990). Friedman et al. (2002) compared RSA (derived from impedance pneumography, Ernst et al., 1999) and MSD during tasks that would elicit distinct cardiac responses (e.g. hand grasp for sympathetic response). MSD and RSA slightly diverged during a mixed sympathovagal task (i.e. playing a video game while wearing a cold facial mask), such that MSD reflected more sympathetic influence while RSA reflected parasympathetic influences. In primarily parasympathetic and primarily sympathetically mediated tasks, RSA and MSD responded similarly (across tasks, except for mixed sympathovagal task, \( r = .89 \)), suggesting MSD captures much but not all of the respiratory-linked variability in cardiac rate during most tasks.

The peak-to-valley or “peak-to-trough” method involves averaging the differences between the shortest IBI during inspiration and the longest IBI during exhalation across respiration cycles, thus, requiring a separate measure of respiration. Although this metric has been criticized for not accounting for slow periodic and aperiodic variations in heart period that are unrelated to respiration (Porges, 1986), Grossman (1992) notes that such variations produce very small effects on the peak to valley estimate of RSA (although for more detail see Weber et al., 1992a,b). Moreover, the peak to valley method correlates highly with both the Porges method (see below) and spectral analysis (Grossman et al., 1990), with within-subject correlations typically greater than .9, and between-subject correlations of .93 during rest and .94 during task conditions. Such convergence would be expected under conditions in which heart rate levels are relatively stable, but under periods of metabolic demands or recovery, slow trends may confound the peak-valley measure but not measures based on a limited frequency band (such as the Porges method or spectral analysis).

The Porges method removes complex baseline low-frequency nonrespiratory trends by using the patented Porges–Bohrer algorithm with a moving polynomial that filters out nonrespiratory frequencies and remove non-stationarities, but with some amplification of signals close to the low frequency cutoff due to a broad ripple in the frequency response of this filtering method (Litvack et al., 1995) The method converts the IBI series to a time series (see also Appendix A for further description with CMetX), applies the filter, and then computes the log-transformed variance of the remaining data (in the respiration range .12–.40 Hz, after loss of data points for the filter; Bohrer and Porges, 1982). The use of an average respiration range for all individuals and populations (e.g. anxious population; Kollai and Kollai, 1992) might result in an attenuated estimate of RSA, as the breathing rate may occur outside .12–.40 Hz (Grossman et al., 1990); however, the Porges method allows specification of the respiration bands based on the respiration rate.

Toichi et al. (1997) developed an alternative assessment of cardiac vagal activity, derived from the logic of a Lorenz plot of each IBI plotted against the subsequent IBI (Fig. 2). The length of the transverse axis (\( T \)) to the line \( IBI_n = IBI_{n+1} \) reflects beat-to-beat variability and large deviations along this axis putatively reflect predominately parasympathetic influences while the length of the longitudinal axis (\( L \)) reflects the overall range of IBIs, resulting from both sympathetic and parasympathetic influences. Two indices are calculated from \( L \) and \( T \): cardiac vagal index (CVI) = \( \log_{10}(L \times T) \); cardiac sympathetic index (CSI) = \( L/T \).

Toichi et al. (1997) examined changes in these metrics during sympathetic and parasympathetic blockades during supine resting, mental arithmetic, sitting, and standing. Although the \( T \) metric was responsive to some extent to both sympathetic and parasympathetic manipulations, the CVI was unaffected during sympathetic blockade with propranolol and significantly decreased under parasympathetic blockade with atropine, especially during the postural change from standing to supine. The CSI, by contrast, was significantly lower during sympathetic blockade, except for in the supine resting condition.

### 1.3.2. Frequency-domain metrics of variability

A variety of frequency domain techniques are available for examining the extent to which heart rate varies within specific frequency ranges, such as those associated with typical respiration. Fourier methods involve taking a time–domain representation of the IBI series and converting it to a frequency–domain representation, usually in the form of a power spectrum, and then summarizing activity in the frequency band of interest (e.g. .12–.40 Hz). An assumption underlying the Fourier transform is that a signal has at least weak stationarity (i.e. has a similar mean and variance across time) and periodicity (i.e. it repeats, and does so at uniformly spaced intervals of time). Although strictly speaking IBI series signals are not stationary nor periodic, as heart rate can shift over time and changes due to respiration and other sources do not recur at uniform intervals, these violations are not likely to be sufficient to invalidate the method (Friedman et al., 2002; Houtveen and Molenaar, 2001). Wavelet methods, an alternative method for frequency decomposition that do not assume stationarity, provide an other approach that produces results that are highly similar to those provided with conventional Fourier methods (Houtveen and Molenaar, 2001).

Autoregressive techniques are based on lagged correlations and also produce an index of periodic fluctuations in a time...
series, such as those due to respiration. Autoregressive and fast Fourier transform methods are highly related \( r = .96; \) Hayano et al., 1991).

An extension of the Fourier-based frequency–domain method involves comparing the IBI series with a measure of respiration to assess the degree to which there is covariation between the IBI series and respiration. These two signals may be compared using cross-spectral analysis (e.g., Porges and Bohrer, 1990) to derive an estimate of the coherence (ranging from 0 to 1) between the signals at a given frequency, or the weighted coherence (see Porges et al., 1980) for a range of frequencies such as those that are within the respiratory range. A variant of this method calculates the transfer magnitude (e.g., Freeman et al., 1995), which expresses the gain between heart rate (in beats per minute) per liter of lung volume, with a large gain indicating that relatively small changes in lung volume result in sizable changes in heart rate.

Although this lengthy list of metrics is not exhaustive, it covers the majority of those that have been used in the attempt to estimate vagal influence on cardiac chronotropy. In the present study, a subset of these measures are examined that are widely used and easy to obtain using only an EKG signal, and that can be derived using the freely-available software tools described in Appendix A.

1.4. Comparisons of measures

A few studies have compared the many metrics of cardiac chronotropy, typically comparing a subset of the measures to each other (Fahrenberg and Foerster, 1991; Friedman et al., 2002; Grossman et al., 1990; Hayano et al., 1991; Kleiger et al., 1991). In an examination of time and frequency domain measures derived from 24 h ambulatory Holter monitors, Kleiger et al. (1991) reported high correlations between SDNN, pnn50, RMSSD, and spectral analysis, with moderate correlations between SDNN and the other metrics \( .68–.78 \), and strong correlations amongst pnn50, RMSSD, and spectral analysis \( r = .92–.98 \). Similarly high correlations \( r = .85 \) between RMSSD and spectral high frequency power were found by Berntson et al. (2005).

Despite suggestions that the peak-valley estimation is vulnerable to artifacts associated with low frequencies (Byrne and Porges, 1993; Porges, 1985; Porges and Bohrer, 1990) and concerns that spectral analysis and the Porges–Bohrer method do not individually tailor the respiration range and instead use a mean or modal range of respiration (typically somewhere in the range of 6–30 breaths per minute; e.g. Grossman and Wiens, 1986), a comparison suggests near equivalency of the peak-valley estimation, the Porges method, and spectral analysis during a 5 min period (Grossman et al., 1990). Moderate relations between MSD and the peak-valley method and spectral analysis also exist \( r = .58–.9; \) Fahrenberg and Foerster, 1991; Hayano et al., 1991).

Despite the comparison of methods, no single measure has been hailed as the "gold standard." The Society for Psychophysiological Research’s Task Force committee report concluded "A number of approaches are currently available for analyzing periodic components of heart rate variability . . . and direct comparisons have revealed generally comparable results. Each of these approaches has advantages and disadvantages, and no general consensus has emerged on a single optimal analytic method" (Berntson et al., 1997, p. 641). There may, however, be specific research questions and research designs when one measure is preferable over the other (see pp. 151–154; Grossman, 1992), and some measures are more closely tied to respiratory-linked variability and may thus be preferred over global measures (HRV, SDNN) of variability.

1.5. Methodological concerns

1.5.1. Participant characteristics and behaviors

There are numerous issues that should be considered when deriving heart rate metrics as summarized by the Committee Report of Berntson et al. (1997). Beyond the issues that are summarized in the committee report, it is worth noting that there are a number of study participant behaviors and demographics that can influence indices of heart rate variability and, specifically, respiratory-linked variability. These factors may be considered when designing a study or assessed in the context of the study, and include: use of caffeine or alcohol, exercise, smoking, age, gender, and obesity. Table 1 provides a tabular summary of the impact of these various factors.\(^1\)

1.5.2. The thorny issue of respiration

1.5.2.1. Might RSA be an imperfect index of vagal control?.

A concern that has inspired considerable debate is the question of controlling for respiration. The principal issue is whether RSA is primarily a reflection of cardiac vagal control or whether RSA can under certain circumstances also reflect changes in respiration that are independent of central vagal effects. Investigators want to determine whether there are legitimate changes in vagal control, and not merely the influence of changes in respiration on the imperfect measure, RSA. This problem arises when respiration rates differ between groups, or between conditions.

Grossman et al. (1991) demonstrated that when there is large variability in respiration rates within individuals, rapid breathing will reduce RSA and slow breathing will increase RSA, independent of changes in tonic vagal modulation of heart rate, in a study designed to eliminate sympathetic contributions by administering 10 mg propranolol to block sympathetic influences. Houtveen et al. (2002) concur that RSA does not reflect solely tonic vagal modulation of heart rate during activities that affect the central respiratory drive (e.g. exercise), but they conclude, however, that during activities when respiration is not expected to greatly vary (i.e. during resting conditions and most clinical mental stress tasks), RSA uncorrected for respiration accurately reflects vagal modulation of heart rate.

Some studies pace participants’ breathing at a fixed rate or rates (e.g. Grossman et al., 1991) in order to avoid the

\(^1\) Articles were included in this synopsis if they included healthy adult samples.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Specific comparisons</th>
<th>Description of sample</th>
<th>Study design</th>
<th>Cardiac measures</th>
<th>Effect on HRV and RSA</th>
<th>Effect size (Cohen’s $d$)</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Chronic smoking</td>
<td>Resting RSA of non-smokers vs. moderate smokers (1–24 cigarettes per day) who are less than 30 years of age</td>
<td>28 males; aged 19–30 years; 15 non-smokers and 13 moderate smokers; refrained from smoking or drinking caffeine or alcohol 8 h before the study and consumed a light breakfast</td>
<td>5 min resting recording in the supine position</td>
<td>RSA calculated by power spectral density of RR interval variability</td>
<td>No difference in resting levels of RSA</td>
<td>Not significant</td>
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<td></td>
<td>Resting RSA of non-smokers vs. heavy smokers (&gt;25 cigarettes per day) who are less than 31 years of age</td>
<td>26 males; aged 19–30 years; 15 non-smokers and 11 heavy smokers; refrained from smoking or drinking caffeine or alcohol 8 h before the study and consumed a light breakfast</td>
<td>5 min resting recording in the supine position</td>
<td>RSA calculated by power spectral density of RR interval variability</td>
<td>Reduced levels of RSA (power spectral density) in heavy smokers &gt;31 years of age</td>
<td>$d_{RSA} = .88$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resting RSA of non-smokers vs. moderate and heavy smokers greater than 31 years of age</td>
<td>26 males; aged 30–52 years; 10 non-smokers, 18 moderate smokers, and 14 heavy smokers; refrained from smoking or drinking caffeine or alcohol 8 h before the study and consumed a light breakfast</td>
<td>5 min resting recording in the supine position</td>
<td>RSA calculated by power spectral density of RR interval variability</td>
<td>No difference between groups</td>
<td>Not significant</td>
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<tr>
<td>Acute effects of smoking</td>
<td>Acute effects of smoking in regular smokers</td>
<td>Nine males: aged 24–30 years who were regular cigarette smokers (mean 27 ± 8 cigarettes per day) refrained from smoking or drinking caffeine or alcohol 8 h before the study and consumed a light breakfast</td>
<td>5-min pre-smoking recording and post-smoking resting recording 3, 10, 17, and 24 min after start of smoking in the supine position. Participants smoke 4 cm of 1 cigarette containing 1.0 mg of nicotine during 2 min in the supine position</td>
<td>HRV calculated by standard deviation of the R–R interval; RSA calculated by power spectral density of RR interval variability</td>
<td>No changes in HRV. Reduced RSA at 3 min post-smoking and returned to control level by 10 min</td>
<td>$d_{HRV} = $ not significant; $d_{RSA} = 1.01$</td>
<td>Hayano et al. (1990)</td>
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<td>Change during smoking in regular smokers (mean ± 25.75 ± 11.9 cigarettes)</td>
<td>16 participants (8 female) aged 18–75 who smoked regularly (mean 25.75 ± 11.9); refrained from smoking and from drinking alcoholic or caffeinated beverages for 12 h before study</td>
<td>10-min baseline and the last 10 min of each 30 min cigarette smoking period resting recording in a seated position. Ten fixed doses of 1.0 mg of nicotine were administered in a standardized manner for three separate cigarettes spaced 30 min apart</td>
<td>Autoregressive spectral analysis from the IBI series in the full spectrum for HRV and in the respiratory frequency range for RSA</td>
<td>Reduced HRV and RSA</td>
<td>$d_{HRV} = 1.86; d_{RSA} = .52$ (effect sizes reported for only the effects of the first cigarette as cardiac measures were not significantly different for number of cigarettes)</td>
</tr>
<tr>
<td>Variable</td>
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<tr>
<td><strong>Exercise</strong></td>
<td>Pre- to post-training changes in resting recordings of heart rate after exercise program</td>
<td>Nineteen healthy males ages 45–68: 11 in exercise group and 8 in control group. Exercise group underwent a prolonged program of physical training (30 ± 1 week, range 25–36). During first 14 weeks of training, participants walked/jogged 3 days/week for 33 min/day. Level of exercise was progressively increased so that during final 16 weeks of training participants walked/jogged 3.5 days for 43 min per day</td>
<td>5 min in supine position while breathing at a rate of 10 breaths per minute</td>
<td>SDNN for HRV and peak to trough times series analysis for RSA</td>
<td>HRV increased; no change in RSA</td>
<td>$d_{HRV} = .76$ (estimated from graphs)</td>
<td>Seals and Chase (1989)</td>
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<td>Pre- to post-training changes in HRV and RSA in those in an exercise training program for 16 weeks vs. those not exercising</td>
<td>17 healthy males: 10 “young group” ages 19–29; “middle-aged group” ages 50–59. Refrained from smoking, caffeine, and alcohol on the day before EKG</td>
<td>1 h resting condition in supine position for 60 min</td>
<td>Standard deviation of the R-R interval for HRV and spectral analysis in the respiratory frequency for RSA</td>
<td>No differences between exercisers and controls and no differences between pre- to post-resting HRV or RSA in exercisers</td>
<td>Not significant</td>
<td>Catai et al. (2002)</td>
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<td></td>
<td>Comparison of regular exercisers to non-exercisers</td>
<td>30 healthy participants (4 women) ages 22–44. Participants who did not exercise regularly and participants who exercised less than 60 min, three times a week, for more than 6 months and intermittently were those who fell in between the two groups; participants were nonsmokers and refrained from caffeine and alcohol and refrained from moderate, heavy, or sustained exercise on the morning prior to the EKG</td>
<td>24 h Holter and participants avoided moderate, heavy, or sustained exercise</td>
<td>Spectral analysis in the respiratory frequency range; time domain measures of root mean square of successive differences; and the proportion of successive differences greater than 50 ms for measures of RSA</td>
<td>Greater levels of resting HRV and RSA in exercisers compared to non-exercisers</td>
<td>Not available</td>
<td>Goldsmith et al. (1997)</td>
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<td></td>
<td>Between group differences in RSA</td>
<td>12 college aged males (6 aerobically trained). Aerobically trained participants were members of the men’s cross-country team for at least 1 year and had a minimum of 3 years of competitive experience in cross-country events</td>
<td>3 min resting condition</td>
<td>Porges method</td>
<td>No difference in RSA in aerobically trained men</td>
<td>Not significant</td>
<td>Hatfield et al. (1998)</td>
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### Chronic effects of exercise

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Resting conditions</th>
<th>Measured variables</th>
<th>Results</th>
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<tbody>
<tr>
<td>Reland et al. (1994)</td>
<td>80 women ages 60–70 years old; 14 low activity, 13 moderate activity (from adult gymnastics group for &gt;4 years); 14 in high-activity from cycling tour club for &gt;4 years</td>
<td>Resting HRV and RSA levels between senior sedentary controls, moderate exercisers, and high exercisers</td>
<td>Resting HRV and RSA levels were higher in the high activity group in comparison to the low activity group</td>
<td>$d_{SDNN} = .49$; $d_{rMMSD} = 3.75$; $d_{RSA} = 2.86$</td>
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</tbody>
</table>

### Age and gender

**Age**
- HRV and RSA decrease with age

**Gender**
- Mixed Findings

### Caffeine

### Acute effects of caffeine

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Resting levels of RSA from pre- to post-consumption of caffeine</th>
<th>Measured variables</th>
<th>Results</th>
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<tbody>
<tr>
<td>Yataco et al. (1997)</td>
<td>20 healthy participants who regularly consumed 350–700 ml of coffee per day (approximately 180–360 mg caffeine). Participants fasted and abstained from caffeine from 10 p.m. the night before each examination</td>
<td>Breathed 1 breath every 4 s during 5 min resting baseline and 20 min after the beverage was consumed. Each participant had the caffeinated beverage one day and the uncaffeinated beverage the next day</td>
<td>Spectral analysis of the IBI series in the respiratory frequency for a measure of RSA</td>
<td>No change in RSA from pre- to post-consumption of caffeine</td>
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</table>

### Resting levels of RSA from pre- to post-consumption of caffeine

<table>
<thead>
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<td>Hibino et al. (1997)</td>
<td>20 healthy participants who regularly consumed 350–700 ml of coffee per day (approximately 180–360 mg caffeine). Participants fasted and abstained from caffeine from 10 p.m. the night before each examination</td>
<td>Spectral analysis in the respiratory frequency for a measure of RSA</td>
<td>Not significant</td>
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</table>

### Resting HRV and RSA levels between seniorsedentary controls and seniorcompetitive athletes (vigorous exercise for at least 45 min, four times a day)

<table>
<thead>
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</tr>
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<td>Reland et al. (1994)</td>
<td>29 healthy seniors (&gt;60 years old): 14 sedentary persons and 15 athletes (45 min, 4 times per week), who refrained from alcohol and caffeine for 12 h before and during ambulatory recording, and 24–36 h after last bout of exercise</td>
<td>24 h Holter and participants refrained from exercise during Holter</td>
<td>SDNN for HRV and rMMSD and HRV in the respiratory frequency range for RSA derived from time series analysis of the IBI series</td>
<td>Senior competitive athletes had greater HRV and RSA in comparison to sedentary controls</td>
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### Weighted average

<table>
<thead>
<tr>
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<td>Specific comparisons</td>
<td>Description of sample</td>
<td>Study design</td>
<td>Cardiac measures</td>
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<tr>
<td>Acute effects of caffeine in non-habitual caffeine users</td>
<td>Compared resting levels of RSA between placebo, and 100 and 200 mg of caffeine</td>
<td>10 participants (4 women) ages 23–32 randomized to receive 100 or 200 mg of caffeine dissolved in honey or a placebo in a crossover design over 3 days. Referred from caffeine for 4 days.</td>
<td>At baseline, 60 and 90 min after ingestion</td>
<td>Time domain for HRV was standard deviation of IBIs and the root mean-square difference in successive IBI intervals, the percentage of successive RR intervals &gt; 50 ms, and the respiratory frequency all served as measures for RSA</td>
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<td>Long-term effects of caffeine</td>
<td>Compared resting levels of HRV and RSA after 2 weeks of no caffeine in comparison to 2 weeks of caffeine</td>
<td>10 healthy (5 female) mean age 41.4(±10.8). All maintained a low-caffeine diet (&lt;50 mg/day)</td>
<td>48 h Holter pre- and post-2 weeks. Randomized cross-over design for 2 weeks ingested 2 250 mg (comparable to two to three cups of drip coffee) caffeine per day or matched placebo</td>
<td>Time domain measures of counts of RR intervals &gt; 50 ms (sNN50) and spectral analysis in the respiratory frequency for RSA</td>
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<td>Alcohol</td>
<td>Chronic effects of alcohol</td>
<td>Pre- to post-changes in resting levels of RSA after 1 week of daily consumption of 24 g of vodka in comparison to 1 week of no alcohol</td>
<td>21 healthy participants (7 female) aged 21–41 years</td>
<td>Spectral analysis in respiratory frequency</td>
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<tr>
<td>Acute effects of alcohol</td>
<td>Pre- to post-changes in HRV and RSA with consumption of alcohol</td>
<td>18 healthy males (mean age 28.5 ± 4.3 years old) who were infrequent drinkers consumed .3 g of alcohol/kg of body weight</td>
<td>10 min resting recording before and after (at 15, 30, 45, and 60 min post) at 9 a.m.; participants were told to fast overnight</td>
<td>RSA measured by spectral analysis in the respiratory frequency band</td>
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<tr>
<td>Obesity</td>
<td>Effects of obesity</td>
<td>Comparison of HRV and RSA in normal, overweight, and obese participants</td>
<td>653 healthy participants (361 women) mean ages of 40 ± 12 years</td>
<td>HRV measured by standard deviation of RR intervals; RSA by root mean square of successive RR interval differences, percentage of successive normal sinus RR intervals &gt; 50 ms, and spectral analysis in the high frequency range</td>
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<td>Comparison of RSA and body mass index</td>
<td>282 healthy males ages 21–59 years old who refrained from consuming food or beverages 2 h prior</td>
<td>3 min resting heart rate</td>
<td>RSA measured by autoregressive spectral analysis in the respiratory frequency band</td>
<td>Higher levels of RSA with lower body mass index</td>
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<td>Comparison of HRV before and after propranolol</td>
<td>56 males aged 25–36 with stable weight within the last 4 months with body mass index ranging from 2 to 46.3 (mean 24 ± 1.3). Participants consumed a weight-maintaining liquid diet for 4 days preceding heart rate monitoring. Participants refrained from tobacco and caffeine on the day of the recording</td>
<td>6 min heart rate during fixed breathing rate (5 breaths per minute) before and after propranolol</td>
<td>Standard deviation of R–R intervals for HRV and standard deviation of R–R intervals after propranolol during paced breathing for RSA</td>
<td>No relationship between body mass index and HRV; lower RSA with higher body mass index</td>
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</tr>
<tr>
<td>Comparison of RSA in obese and lean participants</td>
<td>84 (39 women) aged 39–60: 46 obese and 26 lean matched controls</td>
<td>24 h Holter</td>
<td>HRV measured by standard deviation of all normal RR intervals; RSA measured by spectral analysis in the respiratory frequency band during 24 h, daytime and evening</td>
<td>Less HRV and RSA in obese patients</td>
</tr>
<tr>
<td>Between group comparison of HRV and RSA in obese and lean women</td>
<td>20 obese women aged years old, weight between kg and 18 women aged 22–39 years old of normal weight</td>
<td>15 min heart rate recording in the supine position</td>
<td>Standard deviation of the R–R interval for HRV and spectral analysis in the respiratory frequency range for RSA</td>
<td>HRV and RSA less in obese women</td>
</tr>
<tr>
<td>Between group comparison of HRV and RSA in obese and lean participants</td>
<td>120 participants: 42 obese patients (24 females) ages 15–55 whose body mass index was greater than 30 and 78 lean healthy participants (30 females) aged 15–69. Participants refrained from caffeine on the day of the study</td>
<td>4-min resting heart rate while breathing deeply at a rate of 6 breaths per minute</td>
<td>The mean of the differences between the maximum and minimum heart rate during three successive breathing cycles measured HRV and cross-correlation function analyses (correlates spectral analysis of the interbeat interval series within the respiratory frequency range with the respiratory signal indexed RSA)</td>
<td>HRV and RSA less in obese participants</td>
</tr>
<tr>
<td>Between group comparison of HRV and RSA in three groups of varying body mass indices</td>
<td>23 patients (16 females) ages in three groups: 17 in 27–32 kg/m² group, 13 in 33–39 kg/m² group, and 12 in above 40 kg/m² group</td>
<td>5 min resting heart rate</td>
<td>Spectral analysis in the respiratory frequency range for RSA</td>
<td>No differences in resting RSA between groups and no relationship between RSA and body mass index</td>
</tr>
<tr>
<td>Circadian rhythm</td>
<td>Circadian rhythm</td>
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</tr>
</tbody>
</table>

Effect sizes are provided when possible.
possibility that changes in respiration, unrelated to central vagal efferent activity, can produce changes in the metric used to assess vagal control, RSA. An unresolved issue, however, is whether paced intentional breathing alters the very system the investigator wishes to assess. Under spontaneous conditions, breathing is a probe that allows investigators to observe the direct effects of the vagal system on cardiac rate, assessing the degree to which rate is responsive to each breath. Changing the probe itself, by pacing breathing for example, could render the assessment invalid for a variety of reasons, among them the fact that one would no longer be observing the spontaneous activity of the system, but the activity under artificial conditions. Whether the behavior of the system under paced conditions is an adequate model for its behavior under spontaneous conditions remains an open question. Moreover, evidence that manipulating the depth and frequency of breathing can impact subjective emotion (Philippot et al., 2003) suggests that pacing breathing may additionally affect behaviors of central interest to researchers utilizing measures of vagal control. The debate over whether to control for respiration is discussed in depth by several authors in this volume (Denver et al., 2007; Grossman and Taylor, 2007; Porges, 2007) and elsewhere (Berntson et al., 1997; Grossman et al., 1991).

1.5.2.2. Statistical “control” for respiration. In addition to attempting to experimentally control respiration by pacing breathing, for example, authors have attempted to statistically control for respiration frequency through the use of covariate analysis (e.g. Hughes and Stoney, 2000) or residualizing data by first accounting for variance that overlaps with respiration frequency. The use of an analysis of covariance (ANCOVA) procedure has both valid and invalid uses, as detailed below, but adjusting estimates of RSA using respiratory frequency as a covariate will not “solve” the problem when experimental conditions or groups of participants differ in terms of respiratory frequency. Such an analysis can address whether variance between groups of participants or between conditions in respiratory frequency may account for any differences in RSA observed between those groups of participants or between conditions. But this analysis does not in any way “fix” the underlying fact that groups or conditions differ in terms of respiration, nor does it allow one to proceed with covariate adjusted RSA data as if one had “corrected for” or “statistically controlled for” the impact of respiration.

This issue has received statistical and conceptual discussions (e.g. Chapman and Chapman, 1973; Miller and Chapman, 2001; Siddle and Turpin, 1980, among others), but the fundamental issue is that covariance analysis is designed to remove variance due to a factor that is statistically independent of (i.e. uncorrelated with) the effect of interest, as in the case of removing variance associated with an individual difference such as body mass index when participants are randomly assigned to conditions. When a dependent variable (RSA) and a covariate (respiration frequency) are correlated, however, removing the effect of the covariate on the dependent variable can remove relevant variance in RSA that is due to the group difference or experimental manipulation, thus, misleading a researcher to conclude that no meaningful differences exist between subjects or conditions in terms of RSA. Vexingly, in other cases, such an ANCOVA can in fact create spurious group or condition effects (e.g. see Wainer’s, 1991 discussion of Lord’s Paradox). In short, this use of covariance may remove too much of the effect of interest, or conversely create spurious effects (Elashoff, 1969; Miller and Chapman, 2001).

Among the recommendations of the Society for Psychophysiological Research Committee Report (Berntson et al., 1997) is “to use respiratory frequency and possibly depth as covariates in statistical analysis or to remove possible contributions by regression prior to analysis” (p. 639). Although this at first glance appears to be a recommendation to use ANCOVA in the problematic manner outlined above, they note one paragraph later that “these correction procedures... may remove actual experimental effects that correlate with respiratory changes” (p. 639), thus reinforcing the message that ANCOVA does not solve the underlying confounding of respiratory parameters and the group or condition differences. The Committee’s recommendation to use ANCOVA makes sense when the variance to be removed is understood to be noise or error variance, rather than variance systematically associated with the independent variable.

Despite such problematic use of ANCOVA with respiration and RSA, there remain some valid uses that can rule out some important alternative hypotheses. Instead of asking whether effects of group or condition on RSA remain after “accounting for” or “controlling for” variance due to respiration, one can ask the question of whether respiration can account for these effects of interest. If an investigator finds significant group or condition effects on RSA in a simple ANOVA, and subsequent results using respiration as a covariate in an ANCOVA leave the effects of interest intact, then it is safe to conclude that respiration cannot account for the effects of interest, and the investigator can then interpret the RSA effects due to group or condition. If, however, including the covariate changes the statistical outcome, one is left not knowing whether the effects of group or condition on vagal control are legitimate, or an artifact of respiration differences between group or condition.

1.5.2.3. Simple recommendations regarding respiration. The Society for Psychophysiological Research’s Task Force committee report recommends the consideration of respiration when interpreting RSA as a measure of cardiac vagal control, specifically to ensure that the frequency band used to define RSA (e.g. .12-.40 Hz) actually encompasses the respiratory frequency of participants included in the analysis (Berntson et al., 1997). Common lower cutoffs for the respiratory band are .12 Hz (one breath every 8.3 s) and .15 Hz (one breath every 6.7 s), but these cutoffs will yield an inaccurate estimate of RSA for participants who breath more slowly than the lower cutoff (and a similar problem would exist in the less likely case that participants breath more rapidly than the upper cutoff). Moreover, the impact of breathing at frequencies near the cutoff will be attenuated to some extent due to the transition band on
most filters (see Fig. A.2 in Appendix A for examples of such transition bands).

Assuming that participants are breathing in the range defined to be captured by a given metric of RSA, there remain several desiderata for experimental design and analysis with respect to respiration:

1. Plan the experiment to increase the likelihood that respiration rates will not differ between conditions (e.g., keep activity levels similar across conditions).
2. Monitor to ensure respiratory rate does not differ between conditions and occurs in a range that will be captured by the metric of RSA. This can be done by monitoring respiration, or alternatively by looking at the peak in the spectral representation of the time-sampled IBI series.
3. If rates differ, use covariate analysis not to adjust means, but to assess whether effects from a standard ANOVA survive after accounting for variance due to respiration. If they do, then respiration rate effects did not account for the effects of interest and interpretations based on RSA can proceed.
4. If after covariate analysis the effects of interest disappear, then one is left with an interpretive enigma with respect to whether the observed differences in the measure of RSA may accurately reflect differences in vagal control per se.

2. Method

2.1. Participants

Participants were undergraduate students recruited by telephone for an experiment on “personality characteristics,” for which they would receive credits toward a course in introductory psychology. These participants were also included in Movius and Allen (2005), but only the single RSA metric and its relationship to personality measures was reported in that paper. Participants who were currently taking cardiovascular medications or those with a history of cardiac disease were ruled ineligible for the study. A total of 116 of the participants contacted by phone agreed to participate in the study. Due to electrode failure (16), resting RSA more than three standard deviations below the mean (2), and too many abnormal beats (2), data from a total of 96 participants (51 females) were available.

2.2. Procedures

After providing informed consent, three Ag/AgCl electrodes were attached to each participant in a Lead-II formation (Einthoven et al., 1913) plus a right forearm ground, with impedances reduced to less than 20 kΩ on all electrodes. EKG signals were amplified 1000 times with a bandpass of .05–100 Hz, then digitized at 500 Hz.

2.2.1. Tasks for recording

Participants were seated in a sound-damped chamber and briefly oriented to their surroundings. Participants sat quietly for five minutes to obtain baseline values. For a measure of heart rate reactivity, participants were then asked to perform serial paced mental arithmetic by counting backward in varying intervals, starting with a four-digit number for five 1 min periods. Following the paced arithmetic stressor task, participants sat quietly for another 5 min period.

2.3. Data reduction

2.3.1. EKG signal reduction

Raw digitized EKG signals were analyzed off-line. IBI series were hand corrected for artifacts and then processed by CMetX (see Appendix A) for measures of heart rate and heart rate variability. CMetX converted the IBI series to a time-series sampled at 10 Hz, filtered the series using a 241-point optimal finite impulse response digital filter designed using FWTGEN V3.8 (Cook and Miller, 1992) with half-amplitude frequencies of .12 and .40 Hz, and then took the natural log of the variance of the filtered waveform to be as the estimate of RSA. CMetX also derived several other measures of heart rate variability: the proportion of consecutive interbeat intervals differing by more than 50 ms (pnn50); the mean of the absolute value of the difference between consecutive IBIs (MSD); the cardiac vagal index (CVI; Toichi et al., 1997); the standard deviation of the interbeat intervals (SDNN); the root mean square of successive differences between interbeat intervals (RMSSD); and natural-log-transformed variance of the unfiltered IBI times series, across the entire frequency range (HRV). Finally, CMetX calculated the cardiac sympathetic index (CSI; Toichi et al., 1997), average heart rate, and average heart period. All metrics were calculated for resting baseline and during the stressor task.

3. Results

3.1. Transfer functions of various classes of metric

Two metrics of variability (HRV: natural log of the variance of the IBI series; SDNN: standard deviation of IBI series) are based on the raw IBI series and summarize cardiac variability across all frequency ranges, and thus do not reflect solely vagal contributions to cardiac chronotropy. Other metrics transform the IBI series via various “filters,” and thus may attenuate non-respiratory contributions to heart rate variability. The mean successive difference (MSD) metric is based on successive differences, which have been noted to attenuate lower frequencies, and the root mean square of successive differences between IBIs (RMSSD) might be expected to have a similar effect. The pnn50 is essentially a course successive difference filter, dichotomizing the successive differences as zero or one. And the estimate of RSA (natural log of .12–.40 Hz band-limited time-sampled IBI series) will specifically eliminate those frequencies outside of the typical respiration band.

To derive the transfer functions of these various transformations, for each IBI series (across all participants at baseline and task conditions) a successive-difference (SD) series was created, as well as a dichotomized SD series (to correspond to the pnn50 metric) with values greater than 50 ms receiving a value of one, and those ≤50 receiving a value of 0. Time series with sampling rates of 10 Hz were created for each of these series using cubic-spline interpolation. To compare the frequency response of these series with the method used to estimate RSA (CMetX), an additional series was created by applying a .12–.40 Hz filter to a 10 Hz sampled time series interpolation of the original IBI series.
Power spectral density estimates were obtained for each series by average FFT (successive windows of length 5.12 s, overlapping by 3.84 s, with a 50% Hamming window). These spectral densities were used to calculate the gain function for each derived series, taken as the ratio between amplitudes of the derived and original IBI at each frequency. Average gain functions were obtained for each derived series (SD, dichotomized SD [pnn50] and .12–.40 Hz filter) as the grand mean of the respective transfer functions across all original IBI series (all participants and both resting and stress task).

The gain functions for each metric, representing the average across all participants and task conditions, are presented in Fig. 3, with the inset of Fig. 3 showing the amplitude spectrum from the raw IBI series. As expected, the empirical transfer function for the .12–.40 Hz filtered series closely approximates the transfer function of that filter, and substantially attenuates frequencies outside of that bandwidth. The SD, and pnn50 transfer functions, by contrast, are characterized by: (1) broader transition bands at the low frequency end, thus, allowing some non-respiratory linked low-frequency variance to be included; (2) uneven transfer functions, especially for pnn50, with large changes in gain from one frequency to the next; (3) accentuation of higher frequencies, such that frequencies beyond the normal breathing range are most heavily weighted in the calculation of the metric. This empirical derivation is in general agreement with the transfer ratio modeled by Berntson et al. (2005), who estimated a similar shaped transfer function, based only on successive differences in simulated data based on sinusoidal respiration functions at individual frequencies.

3.2. Convergent validity

As shown in Table 2, measures of heart rate and heart rate variability were highly correlated with one another during both rest (median magnitude of Pearson $r = .75$) and during paced arithmetic stressor (median magnitude of $r = .73$). Metrics putatively measuring parasympathetic nervous system activity were also highly intercorrelated during rest (median $r = .89$) and during paced arithmetic stressor (median $r = .87$).

3.3. Discriminant validity

Although many measures of heart rate and heart rate variability were moderately to highly correlated both during rest and stressor, the putative sympathetic metric, Toichi’s CSI, was significantly negatively correlated to all other measures of heart rate variability both at rest and under stress.

3.4. Exploratory factor analysis

To examine the degree to which the measures were indexing similar constructs, exploratory factor analysis using principal component extraction and varimax rotation was utilized, extracting two factors. Measures of variability were entered into the analysis (HRV, SDNN, RMSSD, CSI, MSD, pnn50, RSA, and CVI), with a separate factor analysis conducted at rest and during stressor. Two factors accounted for 94% and 95% of the variance during rest and stressor, respectively. As shown in Table 3, Factor 1 had high loadings for every metric except CSI, whereas Factor 2 had a very high loading for CSI, and smaller and inverse loadings for most but not all other metrics. The factor loadings were descriptively quite similar at rest and during stressor.

These results suggested that across participants and across tasks, the inter-relationships of the various metrics were highly stable, and that measures putatively reflecting total variability and parasympathetically mediated variability loaded on a single
factor. These analyses addressed the extent to which these various measures shared variance across individuals, but did not address the extent to which they were similarly sensitive to change within individuals. The change in scores from baseline to stressor was therefore examined.

3.4.1. Change scores in measures

To reflect reactivity due to the stress task, change scores (stressor task minus rest) were computed. Intercorrelations amongst change scores for these metrics of heart rate and heart rate variability (Table 2) were moderate to high (median

<table>
<thead>
<tr>
<th></th>
<th>IBIs</th>
<th>HR</th>
<th>HRV</th>
<th>SDNN</th>
<th>RMSSD</th>
<th>CSI</th>
<th>MSD</th>
<th>pnn50</th>
<th>RSA</th>
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<tbody>
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<tr>
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<td>–.62</td>
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<td>.88</td>
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<td>.92</td>
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<td>.92</td>
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<td>–.62</td>
<td>−.33</td>
<td>−.39</td>
<td>−.63</td>
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<td>.94</td>
<td>.92</td>
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<td>.92</td>
<td>.87</td>
<td>.87</td>
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<tr>
<td>CVI</td>
<td>.69</td>
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<td>.84</td>
<td>.83</td>
<td>−.63</td>
<td>.87</td>
<td>.87</td>
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Change from rest to paced arithmetic

<table>
<thead>
<tr>
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<th>SDNN</th>
<th>RMSSD</th>
<th>CSI</th>
<th>MSD</th>
<th>pnn50</th>
<th>RSA</th>
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<tbody>
<tr>
<td>HR</td>
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<td>.52</td>
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<td>.86</td>
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</tr>
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<td>.45</td>
<td>.62</td>
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<td>.78</td>
<td>.64</td>
<td>.53</td>
<td>.45</td>
<td>.35</td>
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<td>CSI</td>
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<td>−.35</td>
<td>.40</td>
<td>−.14</td>
<td>.08</td>
<td>.11</td>
<td>.76</td>
<td>−.27</td>
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<td>−.14</td>
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<tr>
<td>RSA</td>
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<td>−.46</td>
<td>.73</td>
<td>−.45</td>
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<td>−.27</td>
<td>.85</td>
<td>.75</td>
<td>−.37</td>
<td>.93</td>
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</table>

Note: N = 96; correlations greater in magnitude than .199 are significant at the P < .05 level. Each panel has measures of rate (IBIs = mean interbeat interval; HR = mean heart rate), measures of total variability (HRV = natural log of variance of IBIs; SDNN = standard deviation of IBIs; RMSSD = root mean square of differences between IBIs), an estimate of sympathetic-related variability (CSI = Toichi cardiac sympathetic index), and estimates of parasympathetically controlled variability (MSD = mean of absolute value of consecutive IBI differences; pnn50 = proportion of consecutive IBI differences greater than 50 ms; RSA = natural log of variance of filtered (.12–.40 Hz) IBI time series; CVI = Toichi cardiac vagal index).

Table 3

Factor loadings for metrics at rest and during paced arithmetic

<table>
<thead>
<tr>
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<th>Paced arithmetic (PA)</th>
<th>Change from rest to PA</th>
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</thead>
<tbody>
<tr>
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<td>Factor 1</td>
<td>Factor 2</td>
<td>Factor 1</td>
</tr>
<tr>
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<td>.97</td>
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</tr>
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<td>CVI</td>
<td>.89</td>
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<td>.83</td>
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greater than 50 ms; RSA = natural log of variance of filtered (.12–.40 Hz) IBI
secutive IBI differences; pnn50 = proportion of consecutive IBI differences
variability (CSI = Toichi cardiac sympathetic index;), and estimates of para
mean square of differences between IBIs), an estimate of sympathetic-related
HR = mean heart rate), measures of total variability (HRV = natural log of

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Mean (S.E.)</th>
<th>F</th>
<th>P</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Paced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBI</td>
<td>840.2 (12.71)</td>
<td>724.8 (12.60)</td>
<td>325.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HR</td>
<td>73.4 (1.09)</td>
<td>86.0 (1.54)</td>
<td>201.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HRV</td>
<td>7.9 (.08)</td>
<td>8.3 (.07)</td>
<td>28.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SDNN</td>
<td>61.3 (2.90)</td>
<td>68.6 (2.45)</td>
<td>9.0</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>RMSSD</td>
<td>56.2 (3.70)</td>
<td>43.5 (2.60)</td>
<td>27.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CSI</td>
<td>2.2 (.07)</td>
<td>3.5 (.17)</td>
<td>91.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MSD</td>
<td>44.4 (2.97)</td>
<td>32.0 (1.95)</td>
<td>39.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>pnn50</td>
<td>29.4 (2.32)</td>
<td>18.6 (1.62)</td>
<td>66.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RSA</td>
<td>6.7 (.10)</td>
<td>6.5 (.10)</td>
<td>7.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>CVI</td>
<td>4.6 (.04)</td>
<td>4.6 (.04)</td>
<td>.39</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Note: N = 96; analysis included measures of rate (IBI = mean interbeat interval; HR = mean heart rate), measures of total variability (HRV = natural log of variance of IBI time series; SDNN = standard deviation of IBIs; RMSSD = root mean square of differences between IBIs), an estimate of sympathetic-related variability (CSI = Toichi cardiac sympathetic index;), and estimates of para-
sympathetically controlled variability (MSD = mean of absolute value of con-
secutive IBI differences; pnn50 = proportion of consecutive IBI differences
greater than 50 ms; RSA = natural log of variance of filtered (.12–.40 Hz) IBI
time series; CVI = Toichi cardiac vagal index).

magnitude $r = .45$) and metrics of parasympathetically influ-
enced variability were more strongly intercorrelated (median
$r = .61$). Exploratory factor analysis extracted two factors that
were highly similar to those described above, jointly
accounting for 81% of the variance (Table 3).

3.5. Sensitivity to experimental manipulations

To determine whether metrics were able to discriminate
between tasks, separate analyses were conducted using
repeated measures general linear model for each metric. All
metrics except Toichi’s CVI (Table 4) discriminated robustly
between the rest and stressor task, although effect sizes varied
quite substantially.

4. Discussion

Although several metrics converged as expected, the overall
pattern of results suggests that metrics putatively tapping
vagally mediated cardiac variability correlate highly with
metrics summarizing total variability. This may reflect that, at
rest, a majority of variability in cardiac chronotropy is due to
parasympathetic influences. Fig. 3 supports this interpretation,
as most of the power in the raw spectrum is in ranges passed by
the various transformations of the IBI series that form the basis
of the various metrics. The present results apply only to
relatively sedentary laboratory conditions, and generalization
beyond these conditions is not warranted.

Evidence from the analysis of metrics during rest and
arithmetic stressor suggests that measures are differentially
sensitive to the stressor manipulations, with all measures except
for Toichi’s CVI significantly discriminating rest from stressor
task but with markedly different effect sizes. Given the
relatively high correlation of CVI with other measures of
vagally influenced variability, it is surprising that this measure
was not sensitive to the task manipulation, but suggests it may
not be used interchangeably with the more standard measure of
RSA based on respiratory band-limited variance.

Given the present results, it may be tempting to assume the
interchangeability of many of the metrics, but given the
variability between the transfer functions of the various metrics,
a band-limited filtered IBI series (e.g. .12–.40 Hz in the present
study), or power from the same frequency range using spectral
analysis, may be preferred as they adequately summarize cardiac
variability in the respiratory frequency range, and attenuate
slower frequencies with a steep roll-off. Other metrics such as the
Toichi metrics are included as they appear to hold some promise,
but are largely unexplored. Computationally simple metrics with
broad and irregular transfer functions were included merely to
assess comparability across studies. Although at rest all metrics
perform somewhat similarly, it is worth noting that they have
widely different effect sizes in terms of discriminating rest from
the arithmetic stress task, and if researchers are interested in
solely vagal contributions, they would be well advised to use
measures that are most likely to reflect respiratory-linked vagally
mediated control of cardiac chronotopy.

A freely available suite of software tools for obtaining the
IBI series from EKG data and computing many metrics of
cardiac chronotropy is described in Appendix A. Given the
increasing interest in using measures of cardiac vagal control in
research on health, emotion, development, and psychopathol-
ogy, it is hoped that these tools will stimulate further interest in
the field, and encourage researchers new to this field to begin
using measures of cardiac vagal control in their research.

Acknowledgments

Portions of these data were presented at the 2001 and 2002
annual conferences of the Society for Psychophysiological
Research in Montreal, Quebec, and Washington, DC. The
authors wish to thank Hal Movius for assistance with data
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Ottmar Lipp, and two anonymous reviewers for their critiques
of an earlier draft of this manuscript.

Appendix A. QRSTool and CMetX: a software suite to
obtain metrics of cardiac vagal control

A suite of tools for transforming EKG data to metrics of
cardiac variability is freely available from http://www.
psychofizz.org, under the appropriate link. These tools run
under various versions of the Microsoft Windows operating
system. QRSTool provides a graphical user interface that will
allow for the extraction of the IBI series from EKG data,
whereas CMetX is a command-line based utility that will
calculate several metrics of cardiac chronotropy given a simple
IBI series as input. The tools are integrated such that users who
choose to extract the IBI series with QRSTool can have metrics
calculated directly by CMetX. The programs also can be used
independently: CMetX can derive metrics given any IBI series

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as input, and QRSTool can extract the IBI series to then analyze using other programs or algorithms. Each program is described below.

A.1. QRSTool: software for deriving a reliable IBI series from EKG data

There are a number of software packages designed to detect beats in raw EKG data. Typically, such software does not allow online modification of the beat series, and as such, the output must be visually inspected for missed or extra beats. Errors in beat series must be modified manually, e.g., deletion of extra beats, or interpolation of beat times for skipped beats. This process can require multiple passes of correction and visualization before a beat series is acceptable.

QRSTool is an EKG beat detection software program that allows for modification of beat assignments while simultaneously viewing the resulting IBI series. Missed and extra beats can be identified by visual inspection of the IBI series, and corrected by manual addition or removal of individual beats. The EKG and IBI series are displayed in separate vertically stacked time-locked windows, with identified beats marked on the EKG series.

There are a number of EKG transform functions (e.g., filtering) that create additional, separate EKG series, each of which can be selected as the currently visible EKG series. Beat markers are placed directly on the visible EKG series, allowing for comparison of beat placement between different series. This function can be useful in assessing the extent to which features in the transformed data are shifted with respect to the same features in the raw series (e.g., filtering; see below).

QRSTool also includes automated beat detection algorithms. The simplest of these is a threshold function, which assigns beats to all maxima or minima in the EKG time series that exceed a set threshold (typically, the maxima corresponding to the R-wave). Like many of the functions in QRSTool, the threshold detection tool can be applied to the entire series or to manually selected portions. Limiting beat detection to selected portions of the EKG series can be useful in cases where the series varies with respect to signal or noise amplitude.

QRSTool also includes a limited filtering function. Externally generated filters may be imported into QRSTool (as text coefficients), and then applied to the EKG series. It is important to note that, since the PQRST complex is not symmetrical, portions of the filtered complex (e.g., the R-spike) may be phase-shifted with respect to the original series. The degree to which this occurs depends on both the filter parameters and possibly time-varying characteristics of the original EKG signal (e.g., PQRST complex amplitude). As such, if threshold detection is applied to a filtered series, it is often useful to compare beat locations in both the original and filtered series (by changing which is visible in the EKG window).²

QRSTool is equipped to handle those cases where threshold beat detection is not possible. Table A.1 lists common QRS detection problems and the solutions offered in QRSTool. EKG recorded with dc-coupled amplifiers may include baseline drift, making any given threshold valid for only a few beats. The peri-beat filter correction algorithm (described below) may be useful for such data, since the algorithm uses only local signal characteristics. In cases where T-wave amplitudes are similar to or exceed R-spike amplitude, a first-order derivative transform is available (essentially amplifying higher-frequency components). A somewhat more sophisticated function uses the length-transform (Gritzali, 1988) to accentuate R-spikes in the process of beat detection (however, as of this writing, it is not clear that this algorithm is more robust than filtering or derivative transforms).

QRSTool also includes beat correction algorithms, which are applicable to series where at least some beats have already been

² It is not clear how much the phase shift that result from filtering affects measures of heart-rate variability. Unless PQRST morphology varies throughout the ECG signal, the phase-offset for any given filter should be relatively constant.
identified. One of these is a function which locks beats to local maxima or minima in the visible series; this algorithm may be applied, for example, to move beats detected by phase-shifted peaks in a filtered series to the actual maxima or minima in the original series. Another function that has proven useful for both beat detection and correction is the peri-beat filter. This algorithm uses existing beats to create an “average” beat, which is in turn applied as a filter to the EKG time series. Since the center of the filter corresponds to existing beat locations, the newly created series will have maxima at points where the original series is similar to the “average” beat. This algorithm is useful in cases where the EKG signal is not globally similar, e.g., baseline drift, or time-varying changes in PQRST amplitude.

QRSTool also allows hand placement of peaks for those cases where visual inspection is required to identify the beat. Also, in case of ectopic beats due to premature ventricular contraction that are then followed by a lengthy compensatory delay before the subsequent beat, Porges (2007) recommends that a beat be placed midway between beats on either side of the ectopic beat, a feature that is easily implemented with QRSTool. Porges (2007) notes that these ectopic ventricular complexes will artificially inflate the estimate of RSA by adding ventricular-related variance that is independent of the vagal modulation of the sino-atrial node.

Once an acceptable IBI series has been created, the series may be exported for further analysis (as of this writing, QRSTool does not incorporate any functions for the analysis of heart-rate variability). QRSTool was specifically developed to work in conjunction with CMetX, and as such, automates both the export of the IBI series and execution of CMetX on the resulting file. However, QRSTool can export IBI series in a number of different formats for use with other analysis packages. Manual selection, or selection based on events, may be used to export portions of the IBI series. This functionality may be useful for experiments where one EKG record exists for a number of different conditions. Currently, QRSTool allows both manually inserted events, as well as events imported from Neuroscan CNT files.

QRSTool has, in addition to the GUI menu and button driven methods of processing data, some scripting functionality that can automate parts of the process such as exporting the artifact free series, opening files, applying certain types of filters, etc. Commands stored in ASCII text files can be opened and executed within QRSTool.

A.2. CMetX: software for calculating many metrics of cardiac chronotropy

CMetX is a command-line based program that calculates many metrics of cardiac chronotropy, given an IBI series as input. The IBI series is contained within an ASCII file, with each IBI in ms on a separate line. The resultant output provides metrics summarized in Table A.2.

A.2.1. Filtering the IBI series, following transformation to a time series

An IBI series in not, strictly speaking, a time series, as the data occur at uneven intervals, provided that there is variability in cardiac chronotropy, the very phenomenon of interest! An IBI series can be converted to a time series by interpolating data points at a fixed sampling rate. CMetX program implements a 10 Hz sampling rate with linear interpolation, as illustrated in Fig. A.1.

Whereas Porges’ MXEdit program uses a moving polynomial filter, CMetX uses an optimal finite impulse response digital filter designed using FWTGEN V3.8 from Cook and Miller (1992). The default filter is a 241-point FIR filter with a .12–.40 Hz bandpass, constructed using a Hamming windowing option. It is applied to a time-series representation of the IBI series, at a sample rate of 10 Hz. The transfer function of the filter is shown in Fig. A.2. In the process of convolving a filter over a time series, data points at the beginning and end of the series will not be filtered, and are thus “lost” (see Fig. A.3).

CMetX also includes three other filters that can be selected instead of the default .12–.40 Hz filter, including .15–.40 (alternate for adult, in line with the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), .24–1.04 (for infant), and .3–1.3 (for newborn). Additionally, with version 2.6 and later, CMetX users can specify filter parameters ranging from 0 to 5 Hz, and CMetX will design and apply an optimal finite impulse response 241-point digital bandpass filter using the algorithm specified in Cook and Miller (1992) with a hamming window. Finally, users

---

### Table A.2

<table>
<thead>
<tr>
<th>Metrics output by CMetX, with notes concerning computation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metrics of rate, which are influenced by both parasympathetic (PNS) and sympathetic (SNS) influences</strong></td>
</tr>
<tr>
<td>Mean heart rate (HR), calculated as the average of the rate-transformed IBIs, not as the rate-transformation of the average IBI</td>
</tr>
<tr>
<td><strong>Metrics summarizing total heart rate variability, which are influenced by both SNS and PNS</strong></td>
</tr>
<tr>
<td>Standard deviation of IBI series (SDNN); NN in the acronym SDNN is the abbreviation for “normal-to-normal intervals,” which is the artifact-free IBI series</td>
</tr>
<tr>
<td>Root mean square of successive differences between IBIs (RMSSD)</td>
</tr>
</tbody>
</table>

### Putative sympathetic metric

A cardiac sympathetic index (CSI; Toichi et al. (1997), see Fig. 1) in cardiac chronotropy, the very phenomenon of interest! An IBI series can be converted to a time series by interpolating data points at a fixed sampling rate. CMetX program implements a 10 Hz sampling rate with linear interpolation, as illustrated in Fig. A.1.

A cardiac vagal index (CVI; Toichi et al. (1997), see Fig. 1)"
Fig. A.1. The first 40 IBIs for a sample participant in cardiac time (left) and real time sampled at 10 Hz (right).

Fig. A.2. Transfer function of filters used by CMetX. Larger panel shows the default .12–.40 Hz bandpass filter and the alternate .15–.40 Hz filter for adults, whereas inset shows all four available filters. All filters are 241-point FIR filters.

Fig. A.3. Time-series representation of IBI series for two participants (top panels), and the filtered versions of those series (lower panels), resulting in a loss of 12 s of data at both ends of the series. The variability in the lower panel represents that portion of the total variability within the respiratory frequency band, and that putatively reflects vagal influence.
familiar with filter design can create and import their own coefficients as well.

A.2.2. Computation of metrics, and comparison to Porges’ $V_{Hat}$

All metrics are calculated for only the IBIs that correspond to the sampled timepoints that are retained after the filter is applied to band-limit the signal to calculate RSA. The filter results in a loss of 12 s of data at the beginning and 12 s at the end of the file. All metrics are therefore based on the same subset of the data, but users may wish to include data 12 s prior to and 12 s following the time window of interest to accommodate this data loss.

Many metrics are calculated on the raw IBI values, as they involve the standard deviation, the variance, or a root mean square of the raw IBI values (or difference between successive square of the raw IBI values (or difference between successive). Others, such as RSA – which involves the extraction of specific frequencies of variability – require series in real time.

Correlations were obtained between the metric of RSA from CMetX and from MXEdit V2.21 from Porges with a sample of 96 college students (described in Section 2), at rest and paced arithmetic. Correlations were near unity, as presented in Table A.3. Thus, CMetX produces data that appear highly comparable to those obtained using the Bohrer and Porges method that is part of the more user-intensive MXEdit program. Moreover, CMetX can be called directly from QRSTool, obviating the need for a separate user session to derive the metrics of cardiac chronotropy.

Finally, comparisons of the estimate of RSA from CMetX were compared to spectral power from the FFT of the IBI series for these same 96 subjects. Power spectral density estimates were obtained for the 10 Hz sampled time series representation of the IBI series, averaging successive windows of length 5.12 s, overlapping by 3.84 s, with a 50% Hamming window. Natural log-transformed spectral power and natural log-transformed spectral amplitude were extracted from the .12–.40 Hz range. At rest, RSA from CMetX correlated .986 with spectral power, and .984 with spectral amplitude; during the stressor, correlations were .992 for spectral power, and .997 for spectral amplitude. Thus although the filter used for CMetX has a transition band at the low and high cutoff, the resultant time–domain metric (natural log of band-limited variance) provides a result that would be virtually indistinguishable from that derived in the frequency domain (natural log of .12–.40 Hz spectral power or amplitude).

### References


### Table A.3

<table>
<thead>
<tr>
<th>Metric</th>
<th>Baseline</th>
<th>Arithmetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV</td>
<td>.995</td>
<td>.997</td>
</tr>
<tr>
<td>RSA</td>
<td>.992</td>
<td>.995</td>
</tr>
<tr>
<td>Mean IBI</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Mean HR</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td># IBIs</td>
<td>1.000</td>
<td>1.000</td>
</tr>
</tbody>
</table>


