Effects of variation in posture and respiration on RSA and pre-ejection period

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Abstract

The extent to which variation in posture and respiration can confound pre-ejection period and respiratory sinus arrhythmia (RSA) as indices of cardiac sympatho-vagal activity was examined. Within-subjects changes in these measures were assessed in 36 subjects during different postures and (paced) respiratory frequencies. Changes from supine to sitting to standing led to reduced RSA values and longer pre-ejection periods, reflecting the known decrease in vagal but not the increase of sympathetic activity. Multilevel path analysis showed that within-subjects changes in sympatho-vagal balance were faithfully reflected by changes in interbeat interval, but imperfectly by changes in RSA and pre-ejection period. It was concluded that pre-ejection period should be stratified for posture and RSA for respiratory frequency to reliably index changes in sympatho-vagal balance when these factors are prone to change (e.g., during 24-h ambulatory recording).

Descriptors: Sympatho-vagal balance, Posture, Respiration, Interbeat interval, Pre-ejection period, RSA, CO2

In psychophysiology, respiratory sinus arrhythmia (RSA) and pre-ejection period are frequently used as noninvasive measures of within-subjects changes in vagal and sympathetic (beta-adrenergic) influences on the heart. The validity of these measures derives from a large body of controlled experimental studies using exposure to exercise, infusion of beta-adrenergic agonists, mental stressors, and blockade of cardiac muscarinergic and adrenergic receptors to manipulate cardiac sympathetic and vagal activity (Allen & Crowell, 1989; Cacioppo, Berntson, et al., 1994; Grossman & Kollai, 1993; Krzeminski et al., 2000; Mezzacappa, Kelsey, & Katkin, 1999; Newlin & Levenson, 1979; Pentila et al., 2001; Sherwood, Allen, Obrist, & Langer, 1976; Sherwood, Mefetridge, & Hutcheson, 1998; Smith et al., 1989; Svedenhag, Martinsson, Ekblom, & Hjemdahl, 1986). However, two mechanisms have been identified that may affect the validity of these noninvasive indices of cardiac sympatho-vagal balance outside the controlled laboratory environment. Changes in respiratory frequency influence RSA independent of tonic vagal modulation (Berntson, Cacioppo, & Quigley, 1993; Berntson et al., 1997; Grossman & Kollai, 1993; Houtveen, Rietveld, & de Geus, 2002) whereas posture-related changes in preload (ventricular filling) and afterload (aortic diastolic pressure) may influence pre-ejection period independent of cardiac inotropic drive (Lewis, Rittogers, Forster, & Boudoulas, 1977; Sherwood et al., 1990).

In a typical psychophysiological study, the subject’s posture is fixed, usually sitting upright, whereas changes in respiratory frequency in response to the mental (usually emotional) stimuli are relatively mild, for example, increases of 20% over the spontaneous resting frequency. This is different in ambulatory settings, however, particularly those that include both nighttime and daytime recordings. In such settings repeated postural changes are the rule rather than the exception, and respiratory frequency may be much more variable, for instance, due to physical activity and sleep. This problem has arisen with the advent of high quality instruments to reliably measure pre-ejection period and RSA in ambulatory settings (Cybulski, 2000; de Geus & van Doornen, 1996; Grossman, Wilhelm, & Spoerle, 2004; Keenan, 2004; Sherwood et al., 1998; Willemsen, de Geus, Klaver, van Doornen, & Carroll, 1996). Ambulatory designs that capitalize on these new instruments are prone to confound theoretically relevant psychological effects of real-life activities with changes in posture and respiratory frequency. Typical examples are studies that contrast ambulatory recordings from daytime sitting/standing at (stressful) episodes of work to a resting baseline obtained during nighttime sleep recordings (Riese, van Doornen, Houtman, & de Geus, 2004; Vrijkotte, van Doornen, & de Geus, 2004). To properly interpret the outcome of such studies, it is important to obtain a better understanding of the independent effects of changes in posture and respiratory frequency, and their interaction, on changes in pre-ejection period and RSA.

Although the effect of respiration on RSA has been extensively studied before, parallel respiration effects on pre-ejection period are unknown. Postural effects on pre-ejection period and
RSA have been examined simultaneously in only one study (Ca-
cioppo, Berntson, et al., 1994) but, unfortunately, this careful
study did not include a supine position, which is the most relevant
posture from the perspective of an ambulatory study that in-
cludes sleep recordings. In the current study, we capitalized on an
experimental protocol originally designed to validate impedance
cardiography as a means to measure tidal volume (Houtvene,
Groot, & de Geus, 2005). This design combined postural changes
from supine to sitting to standing with paced breathing at three
different frequencies. This allowed us to examine the main and
interactive effects of changes in posture (including a supine po-
sition) and changes in respiratory frequency (and the related
changes in respiratory depth and the arterial partial pressure of
CO2) on RSA, pre-ejection period, and heart period.

Methods

Participants

The participants of the study were 38 healthy subjects aged
18–50. Due to technical problems, only partial data were avail-
able for 2 participants, resulting in 36 complete data sets, 18 men
(age M = 30.1 years, SD = 10.5) and 18 women (age M = 29.8
years, SD = 8.8). The study was presented as an investigation of
breathing patterns. The participants received 10 euros after the
experiment. All participants gave written informed consent.

Posture and Paced Breathing Conditions

The experiment consisted of 12 different breathing conditions,
each of them of 2 min duration. In three different postures (su-
pine, sitting, and standing), the order of which was randomized,
subjects breathed at four paced frequencies, the order of which
was fixed: (a) spontaneous breathing without pacing, (b) paced
breathing at a rate of 25 cpm without pause, (c) paced breathing
at a rate of 15 cpm combined with 0.4 s. pause, and (d) paced
breathing at a rate of 5 cpms combined with 1 s. pause. A visual
pacing signal was presented on a 15-in. monitor, positioned at 80
cm in front of them, and consisted of a respiratory-like sinusoid
signal with adjustable amplitudes (highest during slow breathing,
lowest during fast breathing).

Physiological Recordings

General. Because capnometry was performed after 30 and
90 s of each 2-min breathing condition, the intermediate segment
(60 s) was retained as artifact-free heart period and respiratory
data period. The mean interbeat interval, RSA, pre-ejection pe-
riod, and respiratory frequency and amplitude (depth) values
were pooled over these 60-s segments for each breathing condi-
tion. End-tidal CO2 (PetCO2) values were pooled over the two
observations for each condition.

Interbeat interval, RSA, and pre-ejection period. The electro-
cardiogram (ECG) and the impedance cardiogram (ICG) were
recorded continuously with the Vrije Universiteit Ambulatory
Monitoring System (VU-AMS version 4.3; de Geus, Willemsen,
Klaver, & van Doornen, 1995; Willemsen et al., 1996). This
system uses six disposable, pregelled Ag/AgCl electrodes. The
first ECG/ICG electrode was placed on the sternum over the first
rib between the two collarbones. The second ECG electrode was
placed at the apex of the heart over the ninth rib on the left lateral
margin of the chest approximately 3 cm under the left nipple. The
second ICG measuring electrode was placed over the tip of the
xiphoid complex of the sternum. The ICG current electrodes
were placed on the back over cervical vertebra C4 and between
thorax vertebrae T8 and T9. A ground electrode was placed at
the lower right abdomen. Electrode resistance was kept low by
cleaning the skin with alcohol and rubbing.

The interbeat intervals were obtained from the ECG by an on-
line automated R-wave peak detector. RSA was estimated by
two methods. First, uniformly spaced samples were created and
discrete Fourier transformed to compute the high frequency
heart period variability spectral power values (high frequency
power: 0.125–0.5 Hz). This method does not capture respiratory
sinus arrhythmia below the lowest frequency in this band (i.e.,
0.125 Hz), whereas our 5 cpm pacing condition causes fluctua-
tions in heart rate at a frequency below this range (0.0833 Hz).
Therefore, RSA was also estimated by the peak-to-valley method
(RSApv) as the mean difference between the shortest heart pe-
riod associated with inspiration and the longest heart period as-
associated with expiration for each respiratory cycle (Berntson
et al., 1997; Grossman, van Beek, & Wientjes, 1990).

The impedance signal measured by the ICG was amplified
and led to a precision rectifier. The rectified signal was filtered at
72 Hz (low pass) to give thorax impedance Z0. Filtering Z0 at 0.1
Hz (high pass) supplies dZ, which in turn was filtered at 30.0 Hz
(high pass) to obtain dZ/dt, the high frequent impedance changes
due to the ejection of blood into the aorta during systole. The
resulting dZ/dt were transmitted to the A/D converter of the
microprocessor and sampled at 250 Hz. The usual approach to
dZ/dt data reduction—ensemble averaging—was implemented in
the VU-AMS device at the hardware level. Ensemble averag-
ing involves digitizing the dZ/dt only during a short period
(512 ms) around each R-wave in a block of 30 s duration. These
digitized samples were summed and divided by the number of
synchronized beats in the block. This procedure reduced the im-
portance of single beat fluctuations in the impedance signal through
respiration and slow thorax movement. The pre-ejection period
(in milliseconds) was defined as the interval from the R-wave
peak, minus a fixed interval of 48 ms (Willemsen et al., 1996;
Sherwood et al., 1990) to the upstroke of the dZ/dt (“B-point”),
which signals opening of the aortic valves.

Respiration. Changes in thoracic and abdominal circumfer-
ence (used to assess respiratory frequency, respiratory depth, and
RSApv) were measured with two BioPac TSD201 respiratory
effort transducers (see http://www.biopac.com). The two respi-
atory belts were attached over (a) the rib cage at the level of the
fifth thoracic vertebrae, and (b) the abdomen at the level of the
navel. The transducers have a variable resistance output between
50 and 125 KΩ. These signals were low-pass filtered (1 Hz),
sampled at 25 Hz, and registered by a BIOPAC MP150 system
connected to a data-acquisition computer running the acknowl-
dedge v3.7.3 software package. Both respiration signals (thoracic
and abdominal) were band-pass filtered using a FIR filter 0.05–
0.5 Hz (3–30 cpm). Next, interactive scoring of the peaks and
throughs in these segments yielded the respiratory frequency,
amplitude, and RSV values on a breath-to-breath basis.

Capnometry. The TG-951T CO2 sensor Kit (Nihon Kohden
Corp.) was used to measure the partial pressure of CO2 at the end of
a normal expiration (PetCO2). Digitized PetCO2 values (in milli-
meters of mercury) from the capnometer sensor kit were sent to the
data-acquisition computer through an RS-232 interface cable.
Effects of posture and respiration on RSA and pre-ejection period

Procedure

All experimental sessions took place between 10 a.m. and 4 p.m. and lasted approximately 45 min. First, the six ECG/ICG recording electrodes and the two respiratory belts were attached. Subjects then received a general explanation of the experimental protocol and were seated in a sound-shielded and dimly lit cabin. A practice session took place to familiarize the participants with the pacing. Next, the three 8-min (i.e., four times 2 min: normal breathing, 25 cpm, 15 cpm, and 5 cpm) breathing sessions took place in supine, sitting, and standing postures. During each 2-min breathing condition subjects exhaled through the capnometer mouthpiece after 30 and 90 s. Each breathing session was followed by a short break. Throughout, signal quality of the ECG/ICG and respiratory belts were checked, and, if necessary, the electrodes/belts were reattached during these breaks. At the end of the three breathing sessions, all equipment was disconnected and participants were debriefed and paid.

Statistical Data Analysis

High frequency power, RSApv, and respiratory amplitude values were log10(x + 1) transformed to obtain normal distributions. Repeated-measures Posture (3) x Pacing (4) ANOVA tests (implemented as MANOVA using SPSS 12) were performed for the observed interbeat interval, pre-ejection period, high frequency power, RSApv, PetCO2, respiratory frequency, and respiratory amplitude values.

Next, change scores were computed for each measure and subject across the nine paced breathing conditions by subtracting the value of the sitting, 15-cpm breathing condition. These change scores were Z-transformed across subjects and conditions. A multilevel path-analysis (using Mplus V3.0) was performed for the observed interbeat interval, pre-ejection period, high frequency power, RSApv, PetCO2, respiratory frequency, and respiratory amplitude values.

Results

Repeated-Measures Analysis of Variance Tests

Table 1 shows the mean scores for all the experimental conditions. In analyses of interbeat interval, a main effect of posture was found, F(2,34) = 66.18, p < .001. Within-subjects contrast tests indicated significant differences between all three posture conditions, all p < .001. Changes from supine to sitting to standing postures led to a linear shortening of interbeat interval, p < .001. Changes in pacing were also reflected in interbeat interval, F(3,33) = 19.40, p < .001, but this effect interacted with posture (Posture x Pacing: F[6,30] = 12.80, p < .001). Post hoc decomposition of this interaction showed that the interbeat interval was increased in the 5 cpm condition during sitting and standing, but not during the supine position, p < .01.

In analyses of pre-ejection period, a main effect of posture was found, F(2,34) = 40.89, p < .001. Within-subjects contrast tests indicated significant differences between all three posture conditions, all p < .001. Changes from supine to sitting to standing postures led to a linear effect in the lengthening of pre-ejection period, p < .001. No main effect of pacing and no interaction effect of Posture x Pacing were found for pre-ejection period.

Main effects of posture were found for high frequency power and for RSApv, F(2,34) = 25.66, p < .001; F(2,34) = 37.78, p < .001. For both measures, within-subjects contrast tests indicated significant differences between all three posture conditions, all p < .01. Changes from supine to sitting to standing postures led to a linear decrease of high frequency power and RSApv, p < .01. Main effects of pacing were also found for high frequency power, F(3,33) = 38.11, p < .001, and for RSApv, F(3,33) = 397.41, p < .001. For both measures, within-subjects contrast tests indicated significant differences between all pacing conditions, all p < .001. A decrease in pacing frequency led to a linear increase of RSA, p < .001. Interaction effects of Posture x Pacing were also found for high frequency power, F(6,30) = 6.00, p < .001, and for RSApv, F(6,30) = 8.77, p < .001. For high frequency power, a ceiling effect was found at 5-cpm breathing in the supine position. In the 15- and 25-cpm breathing conditions a significant difference, p < .001, was found between sitting and supine postures.

Table 1. Means (SD) of the Physiological Values

<table>
<thead>
<tr>
<th></th>
<th>IBI</th>
<th>PEP</th>
<th>HF power</th>
<th>RSApv</th>
<th>PetCO2</th>
<th>R amplitude</th>
<th>R frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Supine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pacing</td>
<td>0.990 (0.18)</td>
<td>94.9 (15)</td>
<td>3.14 (0.67)</td>
<td>1.87 (0.30)</td>
<td>34.16 (4.6)</td>
<td>0.454 (0.22)</td>
<td>14.47 (4.3)</td>
</tr>
<tr>
<td>25 cpm</td>
<td>0.966 (0.16)</td>
<td>93.8 (16)</td>
<td>2.89 (0.62)</td>
<td>1.61 (0.29)</td>
<td>32.11 (3.9)</td>
<td>0.380 (0.20)</td>
<td>24.57 (0.28)</td>
</tr>
<tr>
<td>15 cpm</td>
<td>0.954 (0.15)</td>
<td>93.9 (16)</td>
<td>3.04 (0.61)</td>
<td>1.81 (0.29)</td>
<td>33.31 (5.3)</td>
<td>0.467 (0.24)</td>
<td>15.09 (0.53)</td>
</tr>
<tr>
<td>5 cpm</td>
<td>0.948 (0.14)</td>
<td>94.3 (15)</td>
<td>3.09 (0.52)</td>
<td>2.27 (0.27)</td>
<td>36.69 (5.4)</td>
<td>0.648 (0.26)</td>
<td>5.23 (0.31)</td>
</tr>
<tr>
<td><strong>Sitting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pacing</td>
<td>0.902 (0.13)</td>
<td>102.9 (21)</td>
<td>2.89 (0.64)</td>
<td>1.79 (0.33)</td>
<td>34.39 (4.0)</td>
<td>0.409 (0.21)</td>
<td>14.73 (3.5)</td>
</tr>
<tr>
<td>25 cpm</td>
<td>0.880 (0.12)</td>
<td>103.2 (19)</td>
<td>2.64 (0.58)</td>
<td>1.56 (0.25)</td>
<td>30.52 (4.5)</td>
<td>0.346 (0.16)</td>
<td>24.60 (0.25)</td>
</tr>
<tr>
<td>15 cpm</td>
<td>0.865 (0.12)</td>
<td>103.2 (19)</td>
<td>2.84 (0.54)</td>
<td>1.72 (0.29)</td>
<td>31.05 (5.3)</td>
<td>0.419 (0.18)</td>
<td>15.01 (0.18)</td>
</tr>
<tr>
<td>5 cpm</td>
<td>0.886 (0.12)</td>
<td>103.1 (19)</td>
<td>3.09 (0.49)</td>
<td>2.37 (0.29)</td>
<td>34.72 (6.4)</td>
<td>0.630 (0.22)</td>
<td>5.15 (0.40)</td>
</tr>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pacing</td>
<td>0.798 (0.12)</td>
<td>107.9 (21)</td>
<td>2.56 (0.52)</td>
<td>1.63 (0.29)</td>
<td>33.23 (4.8)</td>
<td>0.476 (0.23)</td>
<td>14.42 (3.5)</td>
</tr>
<tr>
<td>25 cpm</td>
<td>0.769 (0.11)</td>
<td>108.9 (21)</td>
<td>2.32 (0.51)</td>
<td>1.32 (0.19)</td>
<td>29.66 (4.6)</td>
<td>0.401 (0.18)</td>
<td>24.56 (0.22)</td>
</tr>
<tr>
<td>15 cpm</td>
<td>0.750 (0.11)</td>
<td>109.9 (20)</td>
<td>2.55 (0.47)</td>
<td>1.53 (0.25)</td>
<td>29.37 (4.8)</td>
<td>0.469 (0.22)</td>
<td>15.14 (0.36)</td>
</tr>
<tr>
<td>5 cpm</td>
<td>0.802 (0.10)</td>
<td>109.5 (20)</td>
<td>3.00 (0.41)</td>
<td>2.26 (0.24)</td>
<td>33.56 (5.5)</td>
<td>0.727 (0.29)</td>
<td>5.49 (0.76)</td>
</tr>
</tbody>
</table>

IBI: interbeat interval (s); PEP: pre-ejection period (ms); HF power: high frequency heart period variability power; RSApv: RSA estimated by the peak-to-valley method; HF power and RSApv are in log10(x + 1) transformed units of ms2 and ms; PetCO2 values are in units of mmHg; respiratory amplitude values are in log10(x + 1) transformed (arbitrary) voltage units; respiratory frequency values are in units of cpm.
but this difference was no longer significant at 5-cpm breathing. For RSApv no ceiling effect was found at 5 cpm, but the difference between RSApv in the 15- and 5-cpm paced breathing conditions was significantly reduced in the supine position as compared to the standing and sitting positions, \( p < .05 \).

Changes in pacing were also reflected in PetCO2. \( F(3,33) = 38.09, p < .001 \). The PetCO2 values were decreased for the 25- and 15-cpm pacing frequencies as compared to no pacing condition, \( p < .001 \). No interaction effect of Posture \( \times \) Pacing was found for PetCO2. An unexpected main effect of posture was, however, found for PetCO2: \( F(2,34) = 14.86, p < .001 \). Within-subjects contrast tests indicated significant differences between all three posture conditions, all \( p < .01 \). Changes from supine to sitting to standing postures led to a linear reduction of PetCO2, \( p < .01 \).

The expected main effects of pacing were found on respiratory amplitude, \( F(3,33) = 67.03, p < .001 \), and respiratory frequency, \( F(3,33) = 25760.36, p < .001 \). For both measures, within-subjects contrast tests indicated significant differences between all three pacing frequencies, all \( p < .001 \). The no pacing condition, however, did not significantly differ from the 15-cpm condition. This simply reflects the closeness of this pacing frequency to the average spontaneous breathing frequency of this group (\( M = 14.87, \text{SEM} = 0.15 \) cpm). No main effect of posture and no interaction effect of Posture \( \times \) Pacing were found for either respiratory amplitude or frequency.

**Exploratory Multilevel Path Analysis**

More insight into the relationships between these physiological measures can be obtained from the results of the exploratory multilevel (between- and within-subjects) path analysis. The final selected model resulted in an acceptable goodness of fit, \( \chi^2(12) = 12.27, p = .42 \). In this model, no significant variance was accounted for at the between-subjects level. The within-subjects model explained 60% of the variance in interbeat interval change, 67% of the variance in RSApv change, 51% of the variance in pre-ejection period change, 35% of the variance in respiratory amplitude change, and 31% of the variance in PetCO2 change. Figure 1 shows the corresponding significant standardized beta values.

Although most beta values replicate the effects of posture and pacing found in the repeated-measures analysis of variance tests (see above), four remarkable additional results were found. First, no significant path (beta = −.12) was found from changes in pre-ejection period to changes in interbeat interval and an unexpected low beta value (.14) was found in the link between changes in RSApv and interbeat interval. This illustrates how, under the conditions of the current study, changes in pre-ejection period and RSA fail to reflect changed cardiac sympathetic and parasympathetic activity. Second, PetCO2 was not only influenced by changes in respiratory frequency but also by postural change. Third, pacing-induced changes in respiratory amplitude (beta = −.03) and PetCO2 (beta = .04) did not have significant paths to RSApv. Finally, although the pacing manipulation did not influence pre-ejection period overall, pacing-induced changes in respiratory amplitude and PetCO2 did have significant effects on pre-ejection period: An increase in PetCO2 decreased pre-ejection period and an increase in respiratory amplitude increased pre-ejection period.

**Discussion**

The purpose of the current study was to estimate the influence of systematically manipulated changes in posture and respiratory frequency on within-subjects changes in two frequently used noninvasive measures of cardiac sympathetic and vagal activity, the pre-ejection period and RSA, respectively. Changes from supine to sitting to standing postures led to a shortening of interbeat interval and a decrease in RSA, reflecting the expected decrease in cardiac vagal activity that has been well documented in studies using either passive head-up tilting or active standing (Cooke et al., 1999; Furlan et al., 2000; Matsushima, Tanaka, & Tamai, 2004; Mukai & Hayano, 1995; Siebert, Drabik, Lango, & Szyndler, 2004).

The same postural manipulation led to a stepwise increase in pre-ejection period, which would suggest a decrease in beta-adrenergic influence on the heart from supine to standing. This is, however, incompatible with the known effects of these changes in posture. Head-up tilting is well known to be accompanied by an increase in muscle sympathetic nerve activity (Cooke et al., 1999; Furlan et al., 2000; Saito et al., 1997; Shoemaker, Hugeman, Khan, Kimmerly, & Sinoway, 2001), noradrenergic spillover (Ermis et al., 2004; Esler et al., 1988; Furlan et al., 2000; Laszlo, Rossler, & Hinghofer-Szalkay, 2001), and cardiac contractility (Vijayalakshmi, Mohan, & Babu, 2002). Physiologically, this increase in sympathetic activity makes good sense. Assumption of the upright posture leads to a gravity-induced displacement of blood to the lower body and a small reduction in total plasma volume (Chae & Suh, 1993; Frey, Tomaselli, & Hoffer, 1994; Laszlo et al., 2001; Toska & Walloe, 2002). This reduces enddiastolic left ventricular filling, which, according to the Frank-Starling principle, in turn, reduces the contractility of the left

Figure 1. Standardized within-subjects path diagram. Only significant path coefficients (estimate/SE estimate > 1.96) are shown. The dark gray boxes signal the experimental manipulations; the direction of causation is fixed for arrows flowing from these boxes. Other arrows reflect correlations and causality could, in principle, have been bidirectional. The linear change in interbeat interval, respiratory amplitude, and PetCO2 with our manipulations, however, suggests that the direction of the arrows is as in our model. The interaction of Posture \( \times \) Respiratory frequency is created by multiplication of both variables and added to the model as an additional variable ("x" in circle).
myocard. Indeed, end-diastolic and stroke volume are found to be reduced in the upright position (Boudoulas, Barrington, Olson, Bashore, & Wooley, 1985; Chae & Suh, 1993; Frey et al., 1994; Shannon, Maher, Santinga, Royal, & Wei, 1991; Sherwood & Turner, 1993; Shoemaker et al., 2001; Toska & Walloe, 2002; Waldstein, Neumann, & Merrill, 1998). The decrease in stroke volume is compensated by an increase in heart rate that is secondary to vagal withdrawal and increased cardiac sympathetic activity. Normally, therefore, we should expect the pre-ejection period to shorten in passive tilting, and this decrease should even be enhanced in active standing when afferent muscle feedback serves to further increase sympathetic activity.

The paradoxical increase in pre-ejection period when going from sitting to standing has been demonstrated before (Boudoulas et al., 1985; Cacioppo, Uchino, & Berntson, 1994; Cacioppo, Berntson, et al., 1994; Sherwood & Turner, 1993; Waldstein et al., 1998), and head-up tilting from supine to upright is also known to systematically increase pre-ejection period (Frey & Kenney, 1979; Lewis et al., 1977; Ovadia, Gear, Thoele, & Marcus, 1995). Importantly, the increase in pre-ejection period during head-up tilting is not abolished by beta blockade (Ovadia et al., 1995). The failure of the pre-ejection period to correctly index changes in sympathetic activity across postural change is likely due to the large afterload effects induced by postural changes. Afterload, or end-diastolic aortic pressure, is reflected in mean arterial pressure, which is known to increase when going from supine to upright (Chae & Suh, 1993; Cooke et al., 1999; Frey et al., 1994; Laszlo et al., 2001; Shannon et al., 1991; Sherwood & Turner, 1993; Shoemaker et al., 2001; Toska & Walloe, 2002; Waldstein et al., 1998). Higher afterload will elongate pre-ejection period by prolonging the time needed to open the aortic valve, even if contractility is unchanged. The low (or even reversed) pre-ejection period reactivity found during cold stress is another instance of the impact of afterload on pre-ejection period, where changes in pre-ejection period fail to detect the strong increase in sympathetic nerve activity (van Doornen, Snieder, & Boomsma, 1998; van Eekelen, Houtveen, & Kerkhof, 2004; Frey & Kenney, 1979; Montoya, Brody, Beck, Veit, & Rau, 1997). In contrast to the strong posture effect, changing the respiratory frequency had virtually no effect on the pre-ejection period. However, pacing-induced decreases in respiratory depth and increases in PetCO₂ both mildly decreased pre-ejection period.

A relationship between within-subjects changes in RSA and changes in respiratory frequency has repeatedly been described and/or demonstrated before (Berntson et al., 1997; Eckberg, 2003; Grossman et al., 2004; Houtveen et al., 2002; Sasano et al., 2002). Our results suggest that the modulation of respiration on the association between RSA and cardiac vagal activity may be posture specific. However, sympathetic influences could have contaminated our RSApv measure, specifically in the 5-cpm breathing conditions and, therefore, could also have been responsible for this interaction effect. At 5 cpm, the typical low frequency sympathetic versus high frequency vagal filter characteristics do not differentiate vagal and sympathetic contributions anymore (see Berntson et al., 1993). Thus, reduced sympathetic activation in the supine position could very well have been responsible for the relatively reduced RSApv values found in the 5-cpm supine condition as compared to the 15-cpm supine condition. Pacing-induced effects of respiratory depth and the arterial partial pressure of CO₂ on RSA have not been demonstrated in the current study. However, our design did not allow us to discriminate between the primary effects of respiratory rate, depth, and CO₂ on RSA. These effects may emerge in a (full factorial) experimental design with independent and larger respiratory depth and CO₂ variation.

Under normal—posture controlled—experimental conditions, within-subjects changes in RSA and pre-ejection period can be used as indices of the vagal and sympathetic beta-adrenergic control of the heart period (e.g., see Cacioppo, Berntson, et al., 1994; de Geus & van Doornen, 1996). The results of the current study, however, demonstrate that changes in posture and respiratory frequency (and the related changes in depth and PetCO₂) exert large effects on these noninvasive sympatho-vagal measures, such that within-subjects changes in heart period can become almost unrelated to changes in RSA and pre-ejection period. The question arises, therefore, whether pre-ejection period and RSA can be used to index changes in cardiac sympathetic and parasympathetic activity under circumstances when no experimental control over posture or respiration is possible, for example, during ambulatory monitoring. We are optimistic that this is still feasible as long as the study design fully appreciates the inherent limitations of these measures demonstrated here. The modulation of the relationship between vagal activity and RSA by respiratory frequency can be explicitly charted in field studies by recording both RSA and respiratory frequency as has been proposed before (Grossman et al., 2004). As long as postural changes are carefully documented, for instance, by inbuilt movement and posture detectors, it is further possible to compare different activities/moods across instances of these activities performed in the same posture.

At first sight, this seems to limit the research questions that can be addressed. Some of the more interesting within-subjects comparisons come with an inherent change in posture, for instance, when daytime work levels of pre-ejection period_RSA are compared to the sleeping baseline value of these measures. Careful interpretation of the results, however, may overcome the potential shortcomings of pre-ejection period and RSA in such naturalistic designs. As an example we point to a recent ambulatory monitoring study that reported increased pre-ejection period values during sleep (+6.4 ms) as compared to daytime sitting (Vrijkotte et al., 2004). In the present study, we demonstrated that the change from sitting to supine posture by itself leads to a decrease in pre-ejection period (–8 ms). Apparently, the decrease in activity of the beta-adrenergic influence on the heart during sleep is strong enough to overcome the opposing afterload effects on pre-ejection period. The conclusions of Vrijkotte et al. (2004) that there is a significant recovery of cardiac sympathetic activity at night, therefore, seems entirely valid, and is supported by studies showing an increase in pre-ejection period from a presleep supine baseline (Burgess, Penve, Schneider, & van Cauter, 2004; Trinder et al., 2001). However, their finding that subjects with the highest work stress showed the least awake/sleep differences in pre-ejection period should be interpreted with more care. As the authors suggested, this effect may reflect a true work stress effect on wake–sleep changes in cardiac sympathetic effects on the heart, driven by beta-receptor down-regulation. Alternatively, however, it may reflect a work stress effect on posture or sleep-induced changes in afterload (blood pressure “dipping”) that may be entirely unrelated to cardiac sympathetic regulation.

In general, the results of the current study confirm the necessity of stratifying for posture and respiration when using pre-ejection period and RSA to index within-subjects changes in sympatho-vagal balance. Valid interpretation of changes in
pre-ejection period and RSA is entirely feasible in studies that, by necessity, confound measurement conditions with changes in posture and respiration, for instance, when ambulatory recordings from daytime sitting/standing at work are compared with nighttime supine sleep. These studies do, however, require a design that takes the significant postural and respiration effects on these variables into account. This can be done by careful recording of daily activities through diaries in combination with a movement detector and coregistration of respiratory behavior and ECG.

REFERENCES


