Impact of changes in respiratory frequency and posture on power spectral analysis of heart rate and systolic blood pressure variability in normal subjects and patients with heart failure

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1. Autonomic dysfunction is a major feature of congestive cardiac failure and may have an important role in determining progression and prognosis. The low-frequency/high-frequency ratio derived from power spectral analysis of heart rate variability has been proposed as a non-invasive method to assess sympatho-vagal balance. However, the effects of different respiratory rates or posture are rarely accounted for, but may be relevant in patients with heart failure in whom clinical improvement is accompanied by a fall in respiratory rate and an increased proportion of the day in the upright position.

2. We have assessed the effect of controlled respiration at different rates (10, 15, 20 breaths/min or 0.17, 0.25 and 0.33 Hz), while supine and standing, on power spectral analysis of heart rate and blood pressure variability in 11 patients with heart failure and 10 normal subjects.

3. Heart rate variance and low-frequency power (normalized units) were reduced in patients with heart failure (absent in six). During controlled breathing while supine, the power of the high-frequency component was significantly greater at 10 breaths/min than at 20 breaths/min in patients with heart failure, whether expressed in absolute units (P=0.005) or percentage of total power (P=0.03).

4. On standing, controlled breathing in patients with heart failure produced less change in high-frequency power (P=0.054), but the low-frequency/high-frequency ratio at lower respiratory rates was reduced (P=0.05). In normal subjects, as expected, respiratory rate had a highly significant effect on high-frequency power. Also, in normal subjects there was the expected increase in heart rate low-frequency power (P=0.04) moving from supine to standing with an increase in the low-frequency/high-frequency ratio (P=0.003), while in the patients with heart failure this was absent, reflecting blunted cardiovascular reflexes.

5. Systolic blood pressure low- and high-frequency components and their ratio were significantly affected by respiration (P<0.03) and change in posture (P<0.03) in both patients with heart failure and normal subjects, with a significant increase in the low-frequency/high-frequency ratio (P=0.03) on standing in patients with heart failure, indicating that autonomic modulation of blood pressure is still operating in heart failure.

6. Thus, respiratory rate and changes in posture have a significant effect on measurements derived from spectral analysis of heart rate and blood pressure variability. Studies that use power spectral analysis as a measure of sympatho-vagal balance should control for these variables.

INTRODUCTION

Autonomic dysfunction is an important feature of congestive cardiac failure, and Eckberg et al. [1] were the first to show that there was defective cardiac parasympathetic control in patients with heart failure. Increased sympathetic activity has also been well documented by increased plasma noradrenaline levels [2], cardiac noradrenaline overflow [3] and muscle sympathetic nerve activity [4]. In addition, baroreceptor gain is impaired in heart failure [5]. Furthermore, it seems clear that this supranormal sympathetic and subnormal parasympathetic activity is involved in the progression of heart failure and is related to prognosis via the genesis of arrhythmias and sudden death [2, 6]. A reliable, non-invasive, non-pharmacological clinical test of cardiac autonomic activity would therefore have considerable application for establishing the diagnosis, predicting prognosis and managing patients with congestive heart failure (CHF). Heart rate variability analysis in the time and frequency domain by power spectral analysis has been suggested to be a

Key words: autonomic nervous system, heart failure, heart rate variability, spectral power.
Abbreviations: CHF, congestive heart failure; HF, high-frequency; LF, low-frequency; nu, normalized units; SBP, systolic blood pressure; VLF, very-low-frequency.
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valid method of assessing sympatho-vagal balance, measured as the ratio of the power of the low-frequency (LF) and the high-frequency (HF) components [7, 8]. Saul et al. [9] found in patients with congestive heart failure that heart rate spectral power was reduced at all frequencies, especially LF, and others have confirmed that LF spectral power is paradoxically reduced or absent in severe heart failure [10]. More recently, studies have used this technique for assessing the effects of drugs and other treatments in heart failure [11-14]. However, in normal subjects it is apparent that the LF and HF components are dependent on factors additional to sympathetic and parasympathetic activity, such as baroreceptor function and respiration [15-18]. Despite this, there is no published study to date of the effect of different breathing rates in the physiological range (10–20 breaths/min, 0.17–0.33 Hz) on power spectral analysis of heart rate and systolic blood pressure (SBP) variability in patients with heart failure, to determine if changes in respiratory rate have an important impact on measurement of the LF and HF components in this group of patients. Many studies in this area use ambulatory ECG recordings (Holter) and little attention is paid to the effects of respiration or posture. These may be important, especially in patients with heart failure, as symptomatic improvement is accompanied by a fall in respiratory rate and an increased proportion of the day spent in the upright position. Therefore, in this study, we have assessed the effects of different paced breathing rates and of posture on the commonly used measurements (LF, HF power and LF/HF ratio) derived from spectral analysis of heart rate and blood pressure variability in patients with CHF and normal subjects.

METHODS

Subjects

Eleven patients with clinically obvious but compensated CHF (NYHA functional class II–IV, mean (±SD) age 57±13 years, nine males), with a mean (±SD) ejection fraction of 35±8% measured by two-dimensional echocardiography or MUGA scans, and nine normal subjects (mean age 45±2 years, six males) without any evidence of cardiovascular disease (including hypertension, heart failure or diabetes) and not taking any medication were studied. All of the patients with heart failure were taking diuretics, frusemide and an angiotensin-converting enzyme inhibitor. Only one patient was unable to stay supine during the whole recording period because of orthopnoea and he was propped up a few degrees before the recordings were taken.

Recording technique and protocol

The subjects were studied in a quiet, soundproof room initially in the supine position and then after standing for 5 min. ECG, finger blood pressure (via photoplethysmographic transducer; Ohmeda Finapres) and respiration rate (via impedance pneumograph, which also gave semi-quantitative tidal volume estimates) were recorded onto a computer continuously throughout the study period. Recordings were taken in 5–7 min periods during spontaneous respiration and controlled breathing at rates of 10, 15 and 20 breaths/min (0.17 Hz, 0.25 Hz and 0.33 Hz respectively) while supine and standing. Controlled respiration was achieved by asking the subjects to inhale and exhale in synchrony with a recorded message from a cassette tape recorder. The cassette was replayed for each recording session. The tapes were prerecorded to maintain a breathing rate at 10, 15 or 20 breaths/min. Subjects practiced following the tape recorder before data were recorded for analysis. Depth of breathing or tidal volume was not controlled and subjects were allowed to breathe comfortably to avoid hyper- or hyperventilation.

Signal acquisition

As described previously [19], the data were digitized off-line by a 12-bit analogue-to-digital converter at a sampling rate of 500 samples/s. The converter was connected to a Macintosh II computer. A 'C' language program identified all the QRS complexes in each sequence and then located the peak of each R wave. From these data the R–R intervals were obtained. For each step of the protocol at least 256 R–R intervals were analysed. The non-oscillatory (DC) component and slow trends were removed from each sequence by subtraction of that same sequence after 124 long-windows moving procedure, following an algorithm described previously [20]. The respiratory signal obtained from the impedance pneumograph was expressed in arbitrary values (mV output from the device); only the signal occurring at the peak of the R wave was measured. Systolic and diastolic blood pressures were similarly identified. Premature beats were interactively identified and corrected by linear interpolation between the previous and following beats. All data were stored on computer diskettes for further analysis.

Power spectral analysis

Power spectral analysis was applied to respiratory, R–R interval and SBP signals, using an autoregressive model as described previously [19–21]. Spectral components were obtained by a decomposition method [21, 22]. The area below each spectral peak, mean variance and total power in the LF (0.03–0.149 Hz) and HF component (0.15–0.4 Hz) were measured (Figs. 1 and 2). The respiratory component of the HF band could be readily identified by comparison with the respiratory power spectrum. In this way it was possible to be certain
that the HF component at lower breathing rates did not encroach into the preset LF band. In addition, in some recordings a component below 0.03 Hz [very-low-frequency (VLF)] was apparent which contributed significantly to total power. The VLF, LF and HF components are presented in absolute units (ms²) and LF and HF as a percentage of total power (% total), and as normalized units (nu) after subtraction of VLF as described previously [8, 23].

Statistical analysis

Unless otherwise indicated, data are expressed as mean±SEM. Since Gaussian distribution was not certain, non-parametric tests (Wilcoxon signed-rank test for paired data, Mann–Whitney U-test for non-paired data and Friedman non-parametric repeated measures test) were used to evaluate statistical significance of effects of different breathing rates and posture within and between groups. A value of P<0.05 was considered significant.

This study was approved by the Ethical Committee at the Faculty of Medicine of the Chinese University of Hong Kong.

RESULTS (Tables 1 and 2; Figs. 3 and 4)

Spontaneous respiration, supine

The mean respiratory frequency during spontaneous respiration while supine was 0.25±0.02 Hz in normal subjects and 0.27±0.02 Hz in patients with CHF. The LF component of R–R spectra expressed either as % total or as nu was low in the CHF group, and six of these patients had an undetectable LF component. A similar pattern was noted for SBP variability, with a reduced LF component, a relatively stable HF component and a reduced LF/HF ratio compared with normal values (P=0.03).

Spontaneous respiration, standing

On standing, the mean spontaneous respiratory frequency was 0.28±0.03 Hz in normal subjects and
0.29 ± 0.02 Hz in patients with CHF. In normal subjects, R–R variance decreased on standing compared with supine values, and this was associated with a significant increase in LF component ($P=0.04$), a fall in HF component and a significant increase in LF/HF ratio ($P=0.003$). No significant change was seen in the heart failure group for R–R LF and HF components, and R–R LF/HF ratio was unchanged compared with supine values. Thus the different effect of standing on the LF/HF ratio in normal subjects and patients with CHF was also highly significant ($P=0.003$). In the SBP spectra with spontaneous respiration, the heart failure group upon standing showed a non-significant increase in the LF component, a fall in the HF component but a significant increase in the LF/HF ratio ($P=0.03$). In normal subjects the LF component of SBP variability increased significantly on standing ($37±12$ to $60±13$ (% total); $P=0.03$), as did the LF/HF ratio ($P=0.03$). Thus, in patients with CHF, posture was associated with no change in LF, HF or LF/HF ratio in the R–R spectra, while in the SBP spectra, LF/HF did increase. Therefore, the response of heart rate and blood pressure variability to changes in posture differ, and it appears that, unlike heart rate, SBP can still be modulated by autonomic tone.

**Controlled breathing, supine**

For patients with CHF, slowing breathing rates in the R–R spectra from 20 to 10 breaths/min (0.33 Hz to 0.17 Hz) produced a significant increase in HF, whether expressed in absolute units ($P=0.005$) or as % total ($P=0.03$). HF (nu) of R–R variability showed a similar pattern, although the changes were not quite significant ($P=0.06$). R–R variance was similar at breathing rates of 20 and 15 breaths/min but increased significantly at a breathing rate of 10 breaths/min ($P=0.04$ compared with 20 breaths/min). A similar pattern was seen with HF and LF components: differences between respiratory rates of 15 and 20 breaths/min were small, with the major change occurring at a breathing...
Table 1. Heart rate (R-R) variability. Data are expressed as mean±SEM. nu, normalized units (minus VLF power). Symbols refer to statistical significance of (i) changes between supine and standing: *P<0.05, **P<0.005, and (ii) changes with different respiratory rates: $^aP<0.05$, $^bP<0.04$, $^cP<0.02$, $^dP<0.01$, $^eP<0.005$.

<table>
<thead>
<tr>
<th></th>
<th>R-R mean (ms)</th>
<th>R-R variance (ms²)</th>
<th>VLF (ms²)</th>
<th>LF (ms²)</th>
<th>HF (ms²)</th>
<th>LF (nu)</th>
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<td>74.0±7.7</td>
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<td>15 breaths/min</td>
<td>788±45.0</td>
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<td>214.2±108.4</td>
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<td>15.0±7.1</td>
<td>66.1±6.4</td>
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<td>10 breaths/min</td>
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<td>455±147</td>
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<td>20 breaths/min</td>
<td>725±33.2</td>
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Table 2. SBP variability. Data are expressed as mean±SEM. nu, normalized units (minus VLF power). Symbols refer to statistical significance of (i) changes between supine and standing: $^aP<0.03$, and (ii) changes with different respiratory rates: $^aP<0.01$, $^bP<0.03$.

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<th>SBP mean (mmHg)</th>
<th>SBP variance (mmHg²)</th>
<th>VLF (ms²)</th>
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<tr>
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<td>121±7.1</td>
<td>33.9±9.0</td>
<td>7.3±4.9</td>
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<td>53.3±9.2</td>
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<td>2.1±1</td>
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<td>19.4±6.5</td>
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<td>20 breaths/min</td>
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<td>26.1±5.7</td>
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<td>2.1±1</td>
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<td>Standing</td>
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<td>12.1±4.5</td>
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<tr>
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<td>10±5.5</td>
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Table 3. Normal subjects

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<td>2.0±1</td>
<td>46.3±13.0</td>
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<td>2.5±0.5</td>
<td>3.8±0.9</td>
<td>37.2±8.3</td>
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rate of 10 breaths/min. In the SBP spectra, LF power fell (not significantly) but HF power (% total) increased significantly ($P = 0.02$) and there was a significant reduction in SBP LF/HF ratio with slower breathing frequencies ($P = 0.02$). For the normal subjects the effects of respiration on R–R spectra were similar, with an increase in R–R variance with lower respiratory frequency ($P = 0.02$) and a significant ($P = 0.004$) increase in HF (absolute units), although this was not significant when expressed as % total or nu. LF/HF ratio fell with lower breathing frequencies but this was not signifi-
cant ($P=0.97$). In the SBP spectra (normal subjects), LF and HF changes with different breathing rates were not significant. Thus, surprisingly, the effects of different respiratory rates on supine SBP LF/HF ratio appear to be greater in patients with CHF than in normal subjects.

**Controlled respiration, standing**

In the heart failure group, on standing, smaller but comparable changes in LF and HF components of R-R spectra were seen during paced breathing, with a decrease in LF and a small increase in HF at lower breathing rates and a fall in LH/HF ratio ($P=0.05$). More significant changes were seen in the SBP spectra, with a significant fall in LF/HF ratio at lower respiratory frequency ($P=0.03$). In normal subjects the changes in R-R spectra with paced breathing were more obvious on standing, with a significant reduction in LF (nu) and a significant increase in HF ($P=0.004$; absolute units) with lower breathing rates, and a corresponding fall in LF/HF ratio ($P=0.01$). Similar changes were seen in the SBP spectra of normal subjects, with a fall in LF and an increase in HF components, and a significant fall in LF/HF ratio with reduced paced breathing rates ($P=0.01$). In both patients with CHF and normal subjects the LF component with controlled breathing was higher on standing compared with supine, although this was statistically significant only in the normal subjects ($P<0.05$, supine compared with standing at 10, 15 and 20 breaths/min). Thus, in contrast to the supine position, standing exerted much greater changes in normal subjects than in patients with heart failure.

**DISCUSSION**

Many clinical studies have used Holter systems for assessing heart rate variability in the frequency domain, but usually no allowance is made for the effects of respiration or posture. In a review of published studies, Brown et al. [16] found that in nearly 50% of studies the respiratory rate was not controlled during the study period. Although the effect of different respiratory rates has been studied before in normal subjects [15-18], this study has shown for the first time that this effect of respiration is also seen in patients with heart failure, despite the general reduction in heart rate and blood pressure spectral power which is apparent at all frequencies but especially in the LF band. In addition, the important effect of respiration on the spectral components of heart rate and SBP variability in normal subjects is confirmed [15-18]. HF power (expressed in absolute units) increased significantly with lower respiratory rates.

The mechanism of respiratory sinus arrhythmia is not entirely clear [7]. The traditional explanation is that the waxing and waning of the pulse rate is caused by a central 'oscillator' entrained to the respiratory rate as a result of the afferent input from broncho-pulmonary receptors. However, it is clear that other non-neural mechanical mechanisms are involved as inspiration increases heart rate in the denervated transplanted heart [19]. The role of the baroreceptors in the production of respiratory sinus arrhythmia is emphasized in the model proposed by De Boer et al. [24], and this may explain the different response to respiration rate changes between normal subjects and patients with heart failure. These studies emphasize the importance of respiration in cardiovascular control, the need to measure respiration and to examine for coherence with the respiratory signal, particularly if power spectral analysis of heart rate variability is used to assess the effect of drugs or other therapies on sympatho-vagal balance in CHF.

Postural effects on R-R power spectra were as expected. In normal subjects there was the expected rise in LF and reduction in HF components, as reported previously [8, 25]. Postural changes had less effect on R-R LF and HF in the heart failure group, probably because of the blunted cardiovascular reflex responses [5, 26], but interestingly the effects of both posture and respiratory frequency changes appeared to be more obvious on SBP than R-R LF and HF components, possibly indicating a differential effect on cardiac and vascular modulation.

This study has also confirmed the paradoxical reduction in the LF component of R-R and to a lesser extent of SBP spectra variability in patients with heart failure [9, 10, 26]. Although the degree of reduction in the LF component is related to the severity of the disease [27], recent studies have suggested that the LF component is not a measure of sympathetic activity per se [28-30], although the LF/HF ratio of heart rate variability (but not SBP) is a 'crude' measure of sympathetic balance [7, 8]. The mechanism for the reduced or absent LF component in R-R spectra of patients with heart failure is not entirely clear. Some have suggested that it is due to supersaturation of end-organ receptors by excessive and prolonged sympathetic stimulation and decreased responsiveness of the sinus node to neural modulatory influences [10, 27, 28]. It has been suggested recently that the LF component reflects the baroreflexes and is due to the phase lag in the baroreceptor loop [31], generated by the vagally mediated response (mainly cardiac) is fast while the sympathetic response (largely vascular) is slower [24]. The system will oscillate at about 0.1 Hz, the same frequency as the LF component. In a recent study, Ahmed et al. [30] showed in normal subjects that although tilting to an upright position slightly increased LF power and LF/HF ratio, these changes were not produced by other forms of $\beta$-adrenergic stimulation, such as adrenaline and isoprenaline infusion, which caused no significant change in LF or HF power, although this constant $\beta$-adrenergic stimulation does not
mimic the normal phasic oscillations in sympathetic nerve activity. Paradoxically, exercise produced a reduction in both HF and LF power. Similarly, Bernardi et al. [19] found in normal subjects that when approaching peak exercise the relative proportion of LF decreased and HF proportionally increased. These changes clearly cannot be due to decreased adrenergic sensitivity but are more likely to be due to a change in baroreceptor gain. In our study, the LF component of the SBP spectra in patients with CHF appeared to be better preserved (although still subnormal) than in the R–R spectra, and there was even a small (non-significant) rise upon standing. This indicates that the sinus node and vascular system differ in their responsiveness to neural modulation in CHF, but it is not possible to determine in this study if this relates to reduced baroreceptor gain or differing end-organ sensitivities. Baroreceptor gain is known to be reduced in heart failure and there are many possible reasons for this [5, 32].

Tidal volume was not controlled in this study so that the individuals could breathe at a comfortable rate without hyperventilation or significant changes in acid–base balance which might influence the results. Although there must have been minor changes in tidal volume at different respiratory frequencies, Bernardi et al. [33] found that changes in tidal volume are far less important than breathing frequency. During spontaneous breathing there were much wider variations in tidal volume and often the breathing rate changed significantly which gave a broader HF band. However, the respiratory component of the R–R and SBP spectra could be identified by comparison with the respiratory spectral analysis recording, emphasizing the importance of recording the respiratory rate during spontaneous breathing in order for the respiratory HF band to be accurately identified. It is possible that the mental concentration required to follow the breathing instructions could induce a small alerting or stress reaction which might increase sympathetic outflow. Another potential source of error is the presence of ectopics which were more frequent in the heart failure group than in normal subjects. These were removed from the tachogram by linear interpolation. However, this would tend to increase the power in the LF band without affecting the HF power appreciably [34]. The mean age of the normal subjects was lower than the patients with CHF (45±2 years compared with 57±15 years), but according to the study by Piccirillo et al. [25], within the age group 44–64 years there was little effect of age upon power spectral analysis of heart rate variability (although the youngest group did have higher HF power than those over 64 years of age). The age difference is therefore unlikely to be important in this study.

In conclusion, this study has demonstrated that both respiratory frequency and posture have an important effect on measurements derived from power spectral analysis of heart rate and SBP variability in patients with CHF and normal subjects. Studies which utilize this technique should either control for respiration and posture during the period of measurement or identify respiratory rate if comparative studies on different occasions are carried out.

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REFERENCES