Continuous positive airway pressure increases heart rate variability in heart failure patients with obstructive sleep apnoea

Matthew P. GILMAN*, John S. FLORAS†, Kengo USUI‡, Yasuyuki KANEKO*‡, Richard S. T. LEUNG*‡§ and T. Douglas BRADLEY*†‡§

ABSTRACT

Patients with heart failure or OSA (obstructive sleep apnoea) have reduced HF-HRV (high-frequency heart rate variability), indicating reduced cardiac vagal modulation, a marker of poor prognosis. CPAP (continuous positive airway pressure) abolishes OSA in patients with heart failure, but effects on daytime HF-HRV have not been determined. We hypothesized that, in patients with heart failure, treatment of coexisting OSA by CPAP would increase morning HF-HRV. In 19 patients with heart failure (left ventricular ejection fraction < 45 %) and OSA (≥ 20 apnoeas/h of sleep), HF-HRV was quantified before and 1 month after randomization to a control or CPAP-treated group. In the control group (n = 7), there were no changes in HF-HRV over the 1 month study during wakefulness in the morning. In the CPAP-treated group (n = 12), HF-HRV increased significantly during wakefulness in the morning [from 2.43 ± 0.55 to 2.82 ± 0.50 log(ms²/Hz); P = 0.002] due to an increase in transfer function between changes in lung volume and changes in HF-HRV (92.37 ± 96.03 to 219.07 ± 177.14 ms/l; P = 0.01). In conclusion, treatment of coexisting OSA by nocturnal CPAP in patients with heart failure increases HF-HRV during morning wakefulness, indicating improved vagal modulation of heart rate. This may contribute to improved prognosis.

INTRODUCTION

Heart failure affects over 4 million North Americans, and its prevalence is continuing to increase [1] with an annual incidence of half a million [2]. Despite advances in medical therapy, morbidity and mortality remain high. Accordingly, it is important to identify and treat conditions that may contribute to the progression of heart failure. In the last two decades, a growing body of evidence indicates that one such condition may be OSA (obstructive sleep apnoea). Not only does OSA frequently coexist with heart failure [3], but it appears to contribute to a higher mortality rate [4], possibly due to adverse effects on haemodynamics and autonomic cardiovascular regulation [5,6].

The transition from wakefulness to normal sleep is accompanied by increases in cardiac vagal activity and reductions in sympathetic tone [7,8]. However,
obstructive apnoeas and hypopnoeas disrupt this process by subjecting the heart to recurrent hypoxia and arousals from sleep [9]. Recurrent hypoxia and arousals from sleep increase sympathetic nervous activity and BP (blood pressure), whereas arousals inhibit cardiac vagal activity [10,11]. During wakefulness, both heart failure and OSA are associated with reductions in vagal modulation of HR (heart rate) at HF (high frequency) [11,12], an important component of which is respiratory sinus arrhythmia. Whether these effects are additive or redundant is not known. Reductions in HF-HRV (HR variability) are associated with increased mortality rates in patients with cardiovascular diseases [13,14]. Therefore, if additive, the coexistence of OSA could depress HF-HRV further in patients with heart failure and thereby contribute to increased mortality.

In awake patients with heart failure, the acute application of CPAP (continuous positive airway pressure) increases time and frequency domain indices of vagal HR modulation without affecting markers of sympathetic HR modulation [15]. When applied during sleep to patients with heart failure with OSA, CPAP acutely reduces the frequencies of obstructive apnoeas and arousals from sleep, and lowers nocturnal HR and BP [16]. When applied chronically to such patients, it reduces nocturnal ventricular ectopy, daytime sympathetic nervous system activity, HR and BP, and increases daytime LVEF [LV (left ventricular) ejection fraction] [17–19].

Reductions in the frequency of arousals from sleep might also restore daytime cardiac vagal modulation of HR. HF-HRV is an established non-invasive index of cardiac vagal activity [20]. Thus far, there have been no reports on the effects of nocturnal CPAP on daytime HF-HRV in patients with heart failure with OSA. We therefore performed a randomized controlled trial involving patients with HF with OSA to test the hypothesis that treatment of OSA with CPAP would increase HF-HRV during wakefulness.

MATERIALS AND METHODS

Subjects

This was a substudy of a larger randomized controlled trial involving 29 patients with heart failure and OSA [17]. Subjects were recruited from the Heart Failure clinics of the Mount Sinai and Toronto General Hospitals. Patients referred to these clinics routinely undergo overnight polysomnography. Entry criteria included: (i) heart failure due to ischaemic or non-ischaemic dilated cardiomyopathy, (ii) resting LVEF ≤ 45 % by nuclear angiography or echocardiography, (iii) a stable condition for at least 1 month prior to the study while on stable optimal pharmacological treatment, and (iv) the presence of moderate-to-severe OSA on a sleep study, defined as at least 20 apnoeas and hypopnoeas/h of sleep [AHI (apnoea/hypopnoea index) ≥ 20]. Exclusion criteria were: (i) the presence of a cardiac pacemaker, and (ii) unstable angina, myocardial infarction or cardiac surgery within 3 months prior to the study.

The protocol was approved by the Research Ethics Board of the University of Toronto, and all subjects provided written informed consent prior to participation.

Sleep studies

All subjects underwent a baseline overnight sleep study from which sleep stages and arousals from sleep were scored according to standard criteria [21]. Thoracoabdominal movements and airflow were measured by a respiratory inductance plethysmograph calibrated for lung volume against a spirometer using the two positions simultaneous equations technique [16,22]. Oxygen saturation was monitored by an oximeter, and HR by a lead I ECG. Obstructive apnoeas and hypopnoeas were defined as tidal volume excursions of < 100 ml, or a 50 % or greater reduction in tidal volume but above 100 ml respectively, lasting at least 10 s with out-of-phase ribcage and abdominal motion [16]. The frequency of apnoeas and hypopnoeas/h of sleep was quantified as the AHI. The average and lowest SaO2 (arterial oxygen saturation) during sleep was determined as described previously [16]. The respiratory inductance plethysmograph was recalibrated the following morning just prior to assessment of HF-HRV.

Protocol

Following the baseline sleep study, subjects were assigned randomly to either a control group, who continued on optimal drug treatment for heart failure (n = 14), or to a group, who in addition, received CPAP (n = 15) (see Figure 1). The night following the baseline sleep study, those randomized to CPAP underwent an overnight CPAP titration, during which pressure was adjusted to abolish apnoeas and hypopnoeas or to the highest level tolerated. Subjects in the treatment group were provided with a CPAP machine with a built-in time meter to determine the hours of use and were instructed to wear it for > 6 h each night during the 1-month study period. The baseline protocol was replicated 1 month later.

HF-HRV

Because atrial fibrillation and the presence of frequent ventricular premature beats precludes the application of conventional techniques for frequency domain analysis of HRV, subjects with atrial fibrillation, or 15 or more VPBs (ventricular premature beats)/100 heart beats were excluded from further study [23]. In the remainder, the ECG was recorded on both study sessions when subjects were supine approx. 2 h after awakening in the morning. Lung volume, derived from the respiratory inductance plethysmograph signal, and RR interval (R-wave to R-wave interval), from the ECG signal, were sampled at
Heart rate variability and sleep apnoea

200 and 1000 Hz respectively. These signals were then subjected to frequency power spectral analysis via Fast Fourier Transformation with the use of a customized computer program from which HRV and instantaneous changes in lung volume were derived (LabVIEW, National Instruments) [21]. Data were analysed in 14-min segments to allow acceptable resolution at the respiratory frequency [24].

HRV was divided into three spectral components: total HRV (0.005–0.5 Hz), and its HF (0.15–0.5 Hz) and LF (low frequency; 0.05–0.15) components. Because HF-HRV is under the influence of respiration (i.e. respiratory sinus arrhythmia), the degree of relationship between respiration (input) and HRV (output) at a specific frequency was determined by coherence analysis. Coherence was considered significant when it exceeded the 95% CI (confidence interval) for all coherence values across the entire frequency spectrum [24]. The degree of influence of a change in lung volume on RR intervals (i.e. gain) was quantified by transfer magnitude analysis, which expresses the change in RR interval for a given change in lung volume (in ms/l) [25]. HF and LF values were also expressed as a proportion of total HRV power (HF % and LF % respectively).

Data analysis
Data were acquired and analysed in a blinded manner by investigators unaware of the treatment allocation. LF, HF, total power and LF/HF ratios [20] were log-transformed because the data were skewed to the right. Statistical analyses were performed using SigmaStat 2.03 (SPSS Inc.). Paired Student’s t tests were used to evaluate within-group differences, and unpaired Student’s t tests were used to evaluate between-group differences. Two-way repeated measures ANOVA, followed by Tukey’s test, was used to evaluate the time–treatment interactions. Non-normally distributed data were compared by the Mann–Whitney test. Results are expressed as means ± S.D., unless otherwise stated. P values < 0.05 were considered statistically significant.

RESULTS

Subject characteristics
At total of 29 subjects were randomized: 14 to the control group and 15 to the CPAP-treated group (Figure 1). Among the control subjects, five were excluded because of excessive VPBs and two because of atrial fibrillation, whereas, among CPAP-treated subjects, two were excluded because of excessive VPBs and one because of technical difficulties with the ECG recording. Therefore acceptable ECG recordings were obtained in seven patients randomized to the control group and 12 patients to the CPAP-treated group.

As shown in Tables 1 and 2, subjects were generally middle-aged overweight men with mild-to-moderate symptoms of heart failure and markedly reduced LVEF. There were no significant differences between the two groups with respect to age, sex distribution, BMI (body mass index), prevalence of ischaemic and non-ischaemic dilated cardiomyopathy, NYHA (New York Heart Association) class, LVEF, average and lowest Sao2 or sleep structure. Although there was a tendency for the AHI and frequency of arousals to be lower in the CPAP-treated group, these differences were not significant (P = 0.060 and P = 0.118 respectively). In addition, there was no significant relationship between baseline HF-HRV power.
Table 1  Baseline characteristics of the control and CPAP-treated groups
Values are means ± S.D. There were no significant differences between the two groups for any of these variables. ACE, angiotensin-converting enzyme.

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 7)</th>
<th>CPAP-treated group (n = 12)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>58.1 ± 7.1</td>
<td>56.7 ± 8.0</td>
</tr>
<tr>
<td>Sex (n) (male/female)</td>
<td>6/1</td>
<td>11/1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.1 ± 3.9</td>
<td>30.3 ± 6.5</td>
</tr>
<tr>
<td>Aetiology of heart failure (n)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Ischaemic dilated cardiomyopathy</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Non-ischaemic dilated cardiomyopathy</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.2 ± 0.6</td>
<td>2.4 ± 0.8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30.4 ± 10.5</td>
<td>26.4 ± 10.3</td>
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<tr>
<td>Medication (n)</td>
<td></td>
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<tr>
<td>Digoxin</td>
<td>3 (43 %)</td>
<td>7 (58 %)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>5 (71 %)</td>
<td>10 (83 %)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>7 (100 %)</td>
<td>10 (83 %)</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>0 (0 %)</td>
<td>2 (17 %)</td>
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<tr>
<td>Nitrates</td>
<td>2 (29 %)</td>
<td>0 (0 %)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>5 (71 %)</td>
<td>8 (67 %)</td>
</tr>
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and either AH1 at baseline (r = 0.31, P = 0.190) or arousal frequency at baseline (r = 0.35, P = 0.133).

Effects of intervention
There were no changes in group mean values for either BMI or medication during the study. The control group experienced no significant changes in AH1 or any of the other sleep variables from baseline to follow-up (Table 2). In contrast, CPAP (mean pressure of 8.8 ± 2.4 cm H2O used for an average of 6.3 ± 1.5 h/night) reduced significantly both the AH1 and the frequency of arousals (P < 0.001 for each), and increased the average and lowest SaO2 (P = 0.022 and P < 0.001 respectively). In the control group, there was no significant change in LVEF between baseline and follow-up (30.4 ± 10.5 to 29.5 ± 6.3 % respectively). In contrast, the CPAP-treated group experienced an increase in LVEF of 8.4 ± 2.0 % (from 26.4 ± 10.3 % at baseline to 34.8 ± 8.3 % at follow-up; P = 0.002), which was significantly greater than the control group (P = 0.028).

Table 2  Anthropomorphic and polysomnographic data from the control and CPAP-treated groups
Values are means ± S.D. There were no significant differences in baseline values between the control and CPAP-treated groups. P values refer to within-group comparisons. *P = 0.025, †P = 0.033, ‡P = 0.003 and §P = 0.029 compared with the control group. NS, non-significant; REM, rapid eye movement; TST, total sleep time.

<table>
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<th>Control group (n = 7)</th>
<th>CPAP-treated group (n = 12)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.1 ± 3.9</td>
<td>30.6 ± 4.2</td>
</tr>
<tr>
<td>AH1 (number/h of sleep)</td>
<td>41 ± 13</td>
<td>37 ± 18</td>
</tr>
<tr>
<td>Average SaO2 (%)</td>
<td>95.0 ± 2.1</td>
<td>94.7 ± 2.0</td>
</tr>
<tr>
<td>Lowest SaO2 (%)</td>
<td>82.4 ± 6.9</td>
<td>78.5 ± 12.4</td>
</tr>
<tr>
<td>TST (min)</td>
<td>317.0 ± 18.3</td>
<td>323.3 ± 50.9</td>
</tr>
<tr>
<td>Stage I and II sleep (% of TST)</td>
<td>77.0 ± 6.6</td>
<td>81.6 ± 11.9</td>
</tr>
<tr>
<td>Stage III and IV sleep (% of TST)</td>
<td>6.6 ± 5.5</td>
<td>3.1 ± 3.9</td>
</tr>
<tr>
<td>REM sleep (% of TST)</td>
<td>16.4 ± 6.3</td>
<td>15.2 ± 9.0</td>
</tr>
<tr>
<td>Arousals (number/h of sleep)</td>
<td>34.1 ± 13.5</td>
<td>35.1 ± 15.8</td>
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DISCUSSION
In this randomized controlled trial, we have demonstrated, in patients with heart failure, that treatment of co-existing OSA by nocturnal CPAP for 1 month increased...
HF-HRV, both in absolute (HF power) and relative (HF as a percentage of total power) terms, in the morning following sleep. The LF/HF ratio was also lower at this point. The increase in HF as a percentage of total power was due to the increase in absolute HF power, as neither total nor LF power was changed. These effects occurred in conjunction with an alleviation of OSA and nocturnal hypoxia, a reduction in the frequency of arousals and an improvement of LVEF. Our findings therefore indicate that, in addition to improving LV systolic function and reducing sympathetic nervous system activity [17,18,26], CPAP improves parasympathetic modulation of HR in patients with heart failure with OSA during wakefulness within 2 h following nocturnal CPAP use.

As respiratory sinus arrhythmia, an important component of HF-HRV, represents the influence of respiration on heart rhythm, respiration must be taken into account when quantifying HF-HRV [27]. Sinus arrhythmia results from central respiratory entrainment of the cardiovagal motor neurons in the medulla and/or vagal feedback from the pulmonary stretch receptors [8]. We quantified the influence of respiration on HF-HRV by examining the coherence and transfer magnitude between changes in lung volume and RR intervals at the respiratory frequency. First, we found that the coherence between respiration and HF-HRV was significant both at baseline and after 1 month of CPAP, indicating a significant influence of respiration on HF-HRV. Secondly, after 1 month of CPAP, the gain of the transfer function relating changes in RR intervals to changes in lung volume at HF doubled. One potential explanation, therefore, for the increase in HF-HRV is an increase in vagal nerve firing in response to respiratory input after abolition of OSA by CPAP. An alternative explanation is that chronic CPAP treatment removed or ameliorated chronic inhibitory influences on vagal modulation of sino-atrial discharge related to heart failure, such as right atrial stretch.

This can be accomplished through reversal of either hypoxic pulmonary vasoconstriction [28] or the marked increase in noradrenaline (norepinephrine) release from cardiac sympathetic nerves characteristic of heart failure [25,29].

Previous uncontrolled or non-randomized trials reported that, in patients with OSA but without congestive heart failure, the gain of the transfer function relating changes in RR intervals to changes in lung volume increased with CPAP therapy both during sleep and while awake [14,30]. Our results support those previous observations, but in the more robust setting of a randomized controlled trial involving subjects with heart failure. Reversal of OSA by CPAP could augment HF-HRV via several mechanisms. Repetitive arousals at the termination of obstructive apnoeas cause abrupt inhibition of vagal input into the sino-atrial node [10]. This could persist into wakefulness. Acute application of CPAP to patients with heart failure with OSA during sleep reduces arousals and enhances the gain of the arterial baroreceptor–vagal HR reflex. The latter increase persists for approx. 30 min after withdrawal of CPAP [31]. Therefore a reduction in arousals from sleep could have augmented vagal modulation of HR at HF, with a carryover effect that persisted into wakefulness.

Abolition of OSA by CPAP reduces sympathetic nerve traffic to skeletal muscle in patients with [32] and without [33] heart failure. Therefore the reduction in the LF/HF ratio in response to CPAP in the present study is consistent with the concept that reduced sympathetic input to the sino-atrial node increased its responsiveness to vagal modulatory influences [25]. However, because LF spectral power comprises both parasympathetic and sympathetic neural contributions to the modulation of HR [34], we cannot determine from LF power itself whether CPAP also attenuated cardiac sympathetic neural discharge [35].

### Table 3  Morning HRV after sleep in the control and CPAP-treated groups

<table>
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<th>Control group (n = 7)</th>
<th>CPAP treated group (n = 12)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>1 month</td>
</tr>
<tr>
<td>HF [log(ms²/Hz)]</td>
<td>2.40 ± 0.53</td>
<td>2.21 ± 0.41</td>
</tr>
<tr>
<td>LF [log(ms²/Hz)]</td>
<td>2.17 ± 0.62</td>
<td>2.25 ± 0.62</td>
</tr>
<tr>
<td>HF%</td>
<td>11.4 ± 14.7</td>
<td>13.0 ± 8.4</td>
</tr>
<tr>
<td>LF%</td>
<td>0.62 ± 7.5</td>
<td>12.7 ± 5.8</td>
</tr>
<tr>
<td>Total power [log(ms²/Hz)]</td>
<td>3.18 ± 0.70</td>
<td>3.19 ± 0.65</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.64 ± 0.10</td>
<td>0.66 ± 0.18</td>
</tr>
<tr>
<td>Transfer magnitude (ms/l)</td>
<td>147.97 ± 110.91</td>
<td>73.67 ± 51.46</td>
</tr>
</tbody>
</table>

Values are means ± S.D. There were no significant differences in baseline values between the control and CPAP-treated groups. P values refer to within-group comparisons. * P = 0.003, † P = 0.045 and ‡ P = 0.022 compared with the control group. HF%, HF expressed as a percentage of total power; LF%, LF expressed as a percentage of total power; NS, not significant.
As patients randomized to CPAP in our present study experienced a highly significant 8% improvement in LVEF, a third possibility is that improved LV function attenuated disturbances in the neural regulation of HR associated with advanced heart failure [28,29].

Despite randomization, the baseline AHI and frequency of arousals tended to be lower in the CPAP-treated group compared with the control group. These imbalances probably arose because of the substantial number of individuals involved in the main study who had more than 15 VBP/100 heart beats or who had atrial fibrillation rendering them ineligible for this protocol. However, there was no correlation between the power of HF-HRV and either the AHI or arousal index. Thus the baseline AHI and arousal index did not influence the response to CPAP. In addition, because two-way ANOVA takes into account baseline differences in assessing the time–treatment interaction, between-group differences in these baseline variables are not likely to have influenced the primary outcome of our present study.

Our findings have clinical implications. Reduced HF-HRV is associated with an increase in adverse cardiovascular events and death in patients with coronary artery disease and heart failure [13,36,37]. Moreover, the peak occurrence of such events is shortly after awakening in the morning [38,39]. As well, in ischaemic hearts, reduced parasympathetic control of HR increases the risk of cardiac arrhythmias [40], whereas an increase in parasympathetic activity reduces the risk [41]. Accordingly, the striking CPAP-induced increase in HF-HRV and decrease in the LF/HF ratio towards parasympathetic dominance that we observed in the morning following sleep could lead to fewer early morning cardiovascular events in patients with heart failure and coexisting OSA treated with CPAP. This suggests one mechanism through which treatment of OSA by CPAP in patients both without and with heart failure was accompanied by reduced cardiovascular mortality in two observational studies published recently [4,42].

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