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# Improved Ventricular Repolarisation with Long-Term Continuous Positive Airway Pressure in Heart Failure Patients with Obstructive Sleep Apnoea: A Prospective Randomised Controlled Trial

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## Clinical Points:

- Obstructive sleep apnoea (OSA) can coexist with heart failure, contributing to its harmful effects on heart function and the autonomic nervous system.
- Standard treatment for OSA is continuous positive airway pressure (CPAP), which creates a steady flow of air to keep the airway open preventing alveolar collapse.
- Temporal lability in ventricular repolarisation can be measured using beat-to-beat QT variability, referred to as the QT variability index (QTVI).
- Treatment of OSA by CPAP in patients with congestive heart failure improves left ventricular ejection fraction, overall sleep and reduces beat-to-beat QT variability, which may lead to a decrease in sudden cardiac death.

## ABSTRACT

**Background:** Obstructive sleep apnoea (OSA) has a high prevalence in patients with congestive heart failure (CHF) and contributes to its progression. Periodic obstructive events subject the heart to recurrent episodes of nocturnal hypoxia and harmful effects on the autonomic nervous system, which can predispose the heart to ventricular arrhythmias. It has been shown that treatment with continuous positive airway pressure (CPAP) can improve cardiac and autonomic function in CHF patients with OSA. These improvements include increased left ventricular ejection fraction (LVEF), an increase in vagal tone, and a decrease in sympathetic drive. As autonomic tone, hypoxia, and afterload are known to modulate ventricular repolarisation (which is a determinant of malignant ventricular arrhythmias in heart failure patients), in this study we hypothesised that CPAP would improve ventricular repolarisation. The temporal lability of ventricular repolarisation can be measured using beat-to-beat QT variability (QTVI).

**Methods:** Eighteen patients with CHF (LVEF <45%) and OSA (apnoeas and hypopnoeas index (AHI) ≥20) underwent baseline polysomnography and echocardiography. QTVI was assessed from an electrocardiographic lead I during stage 2 sleep. The patients were then randomised to a control group (N=7, AHI=45.0 ± 15.0), or a CPAP treated group (N=11, AHI=40.2 ± 22.8) for one month, after which the above protocol was repeated.

**Results:** OSA was unchanged in the control group, but was alleviated in the CPAP group. The control group did not experience any significant changes in QTVI. In contrast, the CPAP treated group experienced a significant decrease in QTVI after one month (-0.37 ± 0.82 to -0.91 ± 0.55, P=0.006). This decrease in QTVI was significantly different between the two groups (P=0.021).

**Conclusions:** These findings indicate that in patients with CHF, treatment of coexisting OSA by CPAP improves ventricular repolarisation, which could reduce the risk of malignant arrhythmias.

## INTRODUCTION

Congestive heart failure (CHF) affects over 80,000 people in Ireland with an annual incidence of 10,000 (1). It is estimated that with the aging population and high prevalence of coronary artery disease, that by the next decade as many as 300,000 Irish will be diagnosed with CHF (2). Despite advances in pharmacological treatments the rates of morbidity, hospitalisation, and mortality remain unacceptably high. Accordingly, it is important that secondary conditions that may contribute to the progression of CHF be identified and treated appropriately. In the last two decades a growing body of evidence indicates that one such condition, obstructive sleep apnoea (OSA), not only co-exists with heart failure (3,4), but also contributes to its harmful effects on heart function and the autonomic nervous system (5,6). Periodic obstructive events subject the heart to recurrent episodes of hypoxia, reduced vagal activity, surges in sympathetic nerve activity (SNA), heart rate (HR) and blood pressure (BP), and abnormal beat-to-beat changes in ventricular repolarisation (7-9). These nocturnal stresses are hazardous to the heart and have the potential to trigger ventricular arrhythmias (10). It is also well known that OSA triggers nocturnal

myocardial ischaemia (18), which could increase ventricular repolarisation lability (19,20). Abnormal ventricular repolarisation is also frequently seen in association with CHF (14-16) where it predisposes to the development of ventricular arrhythmias and sudden death (14,17).

The standard treatment for OSA is continuous positive airway pressure (CPAP), which effectively creates a steady flow of air to keep the airway open thereby preventing the collapse that leads to an apnoea. It is well known that CPAP decreases the apnoea/hypopnoea index (AHI) (apnoeas and hypopnoeas/hr of sleep) and improves overall sleep quality measured by polysomnography (11-13). The nocturnal stresses caused by OSA on the already failing heart can be acutely reversed by application of CPAP (11-13). CPAP has been shown to improve mechanical heart function (12), specifically by augmenting left ventricular ejection fraction (11,13). This is thought to be due to beneficial effects of dipping nocturnal blood pressure and decreasing sympathetic nerve activity (11,13). Despite these favourable improvements, the potential benefits of CPAP on ventricular arrhythmias are not yet established.
Temporal lability in ventricular repolarisation can be measured using beat-to-beat QT variability, referred to as the QT variability index (QTVI). Increased QTVI has been demonstrated in patients at risk of malignant ventricular arrhythmias including patients with dilated cardiomyopathy, unsuccessful reperfusion post-MI, and long QT syndrome (14,15). Because ventricular repolarisation can be modulated by autonomic tone, hypoxia, and afterload, we hypothesised that CPAP would not only improve LVEF, overall sleep, and abolish apnoeas, but would improve ventricular repolarisation as manifest by a decrease in QTVI. In the present study, we compared QTVI during stage 2 sleep in heart failure patients with OSA randomised to one month of CPAP versus no CPAP.

## METHODS

### Recruitment of Participants

Subjects were referred from the heart failure clinics at Mount Sinai Hospital and the Toronto General Hospital/University Health Network in Toronto for the investigation of possible sleep apnoea. Entry criteria consisted of: (i) CHF due to ischemic or non-ischaemic dilated cardiomyopathy, (ii) a resting left ventricular ejection fraction (LVEF) of 45% or less, (iii) stable functional capacity for at least one month prior to the study while on stable optimal heart failure medical management, (iv) the presence of OSA on a sleep study, defined as an AHI (apnoeas and hypopnoeas/hr of sleep) ≥ 20 and (v) a 5 minute continuous ECG recording at the end of the night during stage 2 sleep, devoid of apnoeas and hypopnoeas. Exclusion criteria were: (i) primary valvular heart disease, (ii) the presence of a cardiac pacemaker, (iii) atrial fibrillation, (iv) ventricular premature beats occurring at a rate greater than 5 per 100 heart beats (15) and (v) unstable angina, myocardial infarction, or cardiac surgery within 3 months of the study.

### Assessment of Participants

The protocol was approved by the Human Subjects Review Committee of the University of Toronto and all subjects provided written informed consent prior to the study. Following a baseline sleep study and echocardiography, the subjects were randomly assigned to either a control group that were maintained on their optimal heart failure medical management (N=7), or a treatment group (N=11) that received CPAP in addition to their optimal heart failure medical management (see Table 1). The sleep study measured the AHI, oxyhaemoglobin saturation ($SaO_2$), arousals, heart rate, additional polysomnographic data (see Table 2), and QTVI analysis of the ECG tracing. The echocardiogram measured left ventricular function as LVEF upon waking. Subjects in the treatment group underwent an additional overnight sleep study during which CPAP was titrated to the pressure at which apnoeas and hypopnoeas were abolished, or to the highest tolerable pressure. They were then sent home with the CPAP device set at the optimum pressure and were instructed to apply it every night for at least six hours during the one month study period. The duration of CPAP usage was recorded via a built-in time metre to determine compliance.At the end of the one month study period, all patients underwent repeat sleep study and echocardiography to determine any changes in both the control and CPAP treated group. During the follow-up sleep study polysomnography was performed in the treatment group while on CPAP.

### Sleep Studies

Sleep stages and arousals were scored according to standard criteria (21). Thoracoabdominal movements and airflow were measured by a calibrated respiratory inductance plethysmography (12). $SaO_2$ was monitored using an ear oximeter and HR via an electrocardiogram (ECG). Obstructive apnoeas were defined as tidal volume excursions of 0 to 100 ml for at least 10 seconds in the presence of out-of-phase movements of the ribcage and abdomen. Obstructive hypopnoeas were defined as 50% or greater reduction in tidal volume but above 100 ml for at least 10 seconds with out-of-phase ribcage and abdominal motion (12). Both these measures were used to calculate the AHI.

### QT Variability Analysis

ECG recordings were taken from lead I over a continuous 5 minute period during stage 2 sleep when breathing was regular at the end of the night. ECG signals were sampled at 1000 Hz. The 5 minute epochs were analysed using a validated QT interval measurement algorithm programmed in MATLAB (Mathworks). Details of the algorithm operation are published extensively elsewhere (15). To measure beat-to-beat QT variability, a normalised QTVI, was derived according to the equation: log10[(QT variance / QT mean2) ÷ (heart rate variance / heart rate mean2)].

Power spectra of the heart rate (Pxx(f)) and QT (Pyy(f)) time series and the cross spectrum between the two (Pxy(f)) were computed from each epoch using the Blackman-Tukey method. The coherence was calculated using [Pxy(f)]^2 / [Pxx(f) Pyy(f)]. The coherence is a

measure from 0-1 of the degree of linear interaction between heart rate and QT fluctuations. Mean coherence was obtained by averaging the coherence over the frequency band from 0-0.2 Hz.

**Left Ventricular Ejection Fraction Assessment**

Two hours after the patient awakened, two-dimensional echocardiographic images were acquired from the parasternal long and short axes, apical long axis, apical four-chamber, and subcostal views by an echocardiographer who was unaware of the patient's treatment assignment. The LV end-diastolic and end-systolic dimensions were determined, and the LVEF was calculated according to a modification of Simpson's method (22).

**Statistical Analysis**

The data are expressed as mean ± standard devistion (SD) unless otherwise stated. A paired t-test was used to evaluate within-group differences while an unpaired t-test was used for between-group differences. Two-way repeated measures ANOVA tests were used to evaluate the time-treatment interactions within and between the groups at baseline and one month later. Non-normally distributed data were compared by the Mann-Whitney test. A P-value less than 0.05 was considered statistically significant. The statistical software package used was Sigmastat 2.03 (SPSS Inc.).

| | Control group (N=7) | CPAP treated group (N=11) |
|---|---|---|
| Age, yr | 57.1± 10.4 | 57.1± 7.8 |
| Sex, M:F | 6 : 1 | 9 : 2 |
| Body mass index | 31.3 ± 5.1 | 28.8 ± 6.1 |
| Epworth Sleepiness Scale score † | 5.1 ± 3.1 | 7.3 ± 3.5 |
| Aetiology – no. of patients | | |
| Ischaemic dilated cardiomyopathy | 3 | 5 |
| Non - ischemic dilated cardiomyopathy | 4 | 6 |
| NYHA class | 2.4 ± 0.5 | 2.4 ± 0.7 |
| LVEF % | 27.7 ± 8.4 | 29.9 ± 13.4 |

**Table 1. Baseline characteristics of the control and the CPAP treated groups.** There were no significant differences between the two groups for any of the variables.
† The Epworth Sleepiness Scale ranges from 0 to 24, with scores of 10 or higher indicating excessive daytime sleepiness.
Abbreviations: NYHA = New York Heart Association, LVEF = left ventricular ejection fraction. Values are means ± SD.

## RESULTS

**Baseline Characteristics of the Subjects**

Thirty subjects were enrolled in this study. Thirteen patients were randomly assigned to the control group and seventeen to the treatment group. Four subjects in the control group and three in the CPAP treatment group with ventricular premature beat rates of greater than 5% were excluded from further analysis. Two subjects in the control group and three subjects in the CPAP group were excluded from further analysis because of significant background noise in the ECG signal, making accurate identification of the QRS and T waves for QT analysis unreliable.

There were no significant baseline differences between the two groups with respect to age, gender, body-mass index (BMI), Epworth Sleepiness Scale scores, prevalence of ischemic and non-ischaemic cardiomyopathy, New York Heart Association functional class, or LVEF (see Table 1). Within the CPAP treated group the average compliance over the one month intervention period was 6.3 ± 1.5 hours per night with a minimum of 3.4 hrs/night and a maximum of 8.9 hrs/night. The average CPAP applied was 8.4 ± 2.4 cm $H_2O$.

**Sleep Study Findings**

There were no significant differences in AHI, sleep stage distribution, sleep efficiency, sleep time, average and lowest $SaO_2$, and arousals between the two groups at baseline. From baseline to follow up the control group experienced no significant changes in BMI, AHI, sleep stage distribution, sleep efficiency, sleep time, average and lowest $SaO_2$, or frequency of arousals. The CPAP treated group also had no significant changes in BMI, sleep efficiency, and sleep time during the one month treatment period. However, the CPAP group did experience significant decreases in AHI, frequency of arousals, and combined stage 1 and 2 sleep (p=0.003, p=0.007 and p=0.043 respectively). The decrease in AHI and frequency of arousals in the CPAP treated group were significantly greater than in controls (p=0.031 and p=0.038 respectively). The CPAP treated group also experienced significant increases in the average and lowest SaO2 throughout the night (p=0.015 and p=0.002 respectively) that were significantly greater than the control group (p=0.019 and p=0.008 respectively) (see Table 2).

**Left Ventricular Ejection Fraction**

After the one month follow up period, there was no significant change in LVEF in the control group (27.7 ± 8.4 to 30.7 ± 9.1%, p=0.38). However, the CPAP group experienced a statistically significant increase in LVEF after one month (29.9 ± 13.4 to 37.4 ± 12.6%, p=0.002) (data not shown).

**QT Variability Results**

There was no significant difference in the QTVI at baseline between the control and CPAP treated group (-0.77 ± 0.83 and –0.37 ± 0.82, respectively). In the control group, there was no significant difference in QTVI from baseline to follow up (-0.77 ± 0.83 to –0.56 ± 0.73). In the CPAP treated group there was a significant reduction in the QTVI from baseline to one month (-0.37 ± 0.82 to –0.91 ± 0.55, p=0.006) that was statistically significant when compared with the control group (p=0.021) (see Fig. 1).

| | Control group(N=7) | | | CPAP treated group(N=11) | | |
|---|---|---|---|---|---|---|
| | Baseline | 1 mo | P-value | Baseline | 1 mo | P-value |
| Body mass index | 31.3 ± 5.1 | 31.7 ± 5.2 | NS | 28.8 ± 6.1 | 29.4 ± 6.1 | NS |
| AHI (no/hr sleep) | 45.0 ± 15.0 | 38.1 ± 15.3 | NS | 40.2 ± 22.8 | 6.0 ± 3.2 | <0.001 ‡ |
| Average $SaO_2$ (%) | 94.5 ± 2.0 | 94.2 ± 1.9 | NS | 94.5 ± 1.5 | 95.9 ± 1.5 | 0.015 * |
| Lowest $SaO_2$ (%) | 82.6 ± 7.0 | 78.8 ± 13.1 | NS | 81.8 ± 4.8 | 90.4 ± 3.5 | <0.001 \|\| |
| TST (min) | 288.4 ± 41.6 | 318.7 ± 47.3 | NS | 302.2 ± 74.3 | 325.3 ± 87.8 | NS |
| Sleep Efficiency (%) | 68.6 ± 10.8 | 74.0 ± 12.4 | NS | 68.2 ± 17.6 | 74.4 ± 17.3 | NS |
| Stage I and II sleep (% of TST) | 81.4 ± 7.1 | 78.6 ± 14.7 | NS | 83.9 ± 13.0 | 73.9 ± 14.0 | 0.043 |
| Stage III and IV sleep (% of TST) | 4.8 ± 5.2 | 5.2 ± 6.9 | NS | 8.0 ± 9.3 | 11.8 ± 12.1 | NS |
| REM sleep (% of total sleep time) | 13.9 ± 7.5 | 16.2 ± 9.4 | NS | 8.2 ± 5.7 | 14.2 ± 9.0 | NS |
| Arousals (no/hr sleep) | 42.8 ± 17.8 | 38.3 ± 11.6 | NS | 33.0 ± 21.9 | 11.7 ± 6.7 | 0.002 # |

**Table 2. Anthropomorphic and polysomnographic data.**
Abbreviations: NS = not significant, AHI = apnoea/hypopnoea index, SaO2 = arterial oxyhaemoglobin saturation, TST = total sleep time and REM = rapid eye movement. Values are means ± SD. There were no significant differences in baseline values between the control and CP treated groups.
P-values refer to comparisons of within-group baseline to one month values.
‡ P=0.006 compared to the control group
* P=0.019 compared to the control group
|| P=0.003 compared to the control group
# P=0.04 compared to the control group

## DISCUSSION

By measuring QTVI in a randomised group of patients with CHF and OSA we were able to determine the effects of one month of CPAP usage on the temporal lability of ventricular repolarisation. The main finding of this prospective randomized controlled trial, was that nocturnal CPAP therapy for one month significantly decreased beat-to-beat QT variability in patients with CHF and OSA, in conjunction with alleviating OSA. Our findings are the first to suggest that long-term CPAP therapy improves ventricular repolarisation lability which may decrease the risk of ventricular arrhythmias in patients with OSA and existing heart failure.

We speculate that there are at least two mechanisms by which CPAP reduces beat-to-beat QT variability. Firstly, it is well known that myocardial ischaemia can influence ventricular repolarisation through a variety of mechanisms, including acidosis, and elevated extracellular potassium, which can change the duration and shape of the ventricular action potential (20, 23). It has been shown that QTVI increased markedly during ischaemic episodes in patients with coronary artery disease (19). Franklin et al have demonstrated that OSA can trigger nocturnal myocardial ischemia in patients with coronary artery disease (18). Alleviation of OSA and apnoea related hypoxia caused reversal of myocardial ischaemia in these patients. Therefore, the reversal of intermittent nocturnal hypoxia with CPAP, as observed in our study, may have contributed to the reduction in QTVI. Secondly, beat-to-beat QT variability may be influenced by changes in sympathetic and vagal tone (15,17,24,25). Evidence for this autonomic modulation came from a study by Yeragani et al., in which QT variability was found to increase significantly in normal adults after sympathetic stimulation, such as a head tilt test (24). A similar increase in QT variability was also found by Piccirillo et al. in CHF patients (25). Since, application of CPAP to patients with CHF and/or OSA decreases sympathetic nerve activity (26-29) and increases vagal modulation of HR (30-32), accordingly, an improvement in autonomic cardiovascular regulation with CPAP may reduce beat-to-beat QT variability. Additionally, it was found that, along with an abolishment of apnoeas and an improvement in sleep, there was an increase in LVEF. This restitution, which has been shown to be due to a decrease in sympathetic nerve activity (11), further illustrates augmentation of overall cardiac function.

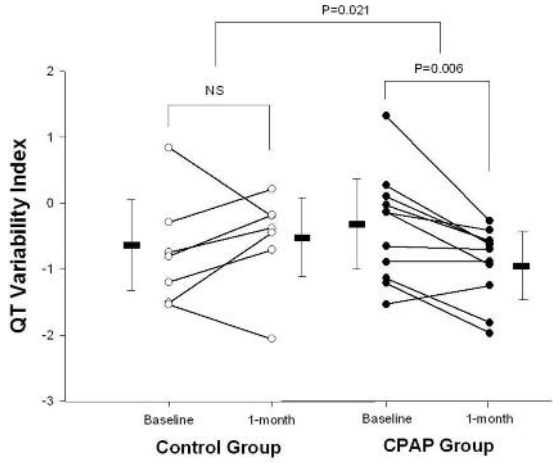


**Fig. 1. A comparison of QT variability index (QTVI) in the continuous positive airway pressure (CPAP) and control groups at baseline and one month follow-up.** In the control group there was no significant (NS) change in the QTVI from baseline to one month (-0.77 ± 0.83 to –0.56 ± 0.73). In contrast, there was a significant decrease in QTVI in the CPAP treated group (-0.37 ± 0.82 to –0.91 ± 0.55).
○ and ● are individual data for control and CPAP group respectively and □ are means ±SD.

## CONCLUSIONS

Long-term treatment of OSA by CPAP in patients with CHF improves LVEF, overall sleep, and reduces beat-to-beat QT variability. Although the mechanism is unknown, the abolition of apnoea related hypoxia with CPAP may serve to reduce myocardial ischemia and improve ventricular repolarisation lability. Furthermore, a decrease in sympathetic nerve activity and/or increases in vagal tone may also play a significant role. Because increased beat-to-beat QT variability identifies patients at higher risk of sudden cardiac death (14), the effect of CPAP in CHF patients with OSA on ventricular arrhythmias merits further study.

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