Heart Vessels (2016) 31:165–172
DOI 10.1007/s00380-014-0592-6

ORIGINAL ARTICLE

Effects of nocturnal oxygen therapy in patients with chronic heart failure and central sleep apnea: CHF-HOT study

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Received: 26 November 2013 / Accepted: 10 October 2014 / Published online: 28 October 2014

Abstract It was previously reported that nocturnal home oxygen therapy (HOT) significantly improved not only sleep disordered breathing (SDB), but also quality of life (QOL) and left ventricular ejection fraction (LVEF) in two trials. To strengthen the statistical reliability of the above efficacies of HOT and to assess the effects of 12-week nocturnal HOT on suppression of ventricular arrhythmias, we combined the two trials and undertook a post hoc analysis. Ninety-seven patients with chronic heart failure (CHF) and central sleep apnea were assigned to receive HOT (45 patients) or not (52 patients). HOT resulted in greater reduction in the apnea–hypopnea index (AHI) (-11.4 ± 11.0 vs. -0.2 ± 7.6 events/h, $p < 0.01$), which is associated with greater improvement in the Specific Activity Scale (0.8 ± 1.2 vs. 0.0 ± 0.6, $p < 0.01$), New York Heart Association (NYHA) functional class ($p < 0.01$), and LVEF ($p = 0.06$). Median number of premature ventricular contraction (PVC) at baseline was 17 beats per hour in both the HOT and the control groups. Overall improvements of PVCs were not different either in the HOT group or in the control. However, in 12 patients with NYHA ≥III and AHI ≥20 events/h, PVC was significantly improved by HOT with a marked reduction in AHI and a substantial increase in LVEF. In conclusion, among patients with CHF and CSA, HOT improves SDB, QOL, and cardiac function. The effectiveness of HOT for ventricular arrhythmias was not observed in the overall analysis, but only in a limited number of patients with severe CHF and SDB. To clarify the effects of HOT on ventricular arrhythmias in patients with CHF and SDB, a further study is needed.

Keywords Heart failure · Home oxygen therapy · Arrhythmia · Quality of life · Sleep apnea

Introduction

Central sleep apnea (CSA) is commonly seen in patients with chronic heart failure (CHF) [1–9], promotes progression of disease [10], and increases risk of mortality and morbidity independent of underlying cardiac disease [7, 11, 12]. CSA is also associated with an increased risk of cardiac arrhythmias [13]. Despite development of a number of pharmacological therapies, morbidity and mortality rates of CHF still remain high [14]. There have been substantial efforts to determine all treatable conditions that exacerbate CHF.

The underlying mechanisms of impaired prognosis in patients with CHF and CSA remain a subject of investigation. One possible explanation is an enhanced malignant arrhythmogenic risk because of alteration in sympathetic and parasympathetic nervous system activity occurring with sleep disordered breathing (SDB)-associated hypoxemia, acidosis, apneas, and arousal [15, 16]. Compared to patients with CHF alone, patients with CHF and CSA have shown an increasing frequency of premature ventricular contraction (PVC) as a surrogate parameter suggesting an augmented ventricular irritability caused by SDB.

In patients with CHF and CSA, nocturnal oxygen supplementation has been shown to improve O_2 saturation, as well

For the CHF-HOT Study Group.

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as to reduce the number of central respiratory events. Nocturnal oxygen supplementation also improves left ventricular function. Although oxygen therapy has also been shown to improve autonomic profile [8, 17], the effects on cardiac arrhythmias including PVC have not been characterized.

In the CHF-HOT study, 12-week treatment with nocturnal home oxygen therapy (HOT) significantly improved New York Heart Association (NYHA) functional class, Specific Activity Scale scores as a measure of quality of life (QOL), along with an improvement of Cheyne–Stokes respiration (CSR)/CSA in CHF patients [18]. Long-term study conducted after the CHF-HOT short-term study showed that the benefits of nocturnal HOT observed in the short-term study were sustained over a prolonged period of time [19]. Therefore, we expected that supplemental oxygen therapy is a valuable option for patients with CHF and CSR/CSA. Both trials recruited participants from the same sites using the same eligibility criteria and used the same methods to capture baseline clinical data and outcome measures. In the present analysis, we combined the data of the first 12 weeks of both clinical trials to strengthen the statistical reliability of previous clinical trials and to assess any potential effects of HOT on cardiac arrhythmias.

Materials and methods

Study design and intervention

The CHF-HOT studies were randomized, open-label, multi-center trials to determine efficacy of nocturnal HOT in patients with CHF and CSA [18, 19]. The short-term study was conducted on 56 patients with CHF and CSA [18]. Subsequently, a long-term trial was carried out on 51 patients to confirm the sustained efficacy [19]. Both studies included patients aged over 20 years from 20 centers with the following criteria: (1) symptomatic but stable NYHA class II or III despite optimal medication; (2) left ventricular ejection fraction (LVEF) equal or less than 45 %; (3) 4 % oxygen desaturation index (ODI) of equal or greater than 5 dips/h; (4) at least 5 episodes of apnea and hypopnea per hour of sleep, of which more than 50 % were central nature at the screening test. Exclusion criteria were predominantobstructive sleep apneas, unstable angina, myocardial infarction within the previous 3 months, and significant renal, neurological, or respiratory disease. Each patient was randomized by the methods of minimization by pre-specified factors and assigned to receive oxygen (at a rate of 3 L/min through a nasal cannula—HOT group) or not (control group). Oxygen was delivered via a 92 % concentrator (TO09003 N, Teijin Pharma Ltd, Japan).

To assess the effects of oxygen therapy on suppression of ventricular arrhythmias, we undertook a post hoc analysis of the CHF-HOT short-term and long-term data sets. We combined the two small trials because some patients can be excluded in this analysis due to artifacts or noise in Holter recordings which have an important effect on the accuracy of electrocardiogram diagnostic statements [20]. In addition, we performed subgroup analyses according to severity of CHF and CSA based on the Japanese Circulation Society (JCS) Guidelines for Diagnosis and Treatment

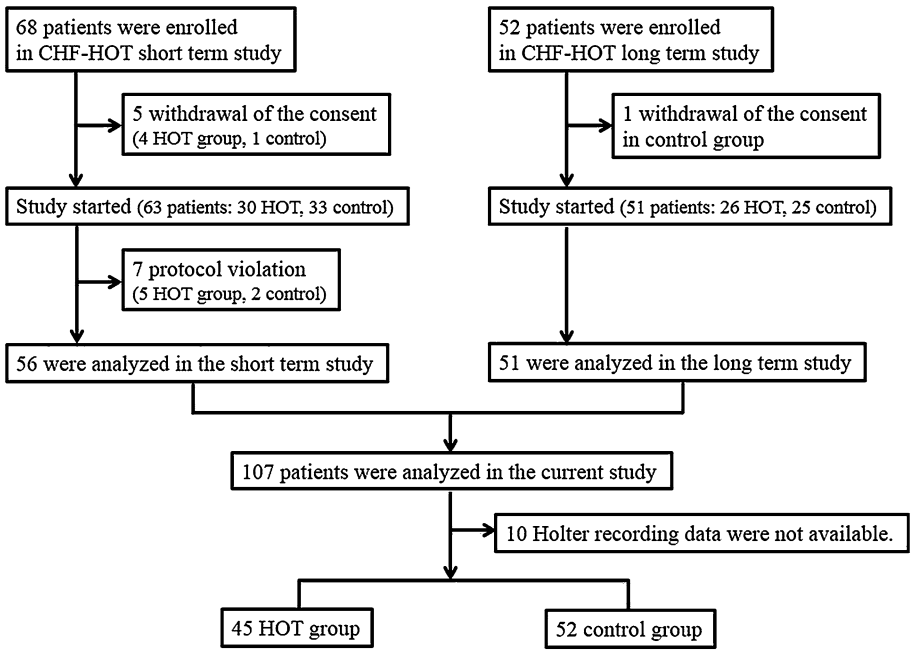

Fig. 1 Study flow chart. *CHF-HOT* chronic heart failure-home oxygen therapy, *HOT* home oxygen therapy

of Sleep Disordered Breathing in Cardiovascular Disease [21], which defined severe patients as those with NYHA classification ≥III and AHI ≥20 events/h.

Holter monitoring

All patients underwent Holter recording with 2-channel real-time recorders during nighttime at baseline and 12 weeks. Holter recordings were evaluated independently by two experienced cardiologists who were blinded to all clinical information. The severity of arrhythmias was classified according to Lown grade for PVCs: 0 = no PVCs; 1 = ≤30 PVC s/h; 2 = >30 PVC s/h; 3 = polymorphic (multiform) PVCs; 4 = repetitive PVCs (two or more consecutive PVCs); 5 = precocious PVCs. The effect of oxygen therapy on arrhythmias was evaluated using percentage changes in PVCs ([{PVCs at 12 weeks} − {PVCs at baseline}]/{PVCs at baseline} × 100 [%]) according to the following categories: significant improvements (≥75 % decrease); moderate improvements (50 % ≤PVCs decrease <75 %); mild improvements (25 % ≤PVCs decrease <50 %); no change (−25 % ≤PVCs decrease <25 %); worsening (>25 % PVCs increased).

Statistical analysis

Changes in NYHA functional class and PVCs improvement were tested by Mann–Whitney *U* test. Paired *t* test or Wilcoxon matched-pair signed-rank test was used to make comparisons within the group data. The comparison of the differences from baseline to 12 weeks between the HOT and control groups were tested by unpaired *t* test. Fisher's exact test was used to evaluate the significance of changes in Lown grade between the HOT and control groups. The comparison of the $p < 0.05$ values was considered statistically significant. All statistical analysis was conducted using STATA, version 12.1 (STATA, TX, USA).

Results

Patients characteristics

Of 107 patients, we excluded 10 patients because the Holter recording data were not available. We included 97 patients, of whom 45 patients were assigned to the HOT group and the remaining 52 patients to the control group (Fig. 1). There were no significant differences between the two groups with regard to any of the baseline characteristics shown in Table 1. PVCs were present in almost all patients, and varied from Lown grade 1–4. Complex PVCs (Lown grade 3–4) were observed in 91 patients (41 HOT group and 50 control group). No episodes of non-sustained ventricular tachycardia, sustained ventricular tachycardia, or ventricular fibrillation were documented at baseline.

Table 1 Clinical characteristics of CHF-HOT study

	HOT	Control	*P* value
n	45	52	
Age (years)	65.3 ± 10.8	66.5 ± 11.6	0.88
Male	36 (80.0 %)	44 (84.6 %)	0.46
Female	9 (20.0 %)	8 (15.4 %)	
Weight (kg)	61.9 ± 10.8	63.8 ± 11.2	0.32
Underlying heart disease			
Dilated cardiomyopathy	18 (40.0 %)	24 (46.2 %)	0.73
Ischemic heart disease	20 (44.4 %)	21 (40.4 %)	
Hypertensive heart disease	2 (4.4 %)	3 (5.8 %)	
Others	5 (11.1 %)	4 (7.7 %)	
Duration of heart failure (months)	32 (9–91)	57 (20–149)	0.25
Concomitant medication			
ACE inhibitor	40 (88.9 %)	35 (67.3 %)	0.85
Beta blocker	28 (62.2 %)	36 (69.2 %)	
Digitalis	23 (51.1 %)	19 (36.5 %)	
Diuretics	41 (91.1 %)	49 (94.2 %)	
Anti-arrhythmic agents	9 (20.0 %)	16 (30.8 %)	
Specific activity scale (Mets)	3.9 ± 1.2	4.1 ± 1.1	0.67
NYHA			
Class II	24 (53.3 %)	34 (65.4 %)	0.23
Class III	21 (46.7 %)	18 (34.6 %)	
Systolic blood pressure (mmHg)	119.2 ± 19.6	117.1 ± 19.0	0.51
Diastolic blood pressure (mmHg)	71.0 ± 10.5	69.5 ± 10.9	0.56
Heart rate (bpm)	67.5 ± 9.8	65.8 ± 9.8	0.96
LVEF (%)	33.6 ± 9.6	32.1 ± 8.3	0.60
CTR (%)	56.7 ± 6.9	56.2 ± 5.9	0.27
ODI (dips/h)	19.8 ± 9.8	18.7 ± 10.8	0.52
AHI (events/h)	20.0 ± 11.5	19.5 ± 11.3	0.74
BNP (pg/ml)	231 (92–564)	200 (93–410)	0.37
ANP (pg/ml)	100 (38–170)	71 (56–155)	0.63
NE (pg/ml)	543 (369–699)	560 (408–775)	0.69
$PaCO_2$ (mmHg)	38.6 ± 4.6	38.3 ± 4.5	0.50
PVCs (beats/h)	17 (3–59)	19 (4–91)	0.95
Percent PVCs (%)	0.5 (0.1–1.5)	0.5 (0.1–2.4)	0.95
Lown classification			
1	4 (8.9 %)	2 (3.8 %)	0.46
2	0 (0.0 %)	0 (0.0 %)	
3	12 (26.7 %)	17 (32.7 %)	
4a	14 (31.1 %)	21 (40.4 %)	
4b	15 (33.3 %)	12 (23.1 %)	

The values are mean ± SD or median (IQR)

ACE angiotensin converting enzyme, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *CTR* cardiothoracic ratio, *ODI* oxygen desaturation index, *AHI* apnea–hypopnea index, *BNP* brain natriuretic peptide, *ANP* atrial natriuretic peptide, *NE* norepinephrine, *$PaCO_2$* arterial partial pressure of carbon dioxide, *PVCs* premature ventricular contractions

Table 2 Effects of nocturnal oxygen on sleep, QOL, cardiac function, and arrhythmias in the overall analysis

	Groups	Baseline[a]	12 weeks[a]	Differences[b]	*P* value
AHI (events/h)	HOT	20.0 ± 11.5	8.6 ± 10.5	−11.4 ± 11.0	<0.01
	Control	19.5 ± 11.3	18.7 ± 12.2	−0.2 ± 7.6	
CAI (events/h)	HOT	8.1 ± 8.6	3.6 ± 6.6	−4.5 ± 7.3	<0.01
	Control	7.7 ± 8.1	7.9 ± 9.2	0.2 ± 6.6	
OAI (events/h)	HOT	2.4 ± 3.9	3.7 ± 6.9	1.3 ± 5.3	0.19
	Control	1.6 ± 2.8	1.7 ± 2.9	0.1 ± 2.6	
HI (events/h)	HOT	9.6 ± 5.6	1.6 ± 2.3	−8.0 ± 5.9	<0.01
	Control	9.6 ± 5.4	9.1 ± 6.7	−0.5 ± 4.9	
ODI (dips/h)	HOT	19.8 ± 9.8	5.4 ± 7.3	−14.4 ± 9.7	<0.01
	Control	18.1 ± 10.5	18.0 ± 11.5	-0.2 ± 7.2	
$PaCO_2$ (mmHg)	HOT	38.6 ± 4.6	39.6 ± 3.7	1.1 ± 3.6	0.83
	Control	38.3 ± 4.6	39.2 ± 5.1	0.9 ± 5.3	
SAS (Mets)	HOT	3.9 ± 1.2	4.7 ± 1.5	0.8 ± 1.2	<0.01
	Control	4.1 ± 1.1	4.1 ± 1.2	0.0 ± 0.6	
HR (bpm)	HOT	67.5 ± 9.8	66.0 ± 8.4	−1.5 ± 6.4	0.50
	Control	65.0 ± 9.4	64.3 ± 10.4	−0.7 ± 6.0	
LVEF (%)	HOT	33.9 ± 9.6	38.8 ± 13.8	5.2 ± 8.7	0.06
	Control	32.2 ± 8.4	34.0 ± 10.4	1.9 ± 7.5	
ANP (pg/ml)	HOT	100 (38–170)	85 (47−190)	−8.7 ± 63.7	0.50
	Control	71 (56–155)	68 (44–120)	−0.9 ± 46.8	
NE (pg/ml)	HOT	543 (369–699)	556 (339–763)	−8.1 ± 256	0.68
	Control	560 (408–775)	581 (409–726)	14.2 ± 271	
PVCs (b/h)	HOT	17 (3–59)	5 (2–61)	−27 ± 150	0.61
	Control	19 (4–91)	15 (4–88)	−13 ± 114	
% PVCs (%)	HOT	0.5 (0.1–1.5)	0.1 (0–1.4)	−0.6 ± 3.6	0.76
	Control	0.5 (0.1–2.4)	0.4 (0.1–2.1)	−0.3 ± 3.1	

QOL quality of life, *AHI* apnea–hypopnea index, *CAI* central apnea index, *OAI* obstructive apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index, $PaCO_2$ arterial partial pressure of carbon dioxide, *SAS* specific activity scale, *HR* heart rate, *CTR* cardiothoracic ratio, *LVEF* left ventricular ejection fraction, *BNP* brain natriuretic peptide, *ANP* atrial natriuretic peptide, *NE* norepinephrine, *PVCs* premature ventricular contractions, *b/h* beats per hour

‡ $p < 0.05$

¶ $p < 0.01$ compared with baseline with-in group by paired *t* test or Wilcoxon matched–pairs signed-ranks test

[a] Mean ± standard deviation or median (IQR)

[b] Data at 12 weeks minus at baseline

Effects of oxygen therapy on SDB, QOL and cardiac function

At 12 weeks, the patients assigned to the HOT group had a greater reduction in the AHI (apnea–hypopnea index), CAI (central apnea index) and HI (hypopnea index) than those in the control group (the change in AHI being −11.4 ± 11.0 vs. −0.2 ± 7.6 events/h, $p < 0.01$) (Table 2). LVEF improved significantly during the 12-week study period in the HOT group, while it remained unchanged in the control group. More patients improved in NYHA functional class in the HOT group than those in the control group (Fig. 2). Despite the improvement of NYHA and LVEF in the HOT group, there were no obvious changes in the plasma norepinephrine, atrial natriuretic peptide, and brain natriuretic peptide levels.

Effect on PVCs

In the overall analysis, average number of PVC at baseline was 17 beats per hour (b/h) in both HOT and 19 b/h in the control groups. Lown grade did not change over the short intervention period in both groups. Overall improvements of PVCs during 12 weeks were not different in the HOT and the control groups (54.6 vs. 49.9 %, $p = 0.92$). Since anti-arrhythmic agents can be proarrhythmic in heart failure

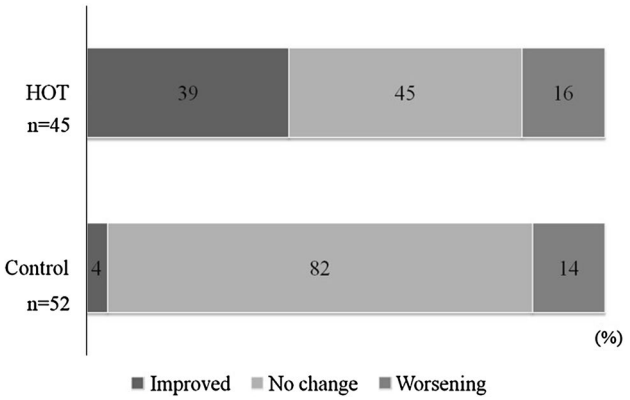

Fig. 2 Changes in NYHA class in the HOT and control groups in the overall analyses. NYHA class in the HOT group significantly improved as compared with the control group ($p = 0.02$). *NYHA* New York Heart Association, *HOT* home oxygen therapy

patients we have assessed the sub-analysis in patients without anti-arrhythmic agents ($n = 36$, each). No significant differences were found in these patients (data not shown).

Subgroup analyses

In subgroup analysis, 12 patients were regarded as severe (7 HOT group and 5 control group; Table 3). An improvement in Lown grade was observed only in the HOT group, although the change did not reach a significant level ($p = 0.21$; Fig. 3). In these patients, the number of hourly episodes of ventricular arrhythmia was reduced from 41 b/h to 4 b/h by 12 weeks of HOT ($p = 0.018$; Table 4). LVEF also improved significantly from 36.1 ± 11.8 to 46.3 ± 16.2 % in severe patients treated with HOT ($p = 0.014$; Table 4). In these severe patients, mean changes in AHI was −21.1 events/h (29.0 ± 8.8 to 7.9 ± 10.9 events/h) in the HOT group and +1.3 events/h (28.8 ± 4.1 to 30.1 ± 5.5 events/h) in the control group ($p = 0.006$; Table 4). Improvement of ODI at 12 weeks was also significantly greater in the HOT group as compared with the control group (−17.7 vs. 0.8 events/h; $p = 0.014$). The change from the baseline in the HOT group (10.1 ± 7.8 %) was significant as compared with the control group (2.0 ± 7.5 %) ($p = 0.016$).

In less severe patients, Specific Activity Scale progressively improved over 12 weeks in the HOT group (4.0 ± 1.2 to 4.8 ± 1.5, $p < 0.01$) while it remained unchanged in the control group (4.1 ± 1.1 to 4.1 ± 1.3). The difference between the groups at 12 weeks was highly significant (0.7 ± 1.2 in the HOT group and 0.0 ± 0.5 in the control group, $p < 0.001$). LVEF also improved significantly in "less severe" patients treated with HOT, but the difference between the two groups did not reach statistical significance.

Discussion

In the present study, the combined analysis of the two multi-center randomized controlled studies confirmed the previous observation that HOT significantly improves SDB,

Table 3 Clinical characteristics in severe and not severe patients

	Not severe (NYHA ≥2 and AHI ≥5 events/h, but not severe)		Severe (NYHA ≥3 and AHI ≥20 events/h)	
	HOT	Control	HOT	Control
n	38	47	7	5
Age (years)	65.3 ± 11.2	65.7 ± 11.8	65.6 ± 8.4	73.8 ± 5.8
Male/female	30/8	39/8	6/1	5/0
Specific activity scale (Mets)	4.0 ± 1.2	4.1 ± 1.1	3.6 ± 1.0	3.7 ± 1.1
NYHA class II/III	24/14	34/13	0/7	0/5
LVEF (%)	33.2 ± 9.3	32.2 ± 8.5	36.1 ± 11.8	30.7 ± 7.1
CTR (%)	56.4 ± 6.7	56.0 ± 6.1	58.7 ± 8.4	57.4 ± 4.3
AHI (events/h)	18.3 ± 11.2	18.5 ± 11.3	29.0 ± 8.8	28.8 ± 4.6
BNP (pg/ml)	228 (82–657)	194 (76–398)	235 (104–417)	236 (148–732)
PVCs (b/h)	16 (1–53)	17 (3–102)	41 (13–218)	77 (4–81)
% PVCs (%)	0.4 (0–1.5)	0.5 (0.1–2.8)	0.9 (0.6–4.4)	1.8 (0.1–1.9)
Lown grade				
1	4 (10.5 %)	2 (4.3 %)	0 (0 %)	0 (0 %)
2	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
3	11 (28.9 %)	16 (34.0 %)	1 (14.3 %)	1 (20 %)
4a	9 (23.7 %)	19 (40.4 %)	5 (29.4 %)	2 (40 %)
4b	14 (36.8 %)	10 (21.3 %)	1 (14.3 %)	2 (40 %)

Values are mean ± standard deviation or median (IQR) when appropriate

HOT home oxygen therapy, *NYHA* New York Heart Association, *LVEF* left ventricular ejection fraction, *CTR* cardiothoracic ratio, *AHI* apnea–hypopnea index, *BNP* brain natriuretic peptide, *PVCs* premature ventricular contractions, *b/h* beats per hour

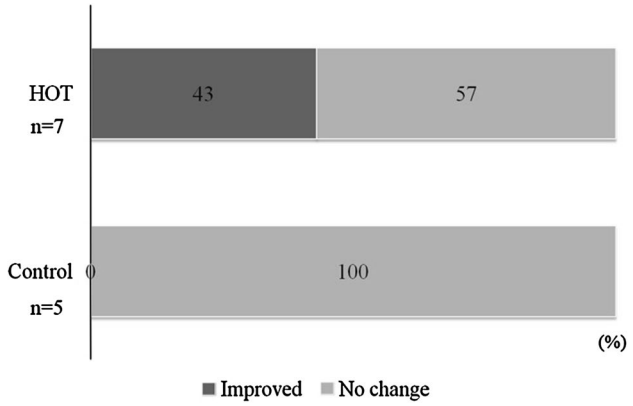

Fig. 3 Changes in Lown grade in patients with severe CHF and SDB. The patients who improved Lown grade appeared only in the HOT group, although the change did not reach a significant level ($p = 0.21$). *HOT* home oxygen therapy, *SDB* sleep disordered breathing

QOL and LVEF. Although overall improvements of PVCs during 12 weeks were not different in the HOT and the control groups, the data presented here show for the first time an efficacy of HOT on reduction of PVCs in patients with severer SDB and severer heart failure.

Ventricular arrhythmias including PVC are non-uniformly distributed over time in patients with congestive heart failure. It has also been suggested that the frequency and severity of ventricular arrhythmia could increase in SDB patients [15, 22, 23]. In moderate-to-severe SDB and CHF patients after implantation of a cardiac resynchronization device with cardioverter–defibrillator, CSA is independently associated with a shortened event-free survival time period until first monitored malignant ventricular arrhythmias [25]. SDB immediately modulates the autonomic nervous system during sleep which may be linked to nocturnal ventricular arrhythmias. In the Sleep Heart Health Study, individuals with SDB had three times the odds of non-sustained ventricular tachycardia, and almost twice the odds of complex ventricular ectopy compared with those without SDB even after adjustment for potential confounders [23]. It has been reported that the relative risk of nocturnal arrhythmia increased nearly 18-fold shortly after the occurrence of apneas and hypopneas during sleep [26]. Mechanisms by which CSA exerts modulatory effects on the autonomic nervous system at night include central respiratory–cardiac coupling in the brainstem, chemoreflexes stimulation, baroreflexes, and reflexes relating to lung inflation [26].

Recent studies provided evidence for CSA being a direct cause of ventricular arrhythmias by the demonstration of a reduction in the frequency of PVC in association with treatment of CSA with positive airway pressure [28–31]. On the other hand, overnight oxygen therapy has been suggested to be effective for ventricular arrhythmias in selected patients with CHF and SDB [32]. This may be related to improvement in cardiac sympathetic nerve activity by HOT [33, 34]. In the present analysis, we also found that the number of hourly episodes of ventricular arrhythmia was significantly improved by 12 weeks of HOT in patients with marked elevation in AHI and severe ventricular dysfunction. In contrast, patients with less severe SDB and heart failure did not respond to HOT in terms of reduction in PVCs.

The current Japanese Circulation Society guideline for Diagnosis and Treatment of Sleep Disordered Breathing in Cardiovascular Disease (JCS 2010) [21] recommends nocturnal oxygen treatment for severe patients defined as NYHA ≥III and AHI ≥20 events/h to improve SDB, QOL, and cardiac function. In our study, the nocturnal oxygen therapy appears to be effective in preventing ventricular arrhythmias in patients with severe heart failure and severe SDB.

This study has several limitations. First, this is the post hoc analysis of a subset of CHF-HOT patients. Second, we evaluated the effect of HOT on ventricular arrhythmias from Holter monitoring during nighttime when parasympathetic activity was dominant. Detailed information regarding daytime arrhythmias prevalence is not readily available. However, the AHI correlated directly with the relative risk of sudden cardiac death during the sleeping hours, and people with SDB have a peak in sudden cardiac death from midnight to 6 a.m. [28]. We evaluated the important ventricular arrhythmias which could lead to sudden cardiac death. Third, 12 weeks duration of therapy has been insufficient to fully demonstrate the potential effects of HOT on cardiovascular outcomes. Adequate investigation of low-frequency events would have required longer durations. Fourth, in this study we could not consider intra-patient day-to-day variability in the frequency and type of arrhythmias. A previous study showed that, since short-term reproducibility of data between Holter recordings was poor, large reduction (63–95 %) in arrhythmia frequency would be required to ensure that the change was an effect of treatment [35, 36]. We would need a relatively large sample to prove a treatment effect.

In conclusion, HOT improves SDB, QOL and cardiac function in patients with CHF and CSA. The effectiveness of HOT for ventricular arrhythmias was not observed in the overall analysis, but only in the subgroup analysis of patients with severe CHF and SDB. To clarify the effects of HOT on ventricular arrhythmias in patients with CHF and SDB, a long-term and large-scale study is needed.

Table 4 Effects of nocturnal oxygen on sleep, QOL, cardiac function, and arrhythmias

	Groups	Not severe (NYHA ≥2 and AHI ≥5 events/h, but not severe) ($n = 85$; 38 in HOT, 47 in control)				Severe (NYHA ≥3 and AHI ≥20 events/h) ($n = 12$; 7 in HOT, 5 in control)			
		Baseline[a]	12 weeks[a]	Differences[b]	*P* value	Baseline[a]	12 weeks[a]	Differences[b]	*P* value
AHI (events/h)	HOT	18.3 ± 11.2	8.7 ± 10.7[¶]	−9.6 ± 9.4	<0.001	29.0 ± 8.8	7.9 ± 10.7[¶]	−21.1 ± 14.7	0.008
	Control	17.9 ± 11.0	17.3 ± 12.0	-0.6 ± 7.6		28.8 ± 4.6	31.7 ± 4.3	2.9 ± 7.0	
CAI (events/h)	HOT	7.2 ± 8.1	3.7 ± 6.9[¶]	−3.5 ± 6.0	0.021	13.3 ± 10.0	3.4 ± 5.5	−9.8 ± 11.5	0.052
	Control	6.9 ± 7.9	6.5 ± 8.5	-0.3 ± 6.0		15.6 ± 6.8	20.1 ± 5.0	4.5 ± 10.5	
OAI (events/h)	HOT	2.5 ± 4.0	3.6 ± 7.2	1.1 ± 5.6	0.372	2.0 ± 4.0	4.3 ± 5.7[‡]	2.4 ± 2.3	0.059
	Control	1.4 ± 2.7	1.6 ± 2.9	0.2 ± 2.7		3.5 ± 3.7	3.1 ± 3.0	−0.4 ± 2.0	
HI (events/h)	HOT	8.9 ± 4.7	1.7 ± 2.3[¶]	−7.2 ± 5.2	<0.001	13.8 ± 8.5	1.6 ± 2.3[¶]	−12.2 ± 8.3	0.032
	Control	9.6 ± 5.6	9.2 ± 7.0	−0.5 ± 4.8		9.8 ± 3.8	8.5 ± 4.4	−1.3 ± 6.0	
ODI (dips/h)	HOT	19.1 ± 9.7	5.3 ± 7.1[¶]	−13.7 ± 8.6	<0.001	23.7 ± 10.3	6.0 ± 8.9[‡]	−17.7 ± 14.8	0.015
	Control	17.4 ± 10.7	16.9 ± 11.7	−0.4 ± 7.5		24.7 ± 5.3	27.0 ± 3.8	2.3 ± 3.0	
$PaCO_2$ (mmHg)	HOT	38.5 ± 4.5	39.5 ± 3.9	1.0 ± 3.4	0.711	39.0 ± 5.8	40.6 ± 2.5	1.6 ± 4.9	0.504
	Control	38.4 ± 4.7	39.0 ± 5.1	0.6 ± 5.4		37.9 ± 3.2	41.6 ± 5.3	3.7 ± 4.6	
SAS (Mets)	HOT	4.0 ± 1.2	4.7 ± 1.5[¶]	0.7 ± 1.2	<0.001	3.6 ± 1.0	4.6 ± 1.5	0.9 ± 1.1	0.109
	Control	4.1 ± 1.1	4.1 ± 1.3	0.0 ± 0.5		3.7 ± 1.1	3.5 ± 0.6	−0.2 ± 1.0	
HR (bpm)	HOT	66.5 ± 8.9	65.6 ± 8.8	−0.9 ± 5.5	0.710	73.0 ± 12.8	68.1 ± 5.2	−4.9 ± 9.9	0.674
	Control	65.2 ± 9.6	64.8 ± 10.6	−0.4 ± 6.2		63.2 ± 8.3	60.4 ± 8.6	−2.8 ± 4.1	
LVEF (%)	HOT	33.2 ± 9.3	37.2 ± 12.9	4.2 ± 8.6	0.276	36.1 ± 11.8	46.3 ± 16.2	10.1 ± 7.8	0.036
	Control	32.2 ± 8.5	34.4 ± 10.6	2.2 ± 7.4		30.7 ± 7.1	29.5 ± 7.7	−1.2 ± 8.1	
CTR (%)	HOT	56.4 ± 6.7	57.8 ± 6.6[¶]	1.4 ± 2.8	<0.001	60.4 ± 7.9	57.8 ± 9.9	−2.6 ± 4.0	0.217
	Control	55.7 ± 6.1	55.0 ± 5.8	−0.6 ± 2.3		57.4 ± 4.3	57.3 ± 4.7	0.0 ± 1.6	
BNP (pg/ml)	HOT	228 (82–657)	296 (3–2960)	41.7 ± 148	0.007	235 (104–417)	105 (50–482)	−67.5 ± 132.7	0.904
	Control	194 (76–398)	150 (2–1130)[‡]	−33.9 ± 94.0		236 (148–732)	287 (102–567)	−58.9 ± 89.6	
ANP (pg/ml)	HOT	105 (33–170)	99 (50–200)	−0.6 ± 58.9	0.953	67 (38–200)	58 (35–89)	−51.1 ± 75.9	0.280
	Control	72 (55–140)	66 (44–115)	0.1 ± 48.3		70 (60–180)	83 (46–120)	−9.4 ± 33.1	
NE (pg/ml)	HOT	545 (351–714)	555 (370–772)	−6.5 ± 246	0.822	483 (459–647)	556 (278–754)	−16.3 ± 324	0.549
	Control	563 (424–786)	577 (396–734)	6.9 ± 283		498 (377–560)	710 (409–725)	78.8 ± 116	
PVCs (b/h)	HOT	16 (1–53)	5 (2–78)	−7.4 ± 103	0.694	41 (13–218)	4 (1–14) [‡]	−68 ± 201	0.963
	Control	17 (3–102)	13 (3–85)	−18.6 ± 157		77 (4–81)	25 (16–134)	−72 ± 92	
% PVCs (%)	HOT	0.4 (0–1.5)	0.2 (0.1–2)	−0.2 ± 2.8	0.788	0.9 (0.6–4.4)	0.1 (0–0.3)[‡]	−1.7 ± 5.1	0.892
	Control	0.5 (0.1–2.8)	0.3 (0.1–1.8)	−0.4 ± 3.9		1.8 (0.1–1.9)	0.6 (0.5–4.2)	−1.4 ± 1.4	

QOL quality of life, *NYHA* New York Heart Association, *AHI* apnea–hypopnea index, *CAI* central apnea index, *OAI* obstructive apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index, *$PaCO_2$* arterial partial pressure of carbon dioxide, *SAS* specific activity scale, *HR* heart rate, *CTR* cardiothoracic ratio, *BNP* brain natriuretic peptide, *ANP* atrial natriuretic peptide, *NE* norepinephrine

[‡] $p < 0.05$

[¶] $p < 0.01$ compared with baseline with-in group by paired *t* test or Wilcoxon matched-pair signed-rank test

[a] Mean ± standard deviation or median (IQR)

[b] Data at 12 weeks minus at baseline

References

1. Javaheri S, Parker TJ, Wexler L, Michaels SE, Stanberry E, Nishyama H, Roselle GA (1995) Occult sleep-disordered breathing in stable congestive heart failure. Ann Intern Med 122:487–492
2. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA (1998) Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation 97:2154–2159
3. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD (1999) Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 160:1101–1106
4. Lofaso F, Verschueren P, Rande JL, Harf A, Goldenberg F (1994) Prevalence of sleep-disordered breathing in patients on a heart transplant waiting list. Chest 106:1689–1694
5. Tremel F, Pépin JL, Veale D, Wuyam B, Siché JP, Mallion JM, Lévy P (1999) High prevalence and persistence of sleep apnoea

in patients referred for acute left ventricular failure and medically treated over 2 months. Eur Heart J 20:1201–1209
6. Solin P, Bergin P, Richardson M, Kaye DM, Walters EH, Naughton MT (1999) Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation 99:1574–1579
7. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P (1999) Prognostic value of nocturnal Cheyne–Stokes respiration in chronic heart failure. Circulation 99:1435–1440
8. Staniforth AD, Kinnear WJ, Starling R, Cowley AJ (1998) Nocturnal desaturation in patients with stable heart failure. Heart 79:394–399
9. Yasuma F, Nomura H, Hayashi H, Okada T, Tsuzuki M (1989) Breathing abnormalities during sleep in patients with chronic heart failure. Jpn Circ J 53:1506–1510
10. Miyata M, Yoshihisa A, Yamauchi H, Owada T, Sato T, Suzuki S, Sugimoto K, Yamaki T, Kunii H, Nakazato K, Suzuki H, Saitoh SI, Takeishi Y (2014) Impact of sleep-disordered breathing on myocardial damage and metabolism in patients with chronic heart failure. Heart Vessels. doi:10.1007/s00380-014-0479-6
11. Garcia-Touchard A, Somers VK, Olson LJ, Caples SM (2008) Central sleep apnea: implications for congestive heart failure. Chest 133:1495–1504
12. Hanly PJ, Zuberi-Khokhar NS (1996) Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. Am J Respir Crit Care Med 153:272–276
13. Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P (2003) Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation 107:727–732
14. Misra A, Mann DL (2008) Treatment of heart failure beyond practice guidelines. Role of cardiac remodeling. Circ J 72(Suppl A):A1–A7
15. Guilleminault C, Connolly SJ, Winkle RA (1983) Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 52:490–494
16. Leung RS, Diep TM, Bowman ME, Lorenzi-Filho G, Bradley TD (2004) Provocation of ventricular ectopy by Cheyne–Stokes respiration in patients with heart failure. Sleep 27:1337–1343
17. Andreas S, Clemens C, Sandholzer H, Figulla HR, Kreuzer H (1996) Improvement of exercise capacity with treatment of Cheyne–Stokes respiration in patients with congestive heart failure. J Am Coll Cardiol 27:1486–1490
18. Sasayama S, Izumi T, Seino Y, Ueshima K, Asanoi H, Group C-HS (2006) Effects of nocturnal oxygen therapy on outcome measures in patients with chronic heart failure and Cheyne–Stokes respiration. Circ J 70:1–7
19. Sasayama S, Izumi T, Matsuzaki M, Matsumori A, Asanoi H, Momomura S, Seino Y, Ueshima K, Group C-HS (2009) Improvement of quality of life with nocturnal oxygen therapy in heart failure patients with central sleep apnea. Circ J 73:1255–1262
20. Zywietz C, Celikag D, Joseph G (1996) Influence of ECG measurement accuracy on ECG diagnostic statements. J Electrocardiol 29(Suppl):67–72
21. JCS Joint Working Group (2010) Guidelines for diagnosis and treatment of sleep disordered breathing in cardiovascular disease (JDS 2010). Circ J 74:963–1051
22. Guilleminault C, Connolly S, Winkle R, Melvin K, Tilkian A (1984) Cyclical variation of the heart rate in sleep apnoea syndrome. Mechanisms, and usefulness of 24 h electrocardiography as a screening technique. Lancet 1:126–131
23. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, Sahadevan J, Redline S, Study SHH (2006) Association of nocturnal arrhythmias with sleep-disordered breathing: the sleep heart health study. Am J Respir Crit Care Med 173:910–916
24. Yamada S, Suzuki H, Kamioka M, Suzuki S, Kamiyama Y, Yoshihisa A, Saitoh S, Takeishi Y (2013) Sleep-disordered breathing increases risk for fatal ventricular arrhythmias in patients with chronic heart failure. Circ J 77:1466–1473
25. Bitter T, Westerheide N, Prinz C, Hossain MS, Vogt J, Langer C, Horstkotte D, Oldenburg O (2011) Cheyne–Stokes respiration and obstructive sleep apnoea are independent risk factors for malignant ventricular arrhythmias requiring appropriate cardioverter–defibrillator therapies in patients with congestive heart failure. Eur Heart J 32:61–74
26. Monahan K, Storfer-Isser A, Mehra R, Shahar E, Mittleman M, Rottman J, Punjabi N, Sanders M, Quan SF, Resnick H, Redline S (2009) Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol 54:1797–1804
27. Leung RS (2009) Sleep-disordered breathing: autonomic mechanisms and arrhythmias. Prog Cardiovasc Dis 51:324–338
28. Gami AS, Howard DE, Olson EJ, Somers VK (2005) Day–night pattern of sudden death in obstructive sleep apnea. N Engl J Med 352(12):1206–1214
29. Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafakas NS, Vardas PE (2004) Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment. A long-term evaluation using an insertable loop recorder. Eur Heart J 25:1070–1076
30. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, Shamsuzzaman A, Somers VK (2003) Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 107:2589–2594
31. Javaheri S (2000) Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 101:392–397
32. Suzuki J, Ishihara T, Sakurai K, Inagaki H, Kawabata M, Hachiya H, Akihiro Hata, Hirano K, Hasegawa M, Isobe M (2006) Oxygen therapy prevents ventricular arrhythmias in patients with congestive heart failure and sleep apnea. Circ J 70:1142–1147
33. Toyama T, Seki R, Kasama S, Isobe N, Sakurai S, Adachi H, Hoshizaki H, Oshima S, Taniguchi K (2009) Effectiveness of nocturnal home oxygen therapy to improve exercise capacity, cardiac function and cardiac sympathetic nerve activity in patients with chronic heart failure and central sleep apnea. Circ J 73:299–304
34. Iwaya S, Yoshihisa A, Nodera M, Owada T, Yamada S, Sato T, Suzuki S, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh SI, Takeishi Y (2013) Suppressive effects of adaptive servo-ventilation on ventricular premature complexes with attenuation of sympathetic nervous activity in heart failure patients with sleep-disordered breathing. Heart Vessels. doi:10.1007/s00380-013-0394-2
35. DiMarco JP, Philbrick JT (1990) Use of ambulatory electrocardiographic (Holter) monitoring. Ann Intern Med 113:53–68
36. Crawford MH, Bernstein SJ, Deedwania PC, DiMarco JP, Ferrick KJ, Garson A Jr, Green LA, Greene HL, Silka MJ, Stone PH, Tracy CM, Gibbons RJ, Alpert JS, Eagle KA, Gardner TJ, Gregoratos G, Russell RO, Ryan TH, Smith SC Jr (1999) ACC/AHA guidelines for ambulatory electrocardiography. A report of the American College of Cardiology/American heart association task force on practice guidelines (Committee to Revise the Guidelines for Ambulatory Electrocardiography). Developed in collaboration with the North American Society for Pacing and Electrophysiology. J Am Coll Cardiol 34(3):912–948