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Effects of Nocturnal Oxygen Therapy on Outcome Measures in Patients With Chronic Heart Failure and Cheyne-Stokes Respiration

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Background The effects of nasal oxygen (O_2) supply at night using conventional home oxygen therapy (HOT) equipment on quality of life (QOL) and sleep-disordered breathing (SDB) were evaluated in patients with congestive heart failure (CHF). Nasal nocturnal O_2 therapy not only stabilizes SDB but also reduces sympathetic activity, and improves exercise capacity in patients with CHF. However, the effects of oxygen on the cardiac function and QOL of heart failure patients have not been fully elucidated.

Methods and Results Fifty-six patients with CHF (New York Heart Association class Ⅱ–Ⅲ, left ventricular ejection fraction (LVEF) ≤45%) and central sleep apnea (CSA) with Cheyne-Stokes respiration (CSR) were randomly assigned to receive either nocturnal O_2 (HOT group, n=25) or usual breathing (control group, n=31) for 12 weeks. Respiration, airflow and arterial oxygen levels were monitored with determination of apnea/hypopnea index (AHI) and oxygen desaturation index (ODI) during sleep. LV function was determined by radionuclide angiography or echocardiography. QOL was assessed by the Specific Activity Scale questionnaire. In the HOT group, nocturnal O_2 resulted in significant improvements in AHI (21.0±10.8 to 10.0±11.6 events/h, mean ± SD, $p<0.001$), ODI (19.5±9.8 to 5.9±8.7 dips/h, $p<0.001$) and Specific Activity scale (4.0±1.2 to 5.0±1.5 Mets, $p<0.001$). LVEF also increased from baseline to the end of the study (34.7±10.4 to 38.2±13.6%, $p=0.022$).

Conclusions In patients with stable CHF and CSR, HOT at night improves SDB, LV function and QOL, and thus is a valuable nonpharmacological option for the treatment of patients with CHF and CSR-CSA. (*Circ J* 2006; **70:** 1–7)

Key Words: Non-pharmacological treatment; Sleep-disordered breathing; Specific Activity Scale

The syndrome of congestive heart failure (CHF) is the common final pathway of many cardiovascular diseases and is regarded as highly lethal[1] Over the past several decades, remarkable advances have been made in the medical treatment of CHF and most recently, there is increasing evidence that sleep apnea may adversely affect the pathophysiology and outcomes of CHF[2–7] Repetitive nocturnal apneas may worsen CHF though a number of mechanisms, including repetitive arterial oxygen desaturation, increased left ventricular (LV) afterload, or activation of the sympathetic nervous system. Although central sleep apnea (CSA) is relatively rare, prospective studies have revealed that 33–82% of patients with CHF have evidence of CSA and characteristic Cheyne-Stokes respiration (CSR), even in the absence of profound oxygen desaturation[8–14] The rate and depth of breathing are normally regulated to maintain the partial pressure of arterial carbon dioxide (CO_2) within a narrow range. In patients with CHF, Javaheri demonstrated a significant positive correlation between sensitivity to CO_2 and the number of episodes of apnea and hypopnea per hour during sleep and suggested that heart failure patients with associated CSA have a greater sensitivity to CO_2 leading to a larger ventilatory response for a given rise in the partial pressure of arterial CO_2 ($PaCO_2$) and resultant CSA with falls of $PaCO_2$ driven by the consequent hyperventilation[15] A number of factors predispose heart failure patients to develop nocturnal hypoxemia, which may play an important role in the further deterioration of heart failure and sleep structure and respiration[16] A potential role of oxygen (O_2) in correcting hypoxemia and reducing CSR, thereby improving CHF, has been suggested by previous studies[16–21] However, in these studies, the sampling size has been small, follow-up period short and the results inconclusive. In the present study, the efficacy of nasal O_2 therapy at night using a conventional O_2 concentrator on ventricular function, severity of heart failure, and quality of life (QOL), together with an improvement in sleep-disordered breathing (SDB) was assessed in ambulatory patients with stable CHF and CSR. In particular, because mortality of patients with heart failure is relatively low in Japan compared with Western populations[22,23] emphasis was placed on an improvement in QOL as an outcome measure.

Methods

Study Population

Ambulatory patients aged over 20 years with clinical evidence of CHF were enrolled from 20 centers if they met the following criteria: (1) symptomatic and New York Heart Association (NYHA) class Ⅱ or Ⅲ despite optimal

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Members of the The CHF-HOT Study Group are listed in Appendix 1

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medication for at least 2 weeks prior to entry, (2) LV ejection fraction (LVEF) determined by radionuclide angiography or left ventriculography within 6 months of the diagnostic sleep study ≤45%, (3) 4% oxygen desaturation index (ODI) of ≥5 dips/h on pulse oximetry, (4) at least 5 episodes of apnea and hypopnea per hour of sleep, of which more than 50% were central at screening test.[24] Exclusion criteria were: predominant obstructive sleep apnea (OSA), pregnancy, unstable angina, myocardial infarction within the previous 3 months, and significant renal, neurological, or respiratory disease.

The study protocol was approved by the Institutional Ethics Review Board and written informed consent was given by all patients prior to entry.

Study Design, Intervention and Procedures

Each patient was assessed by one of the investigators listed in the Appendix. At baseline before randomization and commencement of treatment, a comprehensive history was taken and a physical examination was performed. Each patient underwent routine clinical assessment including radiologic, electrocardiographic and echocardiographic studies and radionuclide or echocardiographic LVEF was determined.

In the preliminary study, the amount of O_2 delivered was determined by pulse oximetry recordings in another group of 11 patients hospitalized with LV dysfunction and periodic oxygen desaturation (LVEF 40.8±17.0, ODI ≥5 dips/h). Patients received an incremental level of overnight nasal O_2 for 3 nights (1, 2 and 3 L/min). Oxygen desaturation frequency was markedly reduced by 3 L/min of O_2, ODI being less than 5 dips/h in all patients. On the basis of these findings, the O_2 dosage was determined to be 3 L/min in this CHF-home oxygen therapy (HOT) study.

The investigators sent a fax to the coordinating center when they enrolled a new patient. Randomization was then performed according to the method of minimization by 5 factors (laboratory, age, sex, Specific Activity Scale score and ODI) and each patient was assigned to receive O_2 at a rate of 3 L/min through nasal cannulae (HOT group) or to allow usual breathing for 12 weeks (control group).

O_2 was delivered via 92% oxygen concentrator (TO-90–3N, Teijin Pharma Ltd, Japan). The patients assigned to the HOT were instructed to use nasal O_2 for at least 6 h per night. Compliance was monitored by patients' reports and the in-built concentrator tachometer (TOMS®, Teijin Pharma Ltd, Japan). Physical examination, assessment of the severity of heart failure (NYHA functional class) and the Specific Activity Scale[25] were repeated every 4 weeks. Polysomnography (PSG) or polygraphic recordings of cardiorespiratory parameters, assessment of LVEF and measurement of plasma norepinephine (NE) levels were performed at baseline and at the conclusion of the study at 12 weeks.

Outcome Variables

SDB Indicators The patients who met the inclusion criteria were monitored by PSG and if that was not available a cardiorespiratory monitoring device (Somté, Compumedics, Australia) was used. Oronasal signals detected by thermister were used as the respiratory sensors, thoracic and abdominal effort was measured by 2 belt sensors. Arterial O_2 saturation (SpO_2) was recorded by digital pulse oximetry (sampling frequency of 1 s). Surface lead electrocardiogram was also monitored throughout the night. The respiratory event detection and oximetry analysis were performed manually. The oximeter signal quality of the cardiorespiratory monitoring device was proved to be valid in comparison with PSG[26] Home respiratory polygraphy has also been confirmed as a useful alternative to overnight PSG for diagnosis of SDB in heart failure.[27]

Standard definitions were used for OSA and CSA on the basis of the presence or absence of rib cage and abdominal excursions with an absence of airflow.[24] OSA and CSA may coexist in the same individual and patients with OSA may have a waxing and waning pattern of breathing. These patients could be identified because they had a constant or increasing respiratory effort during the event.[24] Patients with purely or predominantly OSA were not included in this study. The ODI was the number of times per hour that the oxyhemoglobin saturation fell by 4% and the apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour during the time in bed. CSR-CSA was defined as at least 3 cycles of a crescendo and decrescendo change in breathing amplitude.[24]

Assessment of QOL We used the Specific Activity Scale as a measure of QOL in which self-perceived exercise tolerance is expressed by an energy cost spent with the maximal physical activities that the patient can perform.[25] Most of the exercise tests are designed to evaluate exercise performance at maximal workloads, but daily activities do not require an energy expenditure in the maximal range. In this regard, the Specific Activity Scale allows expression of the extent of submaximal physical activities.

We actually measured the metabolic costs of various types of physical activity by hooking subjects up to a mask to measure oxygen consumption and the volume of CO_2 exhaled. Oxygen consumption can be estimated by the equation $\dot{V}E \times (\text{inspired } [O_2] - \text{expired } [O_2])$, where $\dot{V}E$ is ventilation equivalent and $[O_2]$ is oxygen concentration units (ml/L). By definition, 1 Met is equivalent to a metabolic rate consuming 3.5 ml of oxygen per kilogram of body weight per minute. Next we prepared questionnaires about specific physical activities that a patient would perform either customarily or sporadically in daily life and each patient was asked to specify whether he/she could perform each type of activity without symptomatic limitation. Summarizing the questionnaire data, a given number of metabolic costs (Specific Activity Scale) were derived for each patient regarding the self-perceived exercise tolerance. As a clear linear correlation was observed between Specific Activity Scale and peak O_2 consumption,[25] the Specific Activity Scale was considered to reliably predict exercise capacity.

Ventricular Function LVEF was followed up using either ^{99m}Tc equilibrium radionuclide angiography or 2-dimensional (D) echocardiography at rest during the daytime while patients were awake. In each institution that participated in this study, all the measurements were performed by technicians in the individual laboratories, so they were unaware of the treatment allocation. Gated equilibrium radionuclide angiography was performed using the in vivo red blood cell labeling technique with initial intravenous stannous pyrophosphate followed by ^{99m}Tc pertechnetate. LV time–activity curves were generated by the multiple gated acquisition program and the end-diastolic and end-systolic frames were determined from these 2-D echocardiographic images were acquired from the parasternal long and short axes, apical longitudinal axis, apical 4-chamber, and subcostal views. The LV end-diastolic and end-systolic dimensions were determined according to a modification of

Table 1 Baseline Characteristics of the Patients

	HOT	N	Control	N	p value
Age (years) (range)	*64.1±11.6 (34–78)*	*25*	*64.1±10.2 (40–81)*	*31*	*0.985*
M/F (%)	*20/5 (80.0/20.0)*	*25*	*27/4 (87.1/12.9)*	*31*	*0.472*
Underlying heart disease					
DCM/IHD/others (n)	*12/11/2*	*25*	*14/13/4*	*31*	*0.906*
Duration of CHF (years)	*3.5±4.5*	*25*	*4.8±4.2*	*31*	*0.284*
Concomitant medication					
Digi/Diur/ACE/β (n)	*16/23/20/14*	*25*	*15/28/18/21*	*31*	*–*
SAS (Mets)	*4.0±1.2*	*25*	*4.1±1.1*	*31*	*0.777*
NYHA class II/III (n)	*9/16*	*25*	*14/17*	*31*	*0.489*
LVEF (%)	*34.7±10.4*	*24*	*32.8±8.8*	*29*	*0.480*
ODI (dips/h)	*19.5±9.8*	*25*	*16.4±10.6*	*30*	*0.268*
AHI (events/h)	*21.0±10.8*	*25*	*18.0±10.7*	*31*	*0.306*
NE (pg/ml)	*619.6±310.0*	*25*	*595.4±286.0*	*31*	*0.762*

HOT, home oxygen therapy; DCM, dilated cardiomyopathy; IHD, ischemic heart disease; CHF, congestive heart failure; Digi, digitalis; Diur, diuretics; ACE, angiotensin-converting enzyme inhibitor; β, β-blockers; SAS, specific activity scale; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ODI, oxygen desaturation index; AHI, apnea hypopnea index; NE, norepinephrine.
p value = calculated by the chi-square test, unpaired t-test or Mann-Whitney U test. Mean ± SD.

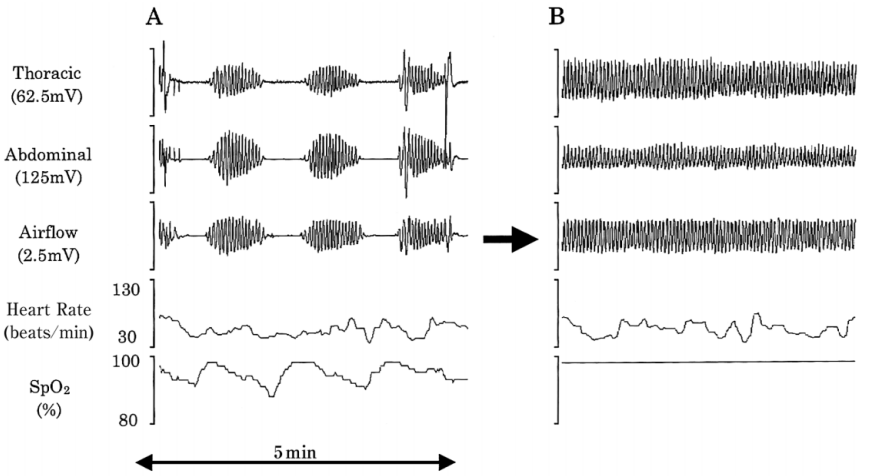

Fig 1. Effect of oxygen on central sleep apnea (CSA). Polygraphical recordings in patient with CSA and severe heart failure with reduced left ventricular function. At the baseline recordings (A), there is gradual waxing and waning of respiration followed by a central apnea. After 12 weeks of oxygen treatment (B), the breathing pattern has completely normalized associated with a stabilization of arterial O_2 saturation (SpO_2).

Simpson's method. LVEF was calculated as end-diastolic minus end-systolic volume divided by end-diastolic volume.

Plasma Concentration of NE Venous blood samples were drawn through an indwelling catheter in the forearm of each patient after they had lain quietly and undisturbed for at least 30 min. Plasma was immediately separated and stored at –70°C before the NE concentrations were determined by high performance liquid chromatography electrochemical detection.

Statistical Analysis

All statistical analyses were performed with StatView® version 5.0 (Abacus Concepts, Calabasus, CA, USA) or SAS® version 8.2 (Cary, NC, USA). Results are expressed as mean ± standard deviation (SD). The target number of patients was calculated to be 20 in each group, based on a 5% type I error, a 2-sided test, and an 80% power, using a t-test.

For the Specific Activity Scale, 2-way repeated measures analysis of variance (ANOVA) with 2 factors (group and time) was applied. When statistical significance was found in group×time interaction, post hoc analyses were performed.

For ODI, AHI, heart rate during sleep, LVEF, blood pressure and plasma NE levels, unpaired t-tests were used to compare data at each point between the control and HOT groups, as well as to compare changes in variables from baseline to the end of study between the 2 groups. Paired t-tests were used to compare within-group data at baseline and the end of the study. Changes in NYHA functional class were summed in each group and the differences in response were tested by Mann-Whitney U test. Missing values were imputed using the Last-Observation-Carried-Forward approach. A value of $p<0.05$ was considered statistically significant.

Results

Patient Characteristics

Total of 68 patients were enrolled from 20 centers: 34 were randomly assigned to treatment with HOT and the remaining 34 maintained normal breathing with conventional therapy. Five patients (4 in the HOT group, and 1 in the control group) dropped out before the start of the trial because of withdrawal of consent or hospitalization because of worsening heart failure. There were 7 dropout cases (5 in HOT and 2 in the control group) during the 12-week study period because of violation of the protocol (changes in the underlying medication, discontinuation by patient request). Accordingly, 25 patients in the HOT

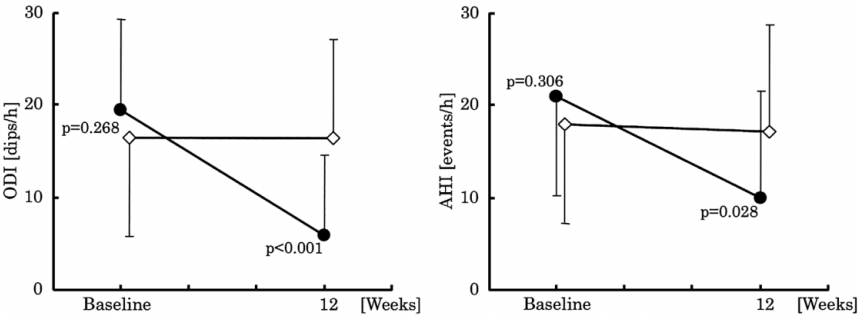

Fig 2. Effects of home oxygen therapy (HOT) on the oxygen desaturation index (ODI) (A) and apnea/hypopnea index (AHI) (B). In the control group, ODI and AHI remained unchanged over the 12 weeks, but in the HOT, significant improvements in both parameters were observed. P values as compared with the control group at each time point were calculated by unpaired t-test. Mean ± SD. –●–, HOT; –◇–, Control.

Table 2 Changes in SDB Indicators, Vital Signs, Plasma NE and Ventricular Function in the HOT and Control Groups

		N	*Baseline*	*N*	*12 week*	*N*	*Difference*	*p value*
ODI (dips/h)	*HOT*	*25*	*19.5±9.8*	*25*	*5.9±8.7***	*25*	*–13.6±11.3*	*<0.001*
	Control	*30*	*16.4±10.6*	*31*	*16.5±10.7*	*30*	*0.2±7.0*	
AHI (events/h)	*HOT*	*25*	*21.0±10.8*	*25*	*10.0±11.6***	*25*	*–11.0±12.6*	*0.001*
	Control	*31*	*18.0±10.7*	*29*	*17.1±11.4*	*29*	*–1.5±5.2*	
CSAI (events/h)	*HOT*	*25*	*7.3±8.6*	*25*	*2.8±4.6***	*25*	*–4.5±7.8*	*0.039*
	Control	*31*	*6.0±7.7*	*29*	*5.6±6.9*	*29*	*–0.6±5.5*	
OSAI (events/h)	*HOT*	*25*	*2.5±4.4*	*25*	*5.2±9.6*	*25*	*2.8±7.6*	*0.053*
	Control	*31*	*1.2±2.0*	*29*	*1.2±1.6*	*29*	*–0.1±1.6*	
HI (events/h)	*HOT*	*25*	*11.2±6.4*	*25*	*2.0±2.6***	*25*	*–9.2±7.2*	*<0.001*
	Control	*31*	*10.8±6.1*	*29*	*10.3±7.5*	*29*	*–0.8±5.4*	
Systolic BP (mmHg)	*HOT*	*25*	*116.9±19.8*	*25*	*118.8±18.9*	*25*	*1.9±18.3*	*0.681*
	Control	*31*	*116.5±20.5*	*31*	*116.5±18.2*	*31*	*0.0±15.9*	
Diastolic BP (mmHg)	*HOT*	*25*	*69.8±9.6*	*25*	*67.9±10.7*	*25*	*–1.9±10.7*	*0.691*
	Control	*31*	*70.1±12.5*	*31*	*69.4±10.7*	*31*	*–0.7±11.0*	
NE (pg/ml)	*HOT*	*25*	*619.6±310.0*	*25*	*575.7±228.3*	*25*	*–43.9±270.4*	*0.463*
	Control	*31*	*595.4±286.0*	*31*	*607.5±318.0*	*31*	*12.2±291.6*	
LVEF (%)	*HOT*	*24*	*34.7±10.4*	*25*	*38.2±13.6**	*24*	*3.9±7.7*	*0.457*
	Control	*29*	*32.8±8.8*	*30*	*34.4±10.9*	*28*	*2.2±8.5*	
HR (beats/min)	*HOT*	*25*	*66.6±11.0*	*25*	*66.3±9.3*	*25*	*–0.3±7.2*	*0.801*
	Control	*31*	*65.7±10.0*	*31*	*65.9±11.5*	*31*	*0.2±7.6*	

SDB, sleep-disordered breathing; NE, norepinephrine; HOT, home oxygen therapy; ODI, oxygen desaturation index; AHI, apnea hypopnea index; CSAI, central sleep apnea index; OSAI, obstructive sleep apnea index; HI, hypopnea index; BP, blood pressure; LVEF, left ventricular ejection fraction; HR, heart rate.
*p values concern the comparison of the differences from baseline to 12 weeks between the HOT and control groups by unpaired t-test. *p<0.05, **p<0.01 compared with baseline within-group by paired t-test. Mean ± SD.*

Table 3 Change in NYHA Class in the HOT and Control Groups

Group	*Improved*	*Unchanged*	*Worsening*	*Total*	*p value*
HOT	*7 (28.0%)*	*17 (68.0%)*	*1 (4.0%)*	*25 (100.0%)*	*0.009*
Control	*0 (0.0%)*	*30 (96.8%)*	*1 (3.2%)*	*31 (100.0%)*	

Values and those in the parentheses are expressed as number of patients and rate of patients, respectively.
NYHA, New York Heart Association; HOT, home oxygen therapy. p value was calculated by Mann-Whitney U test.

group and 31 patients in the control group were assessed finally at 12 weeks.

The characteristics of the patients are shown in Table 1. There were no significant differences between the groups with respect to age, sex distribution, underlying heart disease, NYHA class, Specific Activity Scale values, LVEF or medications. ODI and AHI were also similar in both groups. The mean treatment hours per night with O_2 were 8.50±0.90 h (range: 6.75–10.00 h), and the time in bed with normal breathing in the control group was 8.08±1.40 h (range: 6.25–11.00 h). Thus, compliance with HOT did not appear to be disturbed by the procedure.

Fig 1 shows representative tracings of CSR with CSA in a 70-year-old male patient with LVEF of 19% and NYHA class II heart failure. Typical waxing–waning pattern of airflow during hyperpneas and absence of thoracic and abdominal movement during apneas were observed, indicating their central nature. Arterial oxygen saturation fluctuated in synchrony with the respiratory pattern. After 12-weeks of HOT, CSR-CSA completely disappeared and there was an associated stabilization of arterial oxygen saturation.

Effects of Supplemental O_2 at Night on SDB

In the HOT group, supplemental O_2 for 12 weeks significantly improved SDB, AHI being reduced from 21.0±10.8 to 10.0±11.6 events/h (p<0.001), and CSR being stabilized (Fig 2). Although suppression of OSA was not observed, CSA and hypopnea indexes were significantly decreased (p=0.008 and <0.001, respectively) by HOT (Table 2). The ODI was significantly reduced from 19.5±9.8 to 5.9±8.7 dips/h (p<0.001) (Fig 2). These values remained unchanged in the control group. There were no changes in

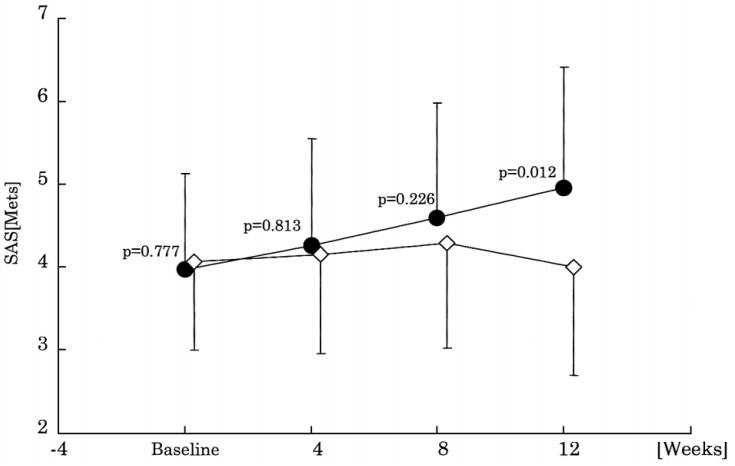

Fig 3. Effect of oxygen on Specific Activity Scale. In the control group, the Specific Activity Scale remained unchanged throughout the study period, but increased gradually by 1.0±1.1 Mets in the HOT group, indicating a significant treatment effect in favor of oxygen therapy. Mean ± SD. P values as compared with the control group at each time point were calculated by unpaired t-test following 2-way repeated measures ANOVA. –●–, HOT; –◇–, Control.

heart rate or blood pressure in either group (Table 2).

QOL According to Exercise Tolerance/Capacity Physiology

NYHA functional class improved in 28.0% of patients in the HOT group but in none of the control group (Table 3).

In the HOT group, the Specific Activity Scale disclosed a significant improvement over time ($p<0.001$ by repeated measures ANOVA); initial values of Specific Activity Scale were almost the same in the 2 groups. Though these values remained unchanged in the control group (4.1±1.1 to 4.0±1.3 Mets), there was a progressive rise over the 12 weeks in the HOT group (4.0±1.2 to 5.0±1.5 Mets, $p<0.001$), the difference between the groups being significant at 12 weeks ($p=0.012$) (Fig 3).

LV Function

LVEF increased significantly from baseline to the end of the study (from 34.7±10.4 to 38.2±13.6%, $p=0.022$) in the HOT group but no change was seen in the control group (from 32.8±8.8 to 34.4±10.9%). The changes in LVEF from baseline to 12 weeks were 2.2±8.5 and 3.9±7.7% for the control and HOT groups respectively, but this difference did no reach statistical significance (Table 2).

Plasma NE Concentration

The 12-week O_2 therapy had no effect on plasma NE concentration in the blood samples obtained every 4 weeks in the early morning after quiet rest (Table 2).

Discussion

In previous studies done in selected patients with impaired LV systolic function, there has been a higher proportion of males and the relative occurrence of SDB is significantly greater in men than in women[9,28] However, a recent study of unselected patients admitted to hospital with decompensated chonic heart failure demonstrated no gender effect on SDB;[29] and the patients enrolled in the present study were similarly a random sample of heart failure patients with CSA. Therefore, the gender-dependent difference was not taken into account for the present analysis.

The nasal O_2 therapy at night virtually eliminated arterial oxyhemoglobin desaturation and decreased the AHI to below 15. Nocturnal supplemental O_2 has been shown to increase total sleep time, improve sleep quality, abolish CSR;[16–20] reduce sympathetic activity[19] and improve exercise capacity.[20] However, 4-week administration of O_2 did not produce an improvement in cardiac function or QOL.[19] The results of the present study demonstrate that 12-week treatment with nocturnal O_2 significantly improved NYHA functional class, Specific Activity Scale scores as a measure of QOL, along with an improvement of SDB in CHF patients with CSR-CSA. LVEF also increased from baseline to the end of the study.

Although there are many factors involved in the development of CSA, the decreased level of $PaCO_2$ plays a major role and small changes in the $PaCO_2$ by O_2 administration can be associated with considerable improvement in CSA.[30,31] Javaheri et al demonstrated that in the presence of low baseline $PaCO_2$, sleep apnea and hypopnea continued even if desaturation was corrected by administration of O_2.[18] Therefore, the overall therapeutic effect of oxygen relates to a widening of the difference between the prevailing $PaCO_2$ and that of the apneic theshold.[18,21] Andreas et al assumed that the addition of CO_2 to O_2 might achieve more effective suppression of CSR by increasing $PaCO_2$ above the apneic threshold and performed a study to evaluate the effects of nocturnal CO_2+O_2 on CSR, sleep and sympathetic activation, which revealed that the combination reduced the duration of CSR, increased arterial O_2 saturation, as well as mean transcutaneous CO_2 tension, but did not improve quality of sleep and increased sympathetic activation. Therefore, those authors concluded that the simple reduction of nocturnal CSR can not be the only objective in the management of patients with heart failure.[32]

The therapeutic effects of O_2 relate to an increase in O_2 stores in the body and SpO_2, thereby improving circulation time between the carotid body and the lung, dampening the respiratory control system and making it more stable. O_2 also reduces the sensitivity of the respiratory control system with suppression of the hypercapnic ventilatory drive and the hypoxic ventilatory drive and increases the arterial partial pressure of O_2 (PaO_2) above the apneic theshold.[16,33] The importance of an increase in PaO_2 as well as in $PaCO_2$ for eliminating apnea has been emphasized by Franklin et al that a large increase in PaO_2 and only a small increase in $PaCO_2$ were noted during oxygen therapy.[17]

The results of the present study imply that the potential of nocturnal O_2 to improve QOL by reducing CSR-CSA in patients with CHF. In Japanese trials of heart failure, the Specific Activity Scale is often used as a measure of QOL because it has been shown to reliably predict exercise capacity and physical activity in daily life.[26] The therapeu-

tic goal of heart failure has recently been aimed at improving mortality in Western societies, but as mortality from heart disease is substantially lower in Japan than in all other Western countries, QOL is considered the primary goal of heart failure treatment in Japan[22,23]

We observed that a 12-week trial of HOT resulted in a statistically significant increase in LVEF from baseline to the end of the study but no change was seen in the control group. Application of continuous positive airway pressure in patients with CHF and CSA-CSR has resulted in a significant improvement in LVEF over a 3-month period,[4,34] attributed to a reduction of cardiac filling pressures, diastolic volumes and afterload in association with the decreased LV transmural pressure gradient.[35] It has been shown that CSR increases muscle sympathetic nerve activity (MSNA) in patients with CHF and induces transient elevations in blood pressure.[36] Therefore, an improvement in the daytime LVEF observed in the present study with nocturnal O_2 may also be achieved in part by sustained reduction in afterload. It is clear that the mean LVEF is significantly lower in patients with sleep apnea than in those without, and there is a strong positive correlation between the AHI and an impairment of LVEF.[3,7] Thus, nocturnal O_2 produces substantial decrease in AHI and this improvement may logically improve hypoxia-related LV dysfunction.

Andreas et al reported an increase in peak O_2 consumption during bicycle exercise following 1 week of O_2 therapy associated with an improvement in CSR, arousals, and nocturnal O_2 saturation.[20] Subsequently, they demonstrated that O_2 desaturation and CO_2 retention increases MSNA, evaluated by microneurography of the peroneal nerve, during apnea and that O_2 reduces this increase in MSNA.[38] Thus, those authors suggested that increased exercise tolerance with nocturnal O_2 is mediated by a reduction in sympathetic nerve activity, which is increased by hypoxia and hypercapnea as well as arousals.

Apnea exerts a sympathoexcitatory effect by O_2 desaturation and CO_2 retention together with disappearance of sympathoinhibitory input from the intrathoracic receptors.[39] We observed no effect of O_2 therapy on plasma NE levels. Staniforth et al also reported that overnight O_2 therapy had no effect on early morning serum NE, which they attributed to the short half-life of serum NE and assumed that it would not be expected to remain elevated once SDB had ceased. They also measured urinary NE excretion as an integrated measurement of overnight serum NE concentration and actually confirmed an increased activation of sympathetic nervous activity in CSR, which could be reduced effectively by oxygen therapy.[19] Less severe disease states in terms of AHI (18.0 and 21 events/h) and LVEF (32.8 and 34.7%) in the present study could have rendered the change in NE in the daytime less prominent.

Despite recent evidence that SDB has adverse effects on patients with CHF, only limited attention has been paid to it as a potential therapeutic target. The O_2 delivery system we used is likely to apply to many CHF patients and has great potential as a non-pharmacological treatment of CHF. However, the effects of supplemental O_2 on morbidity and mortality over more prolonged periods have not been clarified[21] and further studies are warranted to elucidate the long-term benefits of nocturnal O_2 in CHF patients.

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