SCIENTIFIC INVESTIGATIONS

Effects of Oxygen Therapy on Left Ventricular Function in Patients with Cheyne-Stokes Respiration and Congestive Heart Failure

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Study Objectives: Whereas both oxygen therapy and nasal continuous positive airway pressure (CPAP) decrease the apnea-hypopnea index (AHI) in patients with Cheyne-Stokes respiration (CSR) and congestive heart failure (CHF), only nasal CPAP is known to affect the left ventricular ejection fraction (LVEF). We therefore evaluated the effects of 1 month of nocturnal oxygen therapy on LVEF.

Methods: Ten patients (52 ± 12 years) with CHF (LVEF of 12% ± 5%) and CSR (AHI 57 ± 61 events/hour) were studied. Polysomnograms identified CSR and were repeated on oxygen initially (oxygen night 1 [2 L/min]) and after 30 nights (oxygen night 2). LVEF was measured by radionuclide ventriculography.

Results: Oxygen therapy decreased the AHI from a baseline of 57 ± 61 to 9 ± 11 and 12 ± 17 events per hour during oxygen nights 1 and 2, respectively (p < .05), with no difference between treatment nights. The lowest oxygen saturation increased during oxygen nights 1 and 2, from a baseline of 87% ± 7% to 94% ± 4% and 91% ± 7%, respectively (p < .05), with no difference between treatment nights. The LVEF did not significantly change from a baseline of 22% ± 11% to 19% ± 9% after 1 month of nocturnal oxygen (p = .05). Compared to baseline, there was no change in circulation time during oxygen nights 1 and 2, from 24 ± 8 seconds to 30 ± 15 seconds and 23 ± 6 seconds, respectively (p = .2). Total sleep time, sleep efficiency, and sleep architecture, when compared with baseline, remained unchanged during both oxygen therapy nights.

Conclusions: Although 1 month of nocturnal oxygen therapy decreases the AHI in patients with CSR and CHF, there is no improvement in left ventricular function.

Keywords: Cheyne-Stokes respiration, congestive heart failure, apnea-hypopnea index, oxygen therapy, left ventricular ejection fraction, circulation time

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Cheyne-Stokes respiration (CSR) is a form of sleep-disordered breathing characterized by a crescendo-decrescendo alteration in tidal volume, separated by periods of apnea or hypopnea. Present in approximately 45% to 56% of patients with congestive heart failure (CHF) and a left ventricular ejection fraction (LVEF) < 40%,[1-4] CSR has been associated with an increased mortality.[5] Both oxygen therapy[4,6-12] and nasal continuous positive airway pressure (CPAP)[4,13-16] have been shown to be effective therapies for CSR, specifically in regard to decreasing the apnea-hypopnea index (AHI). We have previously demonstrated that oxygen therapy and nasal CPAP are equally effective at decreasing the AHI in patients with CSR and CHF.[4]

In addition to being studied for the treatment of sleep-disordered breathing, nasal CPAP has been studied in regard to its effects on left ventricular function.[13-17] Some studies have shown nasal CPAP to improve left ventricular function in patients with CHF and CSR.[13-16] By increasing intrathoracic pressure and de-creasing the transmural pressure across the left ventricle, nasal CPAP can decrease left ventricular afterload.[18,19] In addition, nasal CPAP has been shown to significantly decrease sympathetic nerve activity in patients with CSR and CHF, as measured by a decrease in urine and plasma catecholamine levels.[20,21] Both mechanisms may result in an increase in LVEF. However, other studies have not demonstrated such beneficial effects with nasal CPAP, in regard to cardiac function,[17] as well as sympathetic nerve activity.[22] Whereas oxygen therapy has been shown to decrease urinary catecholamine levels[12] and increase exercise tolerance,[9] its effect on left ventricular function has not been studied. We therefore prospectively studied a group of patients with severe CHF (LVEF < 40%) and CSR. Our primary endpoint was to evaluate the effects of 1 month of nocturnal oxygen therapy on LVEF. Secondary endpoints included evaluating the effects of therapy on sleep-disordered breathing, sleep quality, and sleep architecture.

MATERIALS AND METHODS

Patient Selection

Ten patients with severe CHF (New York Heart Association class IV, LVEF < 40%) were studied. All patients were recruited from a special inpatient heart failure unit where they were evaluated and listed for heart transplantation, as previously described.[4,23] Patients were medically stable for a minimum of 4 weeks prior to the start of the study, with no change in their treatment regimen during the study period. All patients were ambulatory and active-

ly participating in physical-conditioning classes at the time of the study. Patients were identified as having CSR during a baseline polysomnographic study.

Our institutional review board approved the protocol, and informed consent was obtained from each patient prior to the study. Patients were excluded from the study if they (1) had an episode of acute pulmonary edema within 4 weeks of the study or during the study period, (2) had a prior cerebrovascular accident, (3) underwent transplantation prior to the completion of the study, or (4) refused to sign an informed consent or complete the study protocol.

Protocol

All patients underwent a baseline polysomnographic study that identified the presence of CSR. Patients then had a radionuclide ventriculography to determine the LVEF. A repeat polysomnogram while on oxygen at 2 L per minute (oxygen therapy night 1) was then completed. Patients were then placed on nocturnal oxygen therapy at 2 L per minute for 1 month. At the end of that time, a repeat polysomnogram on oxygen at 2 L per minute was performed (oxygen therapy night 2), followed by a repeat radionuclide ventriculography.

Cardiac Hemodynamics, Echocardiogram, and Radionuclide Ventriculography

Within 1 month of the study (23 ± 12 days), all patients underwent a right-heart catheterization, and medical therapy was optimized. Measurements were recorded just prior to removal of the catheter and included right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. Cardiac output was measured as the mean of 3 recordings using thermodilution technique. LVEF was determined by echocardiogram prior to the study and by radionuclide ventriculography during the study period.

Sleep Studies

The polysomnographic recording consisted of rib-cage and abdominal motion (Resp-EZ; EPM Systems; Midlothian, Calif), oral and nasal thermistors, electrocardiogram, electrooculogram, digastric electromyogram, electroencephalogram, and finger pulse oximetry (model N-100; Nellcor Puritan Bennett; Pleasanton, Calif). All variables were continuously recorded and stored in a computerized system (Alice 3; Healthdyne Information Enterprises; Marietta, GA). Sleep was staged using the standard criteria of Rechtschaffen and Kales.[24] Arousals were defined by an abrupt shift in electroencephalographic frequency lasting at least 3 seconds.[25] Total sleep time (TST) and sleep efficiency (defined as TST divided by the time in bed) were determined. Central apneas were defined by a lack of airflow for more than 10 seconds, associated with the absence of rib-cage and abdominal movement.[23] Central hypopneas were defined by a 50% decrease in airflow for more than 10 seconds, associated with a decrease in rib-cage and abdominal excursion and lack of abdominal–rib cage paradox.[23] The central AHI was expressed as the number of apneas and hypopneas per hour of sleep. CSR was determined to be present when the central AHI was 10 or more events per hour,[26] with events associated with a crescendo-decrescendo alteration in breathing pattern characteristic of CSR. Circulation time was

measured as the time from the end of a central apnea to the nadir in oxygen saturation.[4]

Oxygen Therapy

During the study, oxygen was administered at night by nasal cannula at 2 L per minute. Compliance was documented by the nursing staff and marked on a calendar that was placed in the patient's room.

Statistical Analysis

Data are represented as the mean ± SD. One-way repeated analysis of variance was used to compare variables at baseline and during the 2 oxygen-therapy nights. When significant, pairwise multiple comparisons were made using the Student-Newman-Keuls method. Radionuclide ventriculography data were analyzed using a paired student t test. All statistical analyses were performed using a commercially available computer software program (Sigmastat, version 2.0; Jandel, San Rafael, CA). A p value < .05 was considered significant.

RESULTS

Patient Characteristics

Ten patients (9 men; mean age 52 ± 12 years; body mass index 26 ± 5 kg/m^2) were studied (Table 1). All patients had their medications maximized prior to the study, including the use of a continuous inotropic infusion (Table 1). The mean baseline LVEF by echocardiogram was $12\% \pm 4\%$. Baseline cardiac hemodynamic measurements revealed a cardiac index of 2.3 ± 0.3 L• min^{-1}• m^{-2}, pulmonary capillary wedge pressure of 21 ± 8 mm Hg, mean pulmonary artery pressure of 30 ± 10 mm Hg, and heart rate of $96 \pm$

Table 1—Patient Characteristics*

Characteristic	Values
Age, y	52 ± 12
Men, no.	9
BMI, kg/m^2	26 ± 5
NYHA class IV (ischemic:idiopathic)	4:6
LVEF, %	12
Cardiac output, L/min	4.4 ± 0.8
Cardiac index, L• min^{-1}• m^{-2}	2.3 ± 0.3
PCWP, mm Hg	21 ± 8
Mean pulmonary artery pressure, mm Hg	30 ± 10
Heart rate, beats/min	96 ± 12
Inotropic infusion, μg• kg^{-1}• min^{-1}	
Dobutamine, n = 4	6.3 ± 2.5
Milrinone, n = 5	0.3 ± 0.1
Oral medications, no.	
B-Blocker	3
ACE inhibitor	8
Diuretic	7
Digoxin	5
Nitrates	5
Hydralazine	3
Losartan	5

*Data from 10 patients are presented as mean ± SD or number of patients unless otherwise specified. BMI refers to body mass index; NYHA, New York Heart Association; LVEF, left ventriculography ejection fraction; PCWP, pulmonary capillary wedge pressure; ACE, angiotensin-converting enzyme.
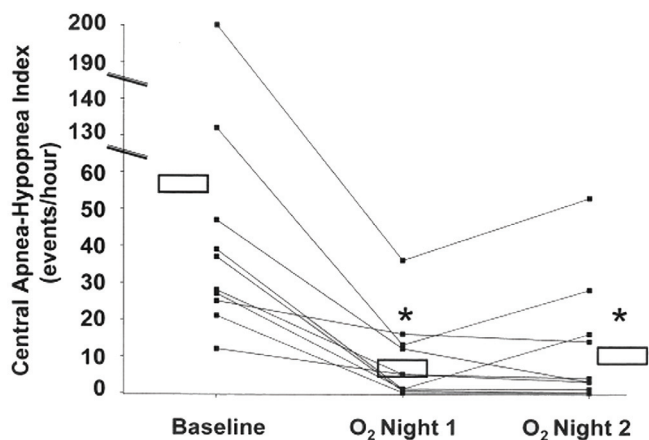
Figure 1—Effects of oxygen therapy on the central apnea-hypopnea index. When compared with baseline, oxygen therapy significantly decreased the apnea-hypopnea index, both acutely during the first night of use (oxygen night 1), as well as after 1 month of use (oxygen night 2) (*p < .05), with no difference between the 2 treatment nights.
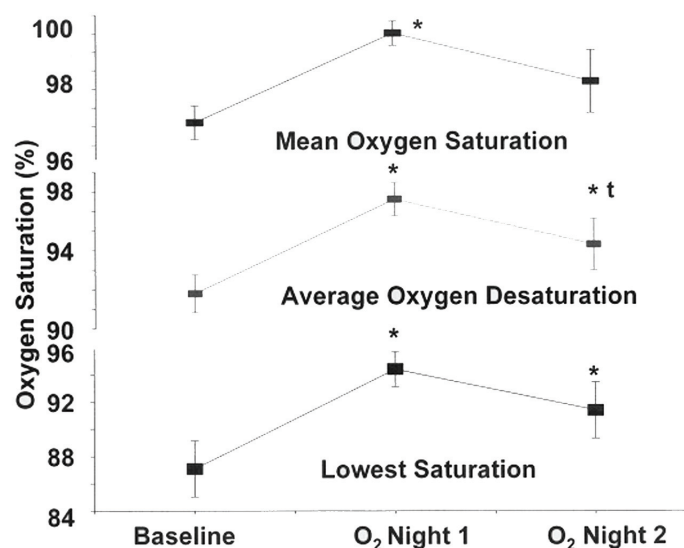

Figure 2—Effects of oxygen therapy on oxygen saturation during the night. When compared with baseline, the average oxygen desaturation and lowest oxygen saturation during the night significantly increased during both oxygen nights 1 and 2 (*p < .05), with only the average oxygen desaturation demonstrating a significant difference between the 2 treatment nights (ᵗp < .05). The mean oxygen saturation, when compared with baseline, only significantly increased during oxygen night 1 (*p < .05), with no difference between the 2 oxygen therapy nights.

12 beats per minute. The mean baseline AHI was 57 ± 61 events per hour, with a TST of 273 ± 90 minutes and a sleep efficiency of 64% ± 18%. The arousal index was 11 ± 9 arousals per hour.

Effects of Oxygen Therapy

When compared with baseline, both oxygen therapy nights 1 and 2 significantly decreased the AHI, from 57 ± 61 to 9 ± 11 and 12 ± 17 events per hour, respectively (p < .05), with no difference between the 2 treatment nights (Figure 1). The mean oxygen saturation, when compared with baseline, significantly increased during oxygen therapy night 1 but not during oxygen therapy night 2, from 97% ± 1% to 99% ± 1% and 98% ± 3%, respectively, (p < .05 as compared with baseline and oxygen night 1), with no difference between the 2 oxygen nights (Figure 2). The average oxygen desaturation during a central apnea significantly decreased during oxygen therapy nights 1 and 2, from a baseline of 92% ± 3% to 97% ± 3% and 94% ± 4%, respectively (p < .05), with a significant difference between the 2 oxygen nights (p < .05) (Figure 2). Similarly, the lowest oxygen saturation, when compared with baseline, significantly increased during both oxygen therapy nights 1 and 2, from 87% ± 7% to 94% ± 4% and 91% ± 7%, respectively (p < .05), but with no difference between the 2 oxygen nights (Figure 2).

The LVEF, as measured by radionuclide ventriculography, did not significantly change after 1 month of nocturnal oxygen therapy, from a baseline of 22% ± 11% to 19% ± 9% (p = .05) (Figure 3). In addition, the circulation time could be determined in all 3 polysomnogram studies in 6 patients due to the continued presence of CSR. Compared with baseline, there was no significant change in the circulation time, from a baseline of 24 ± 8 seconds to 30 ± 15 seconds and 23 ± 6 seconds during oxygen therapy nights 1 and 2, respectively (p = .2).

TST, as compared with baseline, remained unchanged during oxygen therapy nights 1 and 2, from 273 ± 90 minutes to 319 ± 44 minutes and 274 ± 57 minutes, respectively (p = .2). Similarly, sleep efficiency did not change with oxygen therapy, from a baseline of 64% ± 18% to 75% ± 9% and 70% ± 9% during

oxygen therapy nights 1 and 2, respectively (p = .2). The arousal index, as compared with baseline, also did not change on oxygen therapy nights 1 and 2, from 11 ± 9 arousals per hours to 10 ± 7 arousals per hour and 10 ± 3 arousals per hour, respectively (p = .7). Sleep architecture, as a percentage of TST, was not different when compared with baseline on either of the 2 oxygen therapy nights (Table 2).

DISCUSSION

Nocturnal oxygen therapy has been shown to be effective in treating patients with CSR due to CHF.[6-12] While oxygen therapy may improve sleep-disordered breathing in patients with CSR due to CHF, its effect on left ventricular function has not been previously evaluated. There are 3 major findings in this study: (1) oxygen therapy acutely decreases the AHI in patients with CSR and CHF, (2) the decrease in AHI with oxygen therapy is maintained after 1 month of therapy, and (3) 1 month of nocturnal oxygen therapy is not associated with an improvement in the LVEF.

Nocturnal oxygen therapy has been shown to significantly decrease the AHI, both acutely,[4,6,7] as well as after more-prolonged therapy,[9,11,12] in patients with CSR due to CHF. Hanly et al[6] observed a decrease in the central AHI from 30 ± 5 to 14 ± 2 events per hour with 1 night of oxygen therapy in 9 patients with CSR and CHF. We previously demonstrated a similar decrease in the central AHI in 9 patients with CSR and CHF, from 44 ± 9 to 18 ± 5 events per hour, when oxygen was used overnight at 2 L per minute.[4] Franklin et al[7] titrated oxygen from 1 to 5 L per minute overnight in 20 patients with central sleep apnea due to CHF or a prior stroke. They noted a similar decrease in the central AHI, from a baseline of 34 to 5 events per hour while on oxygen. Al-

Table 2—Sleep Architecture*

Variable	Baseline	O_2 night 1	O_2 night 2	p Value
Stage 1, %	16 ± 14	12 ± 8	12 ± 11	.4
Stage 2, %	64 ± 10	67 ± 12	62 ± 9	.6
Stage 3/4, %	0.4 ± 1	1 ± 3	2 ± 7	.5
REM, %	19 ± 9	20 ± 9	23 ± 8	.4

**Data from 10 patients are presented as mean ± SD or as a percentage of total sleep time. REM refers to rapid eye movement.

though Lorenzi-Filho et al[27] did not observe a significant decrease in the central AHI with oxygen therapy in patients with CSR and CHF, they did find a significant decrease in the central apnea index, from 25 ± 7 events per hour at baseline to 16 ± 13 events per hour while on oxygen. Others have noted similar mild, but significant, decreases in the central apnea index with the administration of oxygen.[8]

More-prolonged therapy has been shown to have a similar effect on the central AHI. Andreas et al[9] noted a decrease in the central AHI from 26 ± 24 to 10 ± 9 events per hour after 7 nights of oxygen therapy. In this study, Andreas et al[11] demonstrated a significant decrease in the duration of CSR when nocturnal oxygen therapy was utilized for 1 week, falling from 50% ± 58% to 21% ± 20% of total sleep time. Staniforth et al[12] found a significant decrease in the central apnea index, from a baseline of 13 ± 5 to 4 ± 2 events per hour, after oxygen therapy was utilized during sleep for a period of 1 month. Our findings are consistent with these previous studies, showing a decrease in the central AHI, from 57 ± 61 to 9 ± 11 events per hour, with 1 night of oxygen therapy and a sustained decrease, at 12 ± 17 events per hour, after 1 month of therapy. In addition, because we were administering oxygen during the treatment nights, we did not use a certain level of oxygen desaturation to define a central apnea or hypopnea. Therefore, we believe the observed decrease in the AHI with oxygen therapy accurately reflects the effects of oxygen on sleep-disordered breathing.

There are a number of mechanisms by which oxygen therapy decreases the central AHI in patients with CSR and CHF. Included is an increase in oxygen body stores, resulting in a dampening effect on the central respiratory controller.[6] Andreas et al[11] noted a decrease in the hypercapnic ventilatory response after 1 week of oxygen therapy in patients with CSR and CHF. More recently, hypoxia has been shown to narrow the difference between resting end-tidal CO_2 pressure ($PETCO_2$) and the apneic threshold for $PETCO_2$ (referred to as $\Delta PETCO_2$) during sleep, predisposing the patient to the development of periodic breathing with central apneas.[28] These findings are in contrast to other ventilatory stimuli, such as metabolic acidosis and peripheral chemoreceptor stimulation, which were found to increase the $\Delta PETCO_2$ and protect against the development of central apneas.[28] Whether oxygen therapy increases $\Delta PETCO_2$ in patients with CSR and CHF, thereby eliminating and protecting against the development of periodic breathing, is presently unknown.

The associated increase in $PaCO_2$ that occurs with oxygen administration may be a more important mechanism by which oxygen therapy decreases the AHI.[7,29] Studies in which there is only a mild decrease in the central AHI with oxygen administration have noted no change in transcutaneous PCO_2.[8,27] By removing the hypoxic stimulus to hyperpnea, $PaCO_2$ is able to increase and
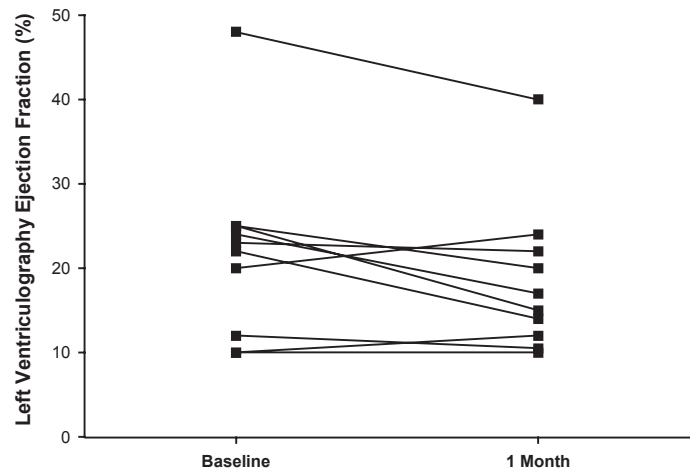

Figure 3—Effects of oxygen therapy on left ventriculography ejection fraction. When compared with baseline, there was no significant change in the left ventriculography ejection fraction after 1 month of nocturnal oxygen therapy (p = .05).

remain above the apneic threshold.

Despite a significant decrease in the AHI, 1 month of oxygen therapy did not improve left ventricular function in our patients. There are conflicting results regarding the effect of nasal CPAP on cardiac function in patients with CSR and CHF.[13-17] Whereas some studies have demonstrated a significant increase in LVEF,[13-16] other studies have shown an actual decrease in the cardiac index in patients with a similar degree of heart failure.[17] However, no previous study has evaluated the effects of oxygen therapy on left ventricular function in these patients. One proposed mechanism to explain how nasal CPAP may increase LVEF is its ability to decrease left ventricular afterload by increasing intrathoracic pressure and decreasing the transmural pressure across the left ventricle.[18,19] In addition, we have recently demonstrated that nasal CPAP also increases oxygen body stores in patients with CSR and CHF.[23] Therefore, by correcting hypoxemia and meeting cardiac oxygen demands, both nasal CPAP and oxygen therapy might be expected to improve cardiac function. Improved exercise tolerance that has been noted to occur with nocturnal oxygen therapy may be explained by such a mechanism.[9] However, we did not see any improvement in cardiac function with oxygen therapy, despite obtaining oxygenation values during the night similar to or higher than those obtained with nasal CPAP.[4,14,16]

Another potential mechanism by which oxygen therapy may improve left ventricular function involves its effects on sympathetic nerve activity. An increase in sympathetic nerve activity has been associated with mortality in patients with CHF, with therapies that decrease sympathetic activity having been shown to improve survival.[30,31] In patients with CSR and CHF, nasal CPAP has been shown to decrease sympathetic activity,[20] which may be partially responsible for the observed improvement in left ventricular function. However, other studies have shown that nasal CPAP can increase sympathetic nerve activity and blood pressure in both patients with CHF, as well as normal controls.[22] The results regarding the effects of oxygen therapy on sympathetic activity have also been mixed.[10,12] Staniforth et al[12] have demonstrated a significant decrease in urinary noradrenaline excretion in patients with CSR and CHF treated with oxygen therapy for 4 weeks. However, Andreas et al[10] found an increase in plasma noradrenaline levels when oxygen therapy and inhaled CO_2 was

used for 1 night in 9 patients with CSR and CHF. In addition, supplemental oxygen has been demonstrated to increase systemic vascular resistance in a dose-dependent manner in patients with CHF.[32] Unfortunately, we did not assess sympathetic nerve activity or measure systemic vascular resistance in the present study.

During the study, we utilized radionuclide ventriculography to assess the effects of oxygen therapy on LVEF. In addition, in 6 patients who continued to have persistent episodes of CSR after 1 month of oxygen therapy, circulation time was also utilized to assess left ventricular function. Circulation time, calculated as the time from the end of a central apnea to the nadir in oxygen saturation, has been shown to be inversely proportional to cardiac output and stroke volume in patients with central sleep apnea.[33] In our patients, there was no significant change in the circulation time, after both 1 night and 1 month of oxygen therapy. However, other factors that affect circulation time, such as increased cardiac chamber size and end-systolic blood volume, which may delay transmission as well as buffer any changes in pulmonary venous blood gas tensions, may also be responsible for the present findings.

Sleep quality did not significantly improve with oxygen therapy, both after 1 night as well as at 1 month. Specifically, TST and sleep efficiency remained unchanged, as did the arousal index and sleep architecture. These results are similar to our previous findings that examined the effect of 1 night of oxygen therapy.[4] Franklin et al[7] noted a decrease in arousals but no change in TST, sleep efficiency, or sleep architecture when oxygen therapy was used acutely. However, Hanly et al[6] reported an increase in TST and a decrease in the arousal index and in the percentage of stage 1 sleep when oxygen was administered for 1 night. More-prolonged use of oxygen does not appear to improve TST or the arousal index,[9,11,12] and only 1 study has reported an improvement in sleep architecture.[9]

Limitations with our study need to be addressed. First, the level of oxygen that was used (2 L per minute) may have been inadequate to improve left ventricular function. However, this level of oxygen is similar to that used in our prior study that resulted in a significant decrease in the central AHI[4] and is similar to other studies that were equally effective in regard to sleep-disordered breathing.[6,9,12] In addition, the lowest oxygen saturation was significantly increased and was greater than 90% during both oxygen-therapy nights. Therefore, it is doubtful that any further increase in SaO_2 would have a significant effect on oxygen content and, thus, supply. Second, oxygen therapy was utilized for only a 1-month period. However, improvement in LVEF has been seen over a similar time period with nasal CPAP.[13,16] Some of these studies, though, included patients with obstructive sleep apnea and left ventricular dysfunction, in addition to patients with predominantly central sleep apnea.[13] Other studies have demonstrated improvement in LVEF only after 3 months of nasal CPAP therapy.[14] Whether more-prolonged use of oxygen therapy would lead to an improvement in cardiac function is unknown. Finally, there was no control group during the study, which would have strengthened our findings. However, the study was designed with patients acting as their own controls, similar to the design of previous studies using nasal CPAP.[13,18] In addition, we believe our negative results, in regard to effects of oxygen on left ventricular function, lessen the significance of an absent control group. Previous studies utilizing controls in a similar group of patients showed no change in LVEF in the control groups when examined at 1 to 3 months.[14-16,20]

In conclusion, nocturnal oxygen therapy is effective at decreasing the central AHI in patients with CSR and CHF. The reduction in the central AHI is sustained after 1 month of therapy. Despite a sustained decrease in the central AHI and improvement in nocturnal oxygenation, 1 month of oxygen therapy does not improve left ventricular function. Sleep quality, as well as sleep architecture, does not improve with nocturnal oxygen therapy. Whether more-prolonged use of nocturnal oxygen therapy would have a beneficial effect on left ventricular function is unknown and awaits further study.

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