Efficacy of Nasal Bi-Level Positive Airway Pressure in Congestive Heart Failure Patients With Cheyne–Stokes Respiration and Central Sleep Apnea

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Background Cheyne–Stokes respiration with central sleep apnea (CSR-CSA) contributes to the poor prognosis in patients with congestive heart failure (CHF). Bi-level positive airway pressure (bi-level PAP) may be an effective alternative for treating CSR-CSA and CHF.

Methods and Results Fourteen patients with CSR-CSA were divided into 2 groups, a control group that included 7 patients who decided to receive only conventional medications and a group of 7 patients that received bi-level PAP. Left ventricular ejection fraction (LVEF), mitral regurgitation (MR) area, plasma brain natriuretic peptide (BNP) concentration and the New York Heart Association (NYHA) functional class were evaluated initially (baseline) and 3 months later. In the control group, there were no significant changes in cardiac function during the study period. In contrast, in the group that received bi-level PAP, there were significant improvements in LVEF (from 36.3±2.9% to 46.0±4.0%, p=0.02), MR area (from 30.4±7.6% to 20.0±5.1%, p=0.02), BNP (from 993.6±332.0 pg/ml to 474.0±257.6 pg/ml, p=0.02) and NYHA functional class (from 3.1±0.1 to 2.1±0.1, p=0.03).

Conclusion Treatment with bi-level PAP improved cardiac functions in CHF patients with CSR-CSA. (Circ J 2005; 69: 913–921)

Key Words: Bi-level positive airway pressure; Brain natriuretic peptide; Central sleep apnea; Cheyne–Stokes respiration; Congestive heart failure

Recent studies have shown that approximately 30–40% of patients with congestive heart failure (CHF) have central sleep apnea, which is characterized by repetitive central apnea events during sleep alternating with a crescendo–decrescendo pattern of tidal volume, described as Cheyne–Stokes respiration (CSR-CSA).1–3 The recovery of spontaneous respiration after such central apnea events is associated with arousals and sympathetic nervous activation.4 Sympathetic nervous activation results in increases of heart rate and blood pressure during sleep, and, moreover, may contribute to the progression of heart failure.5,6 In fact, several studies have shown that CHF patients with CSR-CSA have a poorer prognosis than CHF patients without CSR-CSA.7–9 Therefore, CSR-CSA has been treated using several drugs,10–12 oxygen inhalation,13 carbon dioxide inhalation14 and nasal continuous positive airway pressure (CPAP).15,16 Although some of these treatments, other than CPAP, can improve apnea or sleep quality in CHF patients with CSR-CSA, these treatments result in little or no improvement in cardiac function.17 However, there are patients who show no improvement with CPAP.18 To be effective, CPAP requires spontaneous breathing, and it may sometimes not be effective for central apnea. Compliance with CPAP is sometimes poor because patients feel uncomfortable when they exhale against the high positive pressures required for appropriate treatment.19 Moreover, in a recent randomized prospective trial, CPAP failed to show a mortality benefit in CHF patients with CSR-CSA.20 Therefore, other alternatives need to be considered when treating CHF patients with CSR-CSA.

Recently, a new non-invasive positive airway pressure ventilator with bi-level positive airway pressure (bi-level PAP) has shown benefits for treating acute cardiogenic pulmonary edema.21 We have previously reported that bi-level PAP treatment resulted in significant improvement of abnormal breathing and cardiac function in 1 patient with acute heart failure and CSR-CSA.22 Several reports have shown the efficacy of bi-level PAP for treating abnormal breathing in patients with CSR-CSA and chronic heart failure.23,24 However, little is known about the efficacy of bi-level PAP for treating the underlying chronic heart failure. Therefore, we evaluated the efficacy of appropriate bi-level PAP therapy on cardiac function in chronic CHF patients with CSR-CSA.

Methods

Subjects

We enrolled consecutive patients who were diagnosed as having CSR-CSA between January 2001 and January 2002. All patients were admitted to Toranomon Hospital (Tokyo, Japan), for chronic CHF due to left ventricular (LV) systol-
ic dysfunction, defined as a LV ejection fraction (LVEF) less than 50%. The diagnosis of CSR-CSA was made based on the results of a sleep study, and was defined as at least 15 apnea or hypopnea events per hour of sleep, of which more than 50% were CSR-CSA. After making the diagnosis of CSR-CSA, the patients were divided into 2 groups of their own choice regarding whether or not they would receive bi-level PAP. Bi-level PAP was titrated only for patients who decided to receive bi-level PAP therapy in addition to conventional medical therapy. Then, the patients were put into a treatment group and followed for 3 months after the initiation of bi-level PAP. The patients who decided to receive only conventional medical therapy did not undergo the titration study but were followed up for 3 months as a control group.

Patients with any pulmonary or neurological disorders affecting ventilation or the control of breathing were excluded. This included patients who had chronic obstructive pulmonary disease, pulmonary fibrosis, severe respiratory tract infection, previous stroke or transient ischemic attack, neuropathy, myopathy, and neoplasm. Also, patients with a myocardial infarction within 6 months prior to study entry and acute worsening of CHF within 3 months prior to study entry, cardiac valvë replacement, known obstructive sleep apnea, daily use of sedatives, tranquilizers, theophylline, acetazolamide, and oxygen inhalation therapy were also excluded. Informed consent was obtained from all patients.

Sleep Study
In our institution, most of the chronic CHF patients who agreed to participate in the sleep study underwent an overnight polysomnography (PSG) in our sleep laboratory, using a digital polygraph (SomnoStar Alpha Sleep System, Sensor Medics) equipped with electroencephalograms, electro-oculograms, submental electromyogram, tibialis electromyogram, electrocardiograms, chest and abdominal movement recording using respiratory effort bands, body position monitoring, oronasal airflow monitoring using a pressure-sensor and arterial oxyhemoglobin saturation (SO₂) monitoring using a pulse-oximeter.

Apnea events were defined as a greater than 90% reduction of airflow in the pressure-sensor signal lasting for at least 10s. Central apnea was defined as an absence of chest and abdominal movement during an apnea event, and obstructive apnea was defined as a continuation of chest and abdominal movement during an apnea event. Hypopnea was defined as a 50% to 90% reduction in signal amplitude from the nasal pressure-sensor or from the chest and abdominal bands lasting for at least 10s associated with more than a 3% fall in SO₂. Central hypopnea was defined as the absence of paradoxical chest-abdominal motion and snoring during a hypopnea event. Obstructive hypopnea was defined as the existence of paradoxical chest abdominal motion and snoring during a hypopnea event. The apnea-hypopnea index (AHI) was defined as the total number of apnea events and hypopnea events divided by the total sleep time (TST) and was expressed as the number of events per hour. A central AHI (CAHI) and an obstructive AHI (OAHI) were determined separately. Arousal was defined as a 3 to 15s episode in which there was a return of activity associated with a rise in electromyogram activity. Sleep staging and arousals were scored using 30s epochs according to Rechtschaffen and Kales and American Sleep Association criteria. The arousal index (Arl) was defined as the total number of arousals divided by the TST, and was expressed as the number of events per hour. Sleep stages 1 and 2, slow-wave sleep (SWS) and rapid eye movement (REM) sleep were expressed as a percentage of TST. The percent of time that oxyhemoglobin was less than 90% was also expressed as a percentage of TST. The recurrent central events alternating with a crescendo-decrescendo pattern of tidal volume were recognized as CSR-CSA, and if such central events constituted more than 50% of the total events, this was classified as CSR-CSA. Arterial blood samples were obtained in the early morning just after the sleep study for PaO₂ and PaCO₂.

Bi-Level PAP
In the present study, all patients were treated with the same type of bi-level PAP device (BiPAP Synchro, Respironics). This device is a non-invasive positive airway pressure ventilator using a nasal mask, as well as nasal CPAP. This device has several modes, though only the Spontaneous/Timed mode was used in the present study. During spontaneous breathing, this mode provides assisted ventilation with a fixed higher pressure level during inspiration (inspiratory positive airway pressure, IPAP) and a fixed lower pressure during expiration (expiratory positive airway pressure, EPAP). When an apnea event occurs, the ventilator switches to controlled (timed) ventilation with a preset respiratory rate (RR). The same pressure levels are provided during both assisted ventilation and controlled ventilation. The patients were instructed to use this device while sleeping at home. This device stores the time of usage and other data, including the total volume of leakage, estimated total volume of ventilation, and the number and type of alarms. Therefore, we were able to confirm the patients’ actual usage of the device, as well as other data, at the time of the outpatient clinic visit.

Titration of Bi-Level PAP
Initial titration of bi-level PAP was performed during a 1-night sleep study while receiving bi-level PAP after the proper EPAP level was determined. The proper EPAP level was determined by using auto-CPAP (REMstar Auto, Respironics) during sleep. Patients underwent trials of auto-CPAP with a recording of only the SO₂ by overnight pulse-oximeter a day after the diagnostic sleep study. Then the EPAP level was determined using the overnight pulse-oximeter data and downloaded data from the auto-CPAP. The average pressure level of the auto-CPAP was adopted as the initial EPAP level because it was necessary to reduce the occurrence of mixed obstructive events. The IPAP level was set at 6mmHg above each EPAP level based on prior clinical experience. The RR was set at 15 or 16 per minute depending on the duration of each patient’s central apnea. After the initial titration, the parameters were modulated if the apnea and sleep status did not improve or if the patient felt uncomfortable. Then, a second titration of bi-level PAP was performed a few days after the initial titration, and significant improvements in abnormal breathing and sleep status were confirmed. After these titrations, patients who decided to receive bi-level PAP were started on bi-level PAP treatment.

Measurements
The patients were evaluated for cardiac function, including: LVEF; mitral regurgitation area on echocardiogram; plasma brain natriuretic peptide (BNP) concentration from a venous blood sample; and New York Heart Association
All echocardiographic studies were performed by the same sonographer and evaluated by 2 cardiologists who were not involved in this study. The LVEF was calculated using the Teichholz method based on the LV end-diastolic and end-systolic dimensions. The mitral regurgitation (MR) area was calculated as the area of color-flow Doppler regurgitant jet divided by the area of the left atrium in systole, both in square centimeters and as percentages. Blood samples were obtained in the early morning of the same day that the echocardiogram was undertaken. The NYHA functional class was also assessed at that time.

Statistical Analysis
All values are shown as mean ± standard error of mean. Baseline characteristics and results of the diagnostic sleep study between the control group and the group that received bi-level PAP were compared by using the Mann–Whitney U-test. The Wilcoxon signed rank test was used to compare changes in polysomnographic variables between the diagnostic sleep study and the second bi-level PAP titration. Changes in cardiac function from baseline to 3 months later were evaluated within each group using the Wilcoxon signed rank test. The Mann–Whitney U-test was used to compare differences of each variable between the control and the group that received bi-level PAP and p values of less than 0.05 were considered to indicate a statistically significant difference.

Results
Of the 14 patients who enrolled, 7 received bi-level PAP and 7 constituted the control group. Baseline characteristics of the patients are shown in Table 1, and their drug therapy is shown in Table 2. Most patients were middle- to older-aged men with moderate to severe symptoms of chronic heart failure and impairments of LV contraction. Some patients had a markedly elevated BNP level, which was associated with severe mitral regurgitation (cases 1, 5, 6 in the group that received bi-level PAP and cases 9 and 14 in the control group). In addition, these 5 patients were not given a β-blocker, because they had failed an initial trial of (NYHA) functional class at baseline and 3 months later.

NYHA, New York Heart Association functional; LVEF, left ventricular ejection fraction; BNP, plasma brain natriuretic peptide; MR, mitral regurgitation; IHD, ischemic heart disease; SEM, standard error of mean.
Table 3  Diagnostic Sleep Study Findings

<table>
<thead>
<tr>
<th>Case no.</th>
<th>AH (no./h)</th>
<th>% of TST</th>
<th>Lowest SO(_2) (%)</th>
<th>Ar I (no./h)</th>
<th>Sleep stage (% of TST)</th>
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<tr>
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<td>Obstructive</td>
<td>T&amp;2</td>
<td>SWS</td>
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<td>6</td>
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<td>9.9</td>
<td>2.8</td>
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8 Cases 1–8, receiving bi-level positive airway pressure; cases 9–14, Control group. There were no significant differences between the 2 groups in any variables. AH, apnea hypopnea index; TST, total sleep time; SO\(_2\), arterial oxyhemoglobin saturation; Ar I, arousal index; SWS, slow wave sleep; REM, rapid eye movement; SEM, standard error of mean.

Table 4  Final Setting of Bi-Level Positive Airway Pressure

<table>
<thead>
<tr>
<th>Case no.</th>
<th>IPAP (cmH(_2)O)</th>
<th>EPAP (cmH(_2)O)</th>
<th>RR (/min)</th>
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</tr>
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</tr>
<tr>
<td>7</td>
<td>14</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>13.6±3.6</td>
<td>7.9±3.0</td>
<td>15.7±0.5</td>
</tr>
</tbody>
</table>

IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure; RR, respiration rate; SEM, standard error of mean.

Fig 1. Changes in the polysomnographic findings between the diagnostic and titration sleep studies. Apnea-hypopnea index (AHI), particularly the central event and arousal index and the percent of total sleep time with an arterial oxyhemoglobin saturation (SO\(_2\)) below 90%, significantly decreased at the time of titration. Conversely, slow wave sleep, rapid eye movement (REM) sleep and the lowest SO\(_2\) value increased significantly at the time of titration. bi-level PAP, bi-level positive airway pressure; CAHI, central AHI; OAH, obstructive AHI; TST, total sleep time; ArI, arousal index; SWS, slow-wave sleep.
Bi-Level PAP for CHF and CSR-CSA

The other patients were given β-blocker therapy at least 3 months before the diagnostic sleep study. Two patients in the group that received bi-level PAP and 1 patient in the control group were not given diuretics (Cases 4, 7, and 13). Although these 3 patients had been given diuretics until 1 month prior to the time of the diagnostic sleep study, the diuretics were stopped due to elevated serum creatinine levels. In contrast, 1 patient in each group who had severe symptoms (Cases 1 and 9) had their diuretic dosage increased 2 weeks prior to the time of the diagnostic sleep study. There were no statistically significant differences between the 2 groups in baseline characteristics, including age, gender distribution, body mass index, causes of heart failure, NYHA functional class, LVEF, BNP, MR area, and arterial blood gas data (see Table 1). The polysomnographic findings during the diagnostic sleep study are shown in Table 3. There were also no statistically significant differences between the 2 groups in baseline AHI including OAHI and CAHI, ArI, distribution of sleep stages including stage 1 and 2, SWS and REM, lowest SO2 value, and percent of TST with an SO2 below 90%.

The final results of the bi-level PAP in each patient who decided to receive bi-level PAP are shown in Table 4. With

Fig 2. Illustrative data (510 s) from 1 patient (A) Typical Cheyne–Stokes respiration (CSR-CSA) on diagnostic polysomnography (PSG); note 5 central apneas associated with desaturation. (B) The improvement of CSR-CSA with bi-level PAP on PSG titration. Note the absence of apneas and desaturation. EOG, electro-oculogram; EMG, submental electromyogram; EEG, electroencephalogram; Air flow, nasal air flow; ECG, electrocardiogram; SO2, arterial oxygen saturation.
these results the AHI, CAHI, Arl and percent of TST with an SO2 below 90% decreased significantly, and the SWS, REM sleep and lowest SO2 value increased significantly (Fig 1). The typical waveform of CSR-CSA in the diagnostic PSG and the improvement in the CSR-CSA with bi-level PAP are also shown in Fig 2. In the group that received bi-level PAP, there were no adverse clinical events that were associated with using bi-level PAP. All

Fig 3. Individual values for the left ventricular ejection fraction (LVEF) in all patients. In the control group, there were no significant changes in the left ventricular ejection fraction from baseline to 3 months (from 34.1±3.7% to 32.7±3.2%). In contrast, the LVEF increased in all patients treated with bi-level PAP, and the mean increase was significant (from 36.3±2.9% to 46.2±4.0%, p=0.02). The change in the LVEF from baseline to 3 months was significantly greater in the group that received bi-level PAP than in the control group (1.4±1.9% vs 9.7±2.4%, p=0.004). NS, not significant.

Fig 4. Individual values for the mitral regurgitation (MR) area in all patients. In the control group, there were no significant changes in the MR area from baseline to 3 months (from 29.2±5.6 to 33.0±6.6%). The MR area decreased significantly in all 7 patients who received bi-level PAP (from 30.2±7.6 to 20.0±5.1%, p=0.02). The improvement from baseline to 3 months was significantly greater in the group that received bi-level PAP than in the control group (3.8±1.7% vs 10.5±3.3%, p=0.004). NS, not significant.

Fig 5. Individual values for the plasma brain natriuretic peptide (BNP) concentration in all patients. In the control group, there were no significant changes in the plasma BNP concentration from baseline to 3 months (from 685.4±286.9 to 725.3±311.1 pg/ml). The plasma BNP concentration decreased significantly in all 7 patients who received bi-level PAP (from 993.6±332.0 to 474.7±257.6 pg/ml, p=0.02). The improvement from baseline to 3 months was significantly greater in the group that received bi-level PAP than in the control group (39.9±61.5 vs –518±208.9 pg/ml, p=0.004). NS, not significant.
patients in that group continued to use bi-level PAP appropriately throughout the study period.

There were no changes of medication in any of the patients in either group during the study period. There were no significant changes in the LVEF in the control group during the study period; the mean change in LVEF was 1.4±1.9%, from 34.1±3.7% to 32.7±3.2%. In contrast, the LVEF of the group that received bi-level PAP improved significantly (9.7±2.4%, from 36.3±2.9% to 46.0±4.0%, p=0.02). The mean LVEF change in the group that received bi-level PAP during the study period was significantly greater than that in the control group (p=0.004) (Fig 3). In addition, there was no significant reduction of the MR area in the control group during the study period; the mean change was 3.8±1.7%, from 29.2±5.6 to 33.0±6.6%. However, there was a significant reduction in the MR area of the group that received bi-level PAP (10.5±3.3%, from 30.4±7.6% to 20.0±5.1%, p=0.02). The reduction of the MR area in the group that received bi-level PAP during the study period was significantly greater than that in the control group (p=0.004) (Fig 4). Likewise, while there was no significant change in the BNP in the control group (mean change, 39.9±61.5 pg/ml, from 685.4±286.9 pg/ml to 725.3±311.1 pg/ml), in the group that received bi-level PAP, there was a significant change (mean change, –518.8±208.9 pg/ml, from 993.6±332.0 pg/ml to 474.7±257.6 pg/ml, p=0.02). The mean BNP change during the study period was significantly greater in the group that received bi-level PAP than in the control group (p=0.004) (Fig 5). The NYHA functional class, was noted in the 7 patients who received bi-level PAP, which reduced the number of apnea events and improved sleep status. Willson et al have shown the efficacy of nasal ventilation (using a time-cycled volume preset ventilator, which is different from bi-level PAP and includes a pressure preset ventilator) in CHF patients with CSR-CSA. In their study, the long-term use of this device was associated with an improvement of LVEF. However, not all patients were able to continue using this volume preset device because of difficulty in synchronizing their breathing with this device. Then, Naughton suggested bi-level PAP (pressure preset ventilator) as a treatment option for CSR-CSA. In another study, Willson et al investigated the efficacy of bi-level PAP using 2 different types of bi-level pressure preset device. However, in their study, they only demonstrated an improvement of apnea and sleep status and did not show an improvement of cardiac function. Therefore, this is the first report that has documented a statistically significant improvement in cardiac function with the use of bi-level PAP in CHF patients with CSR-CSA, despite the fact that only a small number of patients were involved.

The improvement of cardiac function documented in the present study might be due to a mechanism similar to that which occurs with CPAP. CPAP has been shown to reduce sympathetic nervous activity in CHF patients with CSR-CSA due to the suppression of their abnormal breathing pattern. CPAP has also been shown to improve the hemodynamics of the failing heart due to the presence of positive airway pressure. The consequent improvement of LVEF, reduction of functional mitral regurgitation and decrease of natriuretic peptide level, have been shown in several studies using CPAP. Bi-level PAP also provides positive airway pressure and improves the abnormal breathing pattern of CSR-CSA. Therefore, the improvements of cardiac function with the use of bi-level PAP in the present study were not unexpected.

However, there are some differences between bi-level PAP and CPAP. Bi-level PAP may fit the abnormal breathing pattern of CSR-CSA better than CPAP. Therefore, bi-level PAP improves an abnormal breathing pattern more immediately and effectively than CPAP. In a recent study, it has been reported that 57% of patients showed no response to CPAP (responsive meaning that the AHI on CPAP decreased below fifteen per hour). That study also

Discussion

In the present study, we evaluated the efficacy of bi-level PAP as a therapeutic option for chronic CHF and CSR-CSA. Improved cardiac function, including improvements in LVEF, MR area, plasma BNP concentration and NYHA functional class, was noted in the 7 patients who received bi-level PAP, which reduced the number of apnea events and improved sleep status. Willson et al have shown the efficacy of nasal ventilation (using a time-cycled volume preset ventilator, which is different from bi-level PAP and includes a pressure preset ventilator) in CHF patients with CSR-CSA. In their study, the long-term use of this device was associated with an improvement of LVEF. However, not all patients were able to continue using this volume preset device because of difficulty in synchronizing their breathing with this device. Then, Naughton suggested bi-level PAP (pressure preset ventilator) as a treatment option for CSR-CSA. In another study, Willson et al investigated the efficacy of bi-level PAP using 2 different types of bi-level pressure preset device. However, in their study, they only demonstrated an improvement of apnea and sleep status and did not show an improvement of cardiac function. Therefore, this is the first report that has documented a statistically significant improvement in cardiac function with the use of bi-level PAP in CHF patients with CSR-CSA, despite the fact that only a small number of patients were involved.

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noted that there was a slight (but not statistically significant) increase in ventricular tachycardia in these non-responsive patients although their oxyhemoglobin desaturation was partly improved, which would indicate that sympathetic nervous activity was not effectively reduced. In a recent randomized prospective clinical trial, CPAP failed to show a mortality benefit in CHF patients, although CPAP improved LV function and reduced sympathetic nervous activity. However, this trial might have included CPAP non-responsive patients, which may have affected this unexpected result. We strongly suspect that such non-responsive patients feel more comfortable with and show better response to bi-level PAP than CPAP because the ventilation pattern of bi-level PAP may better fit the abnormal breathing pattern of CSR-CSA. Furthermore, patients who have failed to accept or continue CPAP may be able to tolerate bi-level PAP. Thus, more patients could be treated if bi-level PAP were offered. However, in the present study, we did not compare bi-level PAP and CPAP. Therefore, further investigation comparing CPAP and bi-level PAP, focusing on the long-term usage of the devices, as well as cardiac function and mortality improvement, is warranted.

Of course, there are some concerns in treating CSR-CSA with bi-level PAP. It is not easy to choose the appropriate pressure level of bi-level PAP. In this regard, as we demonstrated in this study, the clinician can use auto CPAP to titrate the EPAP setting for bi-level PAP. Using auto CPAP to titrate the EPAP setting for bi-level PAP may be a simple way to more easily provide bi-level PAP treatment to more patients.

Study Limitations

The first limitation is that the present study included a small numbers of patients. In addition, the patients themselves decided which treatment to receive; thus, this was not a randomized study. Therefore, the motivation to receive bi-level PAP might have biased the results. Furthermore, although there were no statistically significant differences in the baseline characteristics between the 2 groups, substantial differences could have existed. Therefore, the findings of the study should be interpreted with caution. However, looking at the BNP level, the group that received bi-level PAP might have been more ill, because that group had higher BNP levels, although there was no statistically significant difference between the 2 groups in the BNP level. Nevertheless, given the BNP level in the bi-level PAP group, it could be that bi-level PAP is even more beneficial than this study found. Another limitation of the study is that we could not do PSG 3 months after beginning bi-level PAP treatment. In general, CSR-CSA may be associated with impaired cardiac function! Therefore, the CSR-CSA in the group that received bi-level PAP might have improved at 3 months without the device, based on an improvement of cardiac function. However, in the present study, we did not confirm whether there was improvement of CSR-CSA without using bi-level PAP 3 months after the beginning of the study. Given this, a further randomized prospective study is strongly warranted.

Conclusion

We have demonstrated that the LVEF, functional MR and BNP level, as well as objective symptoms of heart failure, in fair to poor controlled chronic CHF patients with CSR-CSA were improved after using bi-level PAP for 3 months. There were no adverse clinical events, and no patients dropped out from bi-level PAP treatment given at an appropriate pressure setting. These findings indicate that bi-level PAP has a beneficial effect for both abnormal breathing and impaired cardiac function in CHF patients with CSR-CSA.

Acknowledgments

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References


