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ORIGINAL ARTICLE

Role of nasal positive end expiratory pressure valve as an alternative treatment for obstructive sleep apnoea in Chinese patients

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ABSTRACT

Background and objective: **As compliance of continuous positive airway pressure (CPAP) for treatment of obstructive sleep apnoea (OSA) is often suboptimal, a less cumbersome treatment is desirable. We explored the clinical usefulness of nasal positive end expiratory pressure (nPEEP) valves.**

Methods: **Symptomatic OSA patients (apnoea hypopnea index (AHI) >5/h by polysomnography (PSG) or >10/h by type III devices), who declined CPAP, were recruited. A nPEEP valve was attached to each nostril before bed. After successful acclimatization for 1 week, treatment was continued for 4 weeks. The nPEEP valves provided expiratory resistance to build up PEEP. PSG was performed at week 4.**

Results: **Among 196 subjects, 46 (23%) failed acclimatization and 14 (7%) withdrew. Among the 120 patients with a valid PSG, 72 (60%) and 75 (63%) had >50% reduction in mean (standard deviation) overall AHI 26 (16)/h to 18 (18)/h and mean supine AHI 31 (19)/h to 11(16)/h, respectively, $P < 0.001$. Compared with responders, patients with <50% reduction in AHI had a higher mean overall AHI (30/h vs 23/h, $P = 0.03$), higher mean supine AHI (35/h vs 26/h, $P = 0.04$), more severe mean oxygen desaturation nadir (76.7% vs 82.7%, $P < 0.01$) and longer mean period of desaturation <90% SaO_2 (7.7 vs 2.4, $P = 0.02$). Breathing discomfort and dry mouth were the most common side effects. Compared with a dental device, there was a larger mean reduction in supine AHI using nPEEP (29 (14)/h vs 16 (17)/h).**

Conclusion: **nPEEP valves were useful in selected patients with mild or positional-related OSA.**

Clinical trial registration: NCT01553383 at ClinicalTrials.gov

Key words: continuous positive airway pressure, dental device, obstructive sleep apnoea, positive end expiratory pressure, treatment.

SUMMARY AT A GLANCE

The nasal positive end expiratory pressure (nPEEP) valve partially improves apnoea hypopnea index, especially during non-rapid eye movement sleep and in the supine position. It provides an alternative treatment for patients who decline continuous positive airway pressure. Compared with a dental device, it has similar efficacy but is better tolerated. Major side effects were breathing discomfort and a dry mouth.

Abbreviations: AHI, apnoea hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; nPEEP, nasal positive end expiratory pressure; OSA, obstructive sleep apnoea; PSG, polysomnography; REM, rapid eye movement; SDB, sleep disordered breathing.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common form of sleep-disordered breathing (SDB) causing sleep fragmentation, disabling daytime sleepiness, impaired cognitive function and poor quality of life. It is estimated that 2–8% of the general population suffers from this condition.[1,2] Abundant data show that OSA is associated with metabolic syndrome and cardiovascular consequences,[3–5] and the resultant public health impact is high.[6,7] Although continuous positive airway pressure (CPAP) is the standard treatment for patients with OSA with strong evidence showing its efficacy in improving symptoms, cognitive function and quality of life,[8–10] compliance is notoriously low, especially in patients with milder OSA.[11,12] Mask discomfort, claustrophobia and breathing discomfort are common problems hindering compliance.[11] Other treatment modalities such as dental devices or surgery do not provide consistent efficacy.[13,14] Although dental device, which is less cumbersome, is a popular alternative to CPAP, the partial and complete response rate has been reported to be around 40% and 25%, respectively,[15] and side effects have

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been reported to be as high as 86% in one study.[16] New forms of effective treatment that are convenient and comfortable are needed.[17,18]

The nPEEP valves (Provent™ Therapy; Ventus Medical, Inc., Belmont, CA, USA) have recently been approved for treatment of OSA by the Food and Drug Administration in the United States. It is a simple device with self-adhesive tape, designed to be attached to each nostril to produce nPEEP that may keep the upper airway patent during sleep.[19] Several studies have shown effectiveness of this device in improving OSA with variable outcomes. However, the study population was mostly Caucasians and the type of patients who would benefit most was not well defined.[20,21] This study aimed to explore the role of this device as an alternative choice of therapy for patients with OSA who were not using CPAP and the effectiveness was compared with a dental device.

METHODS

Patients were selected from the respiratory specialist clinic at the Prince of Wales Hospital, Hong Kong. This is a regional hospital and the teaching hospital of the Chinese University of Hong Kong. All patients had a sleep study performed to confirm the diagnosis of OSA. Sleep study was performed with either polysomnography (PSG) (Alice 5, Philips, Andover, MA, USA) or a validated level 3 portable monitoring device (Embletta, Natus Medical Inc., Pleasanton, CA, USA). Patients with symptoms of OSA and an apnoea hypopnea index (AHI) >10/h were offered CPAP as the first choice of treatment and an attended CPAP titration study was offered. Those refusing CPAP and other forms of treatment, or had been using a dental device, were invited to participate in this study, after signing informed consent. Patients with known nasal problems such as deformities or significant rhinitis affecting application of nPEEP valves, significant or unstable comorbidities requiring other forms of treatment for OSA and pregnant females were excluded. Patients with SDB conditions other than OSA requiring more complex treatment (e.g. central sleep apnoea, significant Cheyne Stokes respiration or hypoventilation syndrome) were also excluded. There was no age limitation.

There were two groups of patients. One group included patients who refused CPAP and were offered nPEEP valves for 4 weeks. Another group of patients was using dental device as treatment, and then switched to nPEEP valves alone for 4 weeks. All recruited subjects were provided with a pair of the nasal valves to apply each night for a run-in period of 1 week as acclimatization. Participants were encouraged to use the device for a short period of time initially and in a successive longer period in the following nights. The aim was to acclimatize the patients so that they could tolerate the device for the whole night at the end of the week. nPEEP valves were supplied for 4 weeks to those who could tolerate the device. During this period, no other forms of treatment except the nPEEP valves were used for OSA. Those who could not tolerate the device were withdrawn from the study. The nPEEP valves were for single use and subsequently disposed. The subjects were instructed to use the device every night when they slept. According to the manufacturer, the nPEEP valves used in this study provided a standard resistance of 5–15 cm water pressure at an expiratory flow rate ranging between 100 and 170 mL/s. Detailed instruction was provided by the nurses or investigators. To ensure the patients could understand how to use the devices, they were asked to demonstrate its application before going home.

The quality of life was assessed by the Sleep and Health Questionnaire; both the Chinese and English version had been validated and used in clinical studies.[22,23] Patients were instructed to fill in the Chinese version of the questionnaire at the start of the study and at the fourth week. A diary was provided to the patients to record the time they put on and took off the device for recording of compliance. Patients were provided with a phone number so that they could contact staff members of the research team for advice if difficulties arose.

After using the nPEEP valves for 4 weeks, a PSG was repeated using a pair of specially made nasal cannulas that could be attached to the nPEEP valves, so that the residual AHI could be measured. Patients using a dental device for OSA had a sleep study performed wearing it to assess its efficacy. All PSG were conducted and scored according to the updated ASSM guidelines.[24] The efficacy of the nPEEP valves was compared with that of the dental device used in the latter group. Responders were defined as >50% reduction in AHI with nPEEP valves. Student's *t*-test of statistic software (SPSS version 19, IBM, Armonk, NY, USA) was used to generate results.

This study was approved by the Joint CUHK-NTEC (Chinese University of Hong Kong-New Territories East Cluster) Clinical Research Ethics Committee of Hong Kong and was registered in the US-based ClinicalTrials.gov, identifier number NCT01553383.

RESULTS

Altogether 196 Chinese patients were recruited from July 2012 to July 2013, with 108 (55%) males and 88 (45%) females. Forty-six (23%) patients failed acclimatization during the run-in period, 14 (7%) withdrew from the study for intolerance. Sixty-eight patients chose to try a dental device as well as nPEEP valves, but 23 of them failed to tolerate their dental device. Figure 1 shows the distribution of patients. There were no significant differences in baseline characteristics between those patients who were able to finish and those failed to finish the study. Details are shown in Table 1.

Altogether, 120 patients completed the study using the nPEEP valves for 4 weeks with PSG data, with a mean usage time ≥4 h/night. Sixteen patients defaulted sleep study evaluating the nPEEP valves. The mean (standard deviation) AHI was significantly reduced from 263 (16)/h to 18 (18)/h, $P < 0.01$. There was significant reduction in rapid eye movement (REM) AHI, non-REM AHI and supine AHI with the

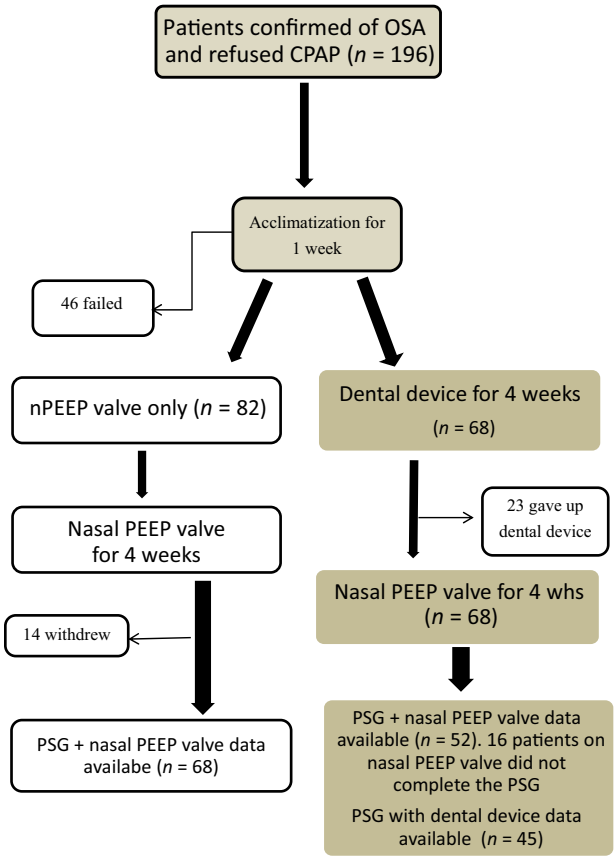

Figure 1 Flow chart of study recruitment.

Table 1 Baseline demographics of patients

Completed versus failed nPEEP trial Mean (SD)	Completed (n = 136)	Failed (n = 60)	P-value
Age	55.3 (10.2)	54.9 (10.9)	0.8
BMI	27.2 (4.4)	26.9 (3.7)	0.7
Neck circumference (cm)	37.4 (3.4)	38.5 (2.6)	0.3
Waist circumference (cm)	95.7 (10.6)	96.8 (10.8)	0.7
Baseline ESS	9.8 (5.6)	8.5 (4.9)	0.4
Baseline AHI	26.4 (16.4)	25.4 (15.6)	0.8
Minimum SaO_2 (%)	80.6 (9.3)	80.0 (9.0)	0.8
ODI (≥3% drop in SaO_2 from baseline/h)	20.2 (16.9)	15.1 (13.4)	0.7
Percentage of time SaO_2 <90%	4.4 (8.1)	3.7 (3.6)	0.9
PSG for diagnosis	108	50	—
Embletta for diagnosis	28	10	—

AHI, apnoea hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; nPEEP, nasal positive end expiratory pressure; ODI, oxygen desaturation index; PSG, polysomnography; SD, standard deviation.

Table 2 Changes in PSG parameters with nPEEP valve (n = 120)

	Mean (SD)		P
	Baseline	With nPEEP	
Overall AHI	26 (16)	18 (18)	<0.01
REM AHI	30 (22)	22 (20)	0.01
NREM AHI	26 (18)	15 (20)	0.01
Supine AHI	31 (19)	11 (16)	<0.01
Non-supine AHI	17 (16)	19 (21)	0.69
Minimum SaO_2	80 (9)	82 (9)	0.09
Mean SaO_2	94 (2)	94 (3)	0.05
Arousal Index	29 (13)	23 (12)	0.07

AHI, apnoea hypopnea index; nPEEP, nasal positive end expiratory pressure; NREM, non-rapid eye movement; PSG, polysomnography; REM, rapid eye movement; SD, standard deviation.

nPEEP valves, $P \leq 0.04$, but not the non-supine AHI. There was no significant difference in oxygen saturation, arousal index and oxygen desaturation index between baseline and after application of the nPEEP valves (Table 2). When using the pre-defined definition of >50% reduction in AHI as successful outcome, 72 (60%) patients were classified as responders and 48 (40%) patients were non-responders using the nPEEP valves. The responding patients had a lower mean AHI, REM AHI, non-REM AHI and supine AHI in baseline PSG. The percentage of time with oxygen saturation <90% at baseline was significantly shorter in the responding group compared with the non-responding group, which had a corresponding lower minimum oxygen desaturation in baseline (Table 3). There were no differences in ages, body mass index (BMI) and the baseline Epworth Sleepiness Scale (ESS) between the responders and non-responders.

For patients who had completed therapy with the nPEEP valves for 4 weeks, there was significant improvement in some parameters in quality of life. Improvements included performance ability, daytime sleepiness, energy level, snoring intensity, awakenings during sleep and ease of falling asleep. The mean ESS also had significant improvement. Other details are shown in Supplementary Table S1.

There were 68 patients who chose to try their dental device as well, but only 45 of them were still using it on the fourth week when they were offered PSG to assess the efficacy. The reduction in mean AHI was similar for both the dental device and nPEEP valve. However, there was a larger reduction in non-REM AHI and supine AHI with nPEEP valve when compared with the non-REM AHI and supine AHI of dental device, $P < 0.01$. There were no significant differences between other parameters (Supplementary Table S2).

The feeling of breathing discomfort was the most common side effect experienced by the patients. Forty out of 118 patients (33.8%) were unwilling to use the nPEEP valves after the trial and this was expressed as the major reason. Among 55 patients who failed to complete the study, 24 (43.6%) patients considered this limitation as a major reason. In 135 patients who completed the trial, 45 (33.3%) complained of dry

Table 3 Baseline characteristic of responders and non-responders

Mean (SD)	>50% improvement (n = 72)	<50% improvement (n = 48)	P
AHI	23 (16)	30 (18)	**0.04**
REM AHI	25 (19)	37 (24)	**0.04**
NREM AHI	20 (16)	32 (21)	**0.01**
Supine AHI	26 (20)	35 (20)	**0.04**
Non-supine AHI	13 (13)	18 (22)	0.22
Minimum SaO_2	83 (8)	77 (11)	**<0.01**
Percentage of time SaO_2 <90%	2 (3)	8 (13)	**0.01**
Compliance on using PEEP valve (hours)	7 (2)	7 (2)	0.63
Improvement in sleep quality with PEEP valve	5 (3)	4 (2)	0.08
Willingness in using PEEP valve	5 (3)	5 (3)	0.34
Improvement in daytime awakening with PEEP valve	5 (3)	4 (2)	0.06

AHI, apnoea hypopnea index; NREM, non-rapid eye movement; PEEP, positive end expiratory pressure; REM, rapid eye movement. P values in bold are statistically significant.

mouth as the major side effect, while breathing discomfort was the major side effect in 23 (17%) patients. The profile of side effects is summarized in Supplementary Table S3.

DISCUSSION

Unlike previous studies using the nPEEP valves as the initial treatment, our study explored the potential role of this innovative device as an alternative choice for patients with mild-to-moderate OSA who had declined CPAP, as well as being an alternative to dental devices.

The efficacy of nPEEP valves was comparable with that of the dental devices used. In addition, there was a consistent larger reduction in mean supine AHI of 29/h compared with the dental devices of 16/h. The non-REM AHI reduction was also larger (17/h vs 7/h). Apart from similar efficacy, the nPEEP valves had an added advantage over the dental devices, not being contraindicated in edentulous patients. There were significant improvements in subjective symptoms, snoring intensity and AHI. Efficacy of nPEEP valve has been documented by a few clinical studies. Berry *et al*. showed that this nasal device was effective in reducing the mean AHI in CPAP naïve patients compared with a sham device in a multicentre randomized control trial.[21] Rosenthal *et al*. showed that it was also effective for patients with moderate OSA, with a reduction of mean AHI from 24/h to 14/h.[25] Patel *et al*. showed that positional variability might predict a positive response.[26] Our study showed that this device improved the AHI significantly, especially in the supine position, similar to the findings of Barry *et al*. and Patel *et al*.[21,26] One major difference between this study and other studies was that obesity was less prominent among the patients in our study, as in our study the mean BMI was 26 kg/m^2, which was lower than other studies with a mean BMI of 30–34 kg/m^2. Yet nPEEP valves still reduced the supine AHI significantly.[20,25] Unfortunately, data on waist circumference, distribution of adipose tissue around the upper airway and the upper airway anatomy were not available to explore the potential interacting factors in relation to nPEEP valve in these less obese subjects. Further studies in this group of patients would be worthwhile.

There were some differences between responders and non-responders. Similar to the results of Walsh *et al*.,[20] we found that the non-responders (reduction of AHI ≤50% after the nPEEP valve) had a higher BMI, baseline AHI, longer time of oxygen desaturation and lower SaO_2 at baseline. The presence of breathing discomfort with nPEEP valves seemed to predict those who could not tolerate the device, as it was the most common side effect in over one-third of patients who either failed or unwilling to use the nPEEP valve. Dry mouth was another prominent side effect but could be tolerated by most patients. Similar to Patel *et al*., we failed to identify other discriminating physical characteristics of patients that could predict success or failure in using the nPEEP valves. Nevertheless, patients with milder OSA seemed to respond more favourably than the more severe ones, as well as those with a prominent element of positional-related OSA, as shown by our study. Two studies had elegantly demonstrated the changes in lung volume with increased nPEEP by magnetic resonance imaging, which could explain the mechanism for nPEEP valves, although neurological responses to CO_2 retention could not be excluded.[26,27] In addition, there was an interesting study by Puhan *et al*. showing didgeridoo playing improved OSA.[28] It is important to note that nPEEP valves did not completely lower the AHI to a normal level.[19–21,25] In a RCT of patients with moderate-to-severe OSA, nPEEP valves were found to be better than placebo, although the patients in that study were already using CPAP before switching to nPEEP valves.[29] Possible factors included that the nPEEP was not constant but fluctuated between inspiration and expiration. The nPEEP could also be significantly reduced if the patient was a mouth breather and this had led to transient period of failure, as demonstrated by Patel *et al*.[26] Lastly, there were some advantages of nPEEP valves over CPAP. The nPEEP valve was more acceptable to our subjects who had refused CPAP. Among the 150 patients who had successfully acclimatized for the nPEEP valves, 80% (120) could continue the therapy during sleep for at least 4 weeks for >4 h/night. This adherence rate in our study was more favourable to the average CPAP adherence and much better than the 65% (45/69) of dental devices. Compared with dental devices, the total failure rate of nPEEP valves was slightly lower, 30% (60/196) compared with 34% (23/68).

There were several limitations of this study. Because this study was not a RCT, patients were motivated that could have biased their response rates. The participants were using the nPEEP valve as a second-line treatment; the results were thus not applicable to CPAP naïve patients. It was also presumed that the weight of the patients was static within the period of the study.

In summary, nPEEP valves were effective in partially reducing AHI. CPAP naïve patients with milder OSA or with prominent positional-related OSA responded more favourably. The efficacy was similar to dental devices with better adherence.

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Supporting Information

Additional Supplementary Information can be accessed via the online version of this article at the publisher's website:

Table S1 Sleep and health questionnaire after using nPEEP valve.

Table S2 Comparison of magnitude of changes between nPEEP valve and dental device.

Table S3 Major side effects with nPEEP valve.

