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Original Article

CPAP therapy improves erectile function in patients with severe obstructive sleep apnea

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ABSTRACT

Objectives: Erectile dysfunction (ED) is highly prevalent in obstructive sleep apnea (OSA), however, the effect of continuous positive airway pressure (CPAP) therapy on erectile function has not yet been thoroughly investigated in these patients.
Methods: Ninety-four men with severe OSA (ie, with an apnea-hypopnea-index $\geq$ 30/h of sleep) were prospectively evaluated for the presence and severity of ED before and after 6–12 months of CPAP therapy. The abbreviated version of the International Index of Erectile Function, (the IIEF-5) was used to rate erectile function. Furthermore, all study participants responded to standard questionnaires of daytime sleepiness (Epworth Sleepiness Scale), quality of life (WHO Wellbeing 5 questionnaire) and depression (Major Depression Inventory).
Results: ED as defined by an IIEF-5 score of $\leq$21 was present in 64 patients (68.1%). CPAP treatment significantly improved erectile function in those patients suffering from moderate and severe ED. Additionally, a trend for a correlation between the improvement of erectile function under CPAP and the hours of its use was observed. Finally, this effect was associated with larger improvements of quality of life in affected patients.
Conclusions: ED is very frequent in men with severe OSA and can at least partly be reversed by long-term CPAP therapy in most seriously affected patients. The beneficial effect on erectile function may depend on CPAP compliance and is accompanied by improvements of quality of life. Randomized controlled trials are needed to confirm these findings.

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1. Introduction

Obstructive sleep apnea (OSA) has been found to be linked to erectile dysfunction (ED). Thus, an increased prevalence of ED as well as an independent association with the extent of nocturnal hypoxia have been reported in patients with OSA [1–5]. Within this context, increased oxidative stress with reduced bioavailability of nitric oxide (NO) and blunted vasodilation is considered an important pathophysiological mechanism [6–8]. Increased levels of catecholamines and endothelin or decreased testosterone may also be factors [9–11]. Additional causative factors may be sleep fragmentation, reduced amounts of REM sleep and daytime sleepiness or impaired vigilance [12,13]. Finally, neural abnormalities such as prolonged bulbocavernosus reflex latency may contribute to the development of ED in OSA [14].

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Some studies have already suggested that CPAP therapy may improve erectile function in affected patients [15–22]. However, most of these studies had methodological drawbacks, eg, low patient numbers, retrospective design and short-time therapeutic intervention. Furthermore, all prior studies did not focus on the patients most likely to gain a benefit from CPAP, ie, those with severe OSA, and did not perform sleep studies at follow-up.

Against this background, we aimed to perform a prospective study on the long-term effects of CPAP therapy on erectile function in a larger number of patients with severe OSA. In addition, we thought to address the roles of daytime sleepiness, reduced quality of life and depression within this context. This is relevant as these factors represent well established clinical features of OSA and may independently contribute to the emergence of ED.

2. Methods

2.1. Patient recruitment and assessment

The patients of the present study were prospectively recruited at centers affiliated with the German Sleep Apnea Research Network (GERSAN). They had been admitted to the sleep lab for suspected sleep apnea as judged by clinical symptoms and the results of home-based polygraphy. All of them were between 18 and 80 years old and had a diagnosis of severe OSA as verified by full-night attended polysomnography (ie, an apnea-hypopnea-index [AHI] $\geq$ 30 per hour of sleep). Furthermore, all study participants had to live in a stable partnership with regular sexual intercourse. CPAP therapy was initiated irrespective of daytime symptoms, ie, also in subjects without excessive daytime sleepiness. Patients with known or treated ED were excluded from the study. The same was true for patients with urological or neurological diseases possibly interfering with erectile function, with such examples as prostate cancer, spinal cord injury or multiple sclerosis. Subjects in whom vasoactive medications (eg, ACE inhibitors, statins and nitrates) had been newly prescribed within the last four weeks before study entry were also not allowed to participate.

Anthropometric parameters were determined, ie age and body mass index (BMI). The presence of co-morbidities was then evaluated by patient history (ie smoking, diabetes, hyperlipidemia, arterial hypertension, coronary or peripheral artery disease). Finally, the intake of β-blockers was noted as these drugs may lead to ED.

Prior to the start of the study, its protocol had been approved by the local ethics committees and it had been registered at *ClinicalTrials.gov*. (NCT01600066). Moreover, all patients had given their informed written consent.

2.2. Sleep studies

The device used for polygraphy recorded the following variables: nasal airflow by pressure cannula (before study inclusion), CPAP pressure (at follow-up), thoracoabdominal breathing movements by inductive plethysmography, oxygen saturation by finger tip pulse oximetry, snoring and body position. While performing polysomnography, additional data were collected, ie EEG (C3A2, C4A1), EOG (both eyes) and EMG (submental and pretibial). Parameters derived from the sleep studies included the AHI and variables of oxygen saturation (ie mean and minimal SpO_2 as well as % of time spent with an SpO_2 below 90%).

At the time of study inclusion, CPAP titration was performed manually with the help of polysomnography. Patients were discharged with a fixed CPAP pressure considered to be optimal. Until follow-up, pressure settings were not changed or adjusted. This was done if polygraphic recordings under CPAP at the time of follow-up had shown residual apneas. For this purpose, the patients were readmitted to the sleep lab after study termination.

2.3. Questionnaires

After diagnostic polysomnography, all patients were asked to respond to four different questionnaires evaluating erectile function, daytime sleepiness, quality of life and depression.

The questionnaires were placed in an envelope carrying an anonymous patient code. A total of 267 patients were approached to take part in the study of whom 74 refused to fill out the questionnaires (screening failure rate: 27,7%). Of the 193 patients who participated in the study, 99 were lost to follow-up or had incomplete data sets. Thus, the data from 94 patients were finally entered into statistical analysis.

The abbreviated version of the International Index of Erectile Function (ie, the IIEF-5) was used to rate erectile function [23]. Within this questionnaire, a score of 1–25 can be reached with a score of $\leq$21 indicating ED. Furthermore, the severity of ED is rated as mild [17–21], mild-to-moderate [12–16], moderate [8–11] or severe ($\leq$7).

The Epworth Sleepiness Scale (ESS) was employed to determine the level of daytime sleepiness [24]. In this questionnaire, the probability of falling asleep in different situations (n = 8) has to be rated on a 4-point scale (0 = 'never' to 3 = 'high probability'). The maximal score of the ESS is 24 and values of >10 are considered to indicate excessive daytime sleepiness.

Quality of life was evaluated with the help of the WHO Well-being 5 questionnaire [25]. It is composed of five questions and in each of them a value ranging from 0 to 5 can be reached. A total score of <13 or a response of 0 or 1 to at least one of the questions is considered to represent reduced quality of life.

Finally, the Major Depression Inventory (MDI) questionnaire was used to assess the presence and severity of depression [26]. It contains a total of 10 questions in each of which a score of 0–5 can be reached. Scores of $\geq$4 in two of the first three items plus scores of $\geq$3 in 2–4 of the last seven items are judged as mild or moderate depression, respectively. Severe depression is diagnosed if scores are $\geq$4 in all of the first three items plus $\geq$3 in $\geq$5 of the last seven items. Overall, higher total scores indicate more pronounced depression.

2.4. Follow-up after CPAP

After 6 to 12 months, the patients were re-evaluated for CPAP compliance and efficacy. This was accomplished by reading out the built-in time counters of the CPAP machines. Furthermore, polygraphy was performed while the patients slept with CPAP at their homes. Finally, all study participants again filled out the aforementioned questionnaires.

2.5. Data analysis

Sleep studies were separately analyzed at each center participating in the study. All data were entered into a web-based case report form and transferred to the University of Giessen Lung center where statistical analysis was performed by one of the investigators (H.G.). Data are presented as n/%, mean ± standard error of the mean or median ± interquartile range as appropriate. Data analysis was performed in subgroups defined by their self-reported degree of erectile function (ie, their response) to the IIEF-5. First, the characteristics of these subgroups were compared (ie, anthropometric data, co-morbidities, sleep apnea parameters pre and post CPAP, duration of follow-up, CPAP compliance and results of the other three questionnaires [ie, ESS, WHO-5 and MDI]). One-way ANOVA with Tukey post-hoc tests and Chi square tests were used

for testing of statistical significance of differences in normally distributed parameters. The Kruskal Wallis test was performed as a non-parametric test. The same tests were employed to evaluate the characteristics of study participants vs. drop-outs.

Next, the effects of CPAP therapy on erectile function, daytime sleepiness, quality of life and depression were investigated by student's t-tests. Finally, it was tested if the effect of CPAP on erectile function depended on therapeutic compliance and/or changes in the other outcome parameters investigated. For this purpose, linear regression analysis and multi-way ANOVA were performed with Δ IIEF-5 as the dependent variable and hours of CPAP use per night as well as Δ ESS, WHO-5 and MDI as constant variables. SPSS 19.0 was used for calculating statistics. A p-value of <0,05 was regarded as statistically significant.

3. Results

3.1. Patient characteristics

The mean age of the 94 men who completed the study was 51.5 ± 0.9 years and their mean BMI was 34.2 ± 0.6 kg/m^2 indicating WHO class I obesity. Based on the inclusion criteria of the study, polysomnography had revealed severe OSA in all subjects with a mean AHI exceeding 50/h. About two thirds of the patients suffered from arterial hypertension and approximately one fourth from metabolic disease (ie, hyperlipidemia and diabetes). One third of the patients were smokers and a similar percentage took β-blockers. The patient characteristics are summarized in Tables 1 and 2.

The patients who were excluded from the study due to loss of follow-up or incomplete data sets had similar anthropometric and sleep apnea data as those finally analyzed (Supplementary Table 1).

3.2. Erectile dysfunction

Based on the results of the IIEF-5 questionnaire, 64 of the 94 patients, (68.1%) were diagnosed to suffer from ED. Most of them had mild or mild-to-moderate ED (n = 34 and n = 18, respectively). In 12 patients ED was moderate or severe (n = 6 in each subgroup). In the drop-out patients the prevalence of ED and the spectrum of its severity were almost identical with those of the included patients (Supplementary Table 1).

3.3. Daytime sleepiness, quality of life and depression

Of the 94 patients, 42 (44.7%) suffered from excessive daytime sleepiness as judged by the results of the ESS. Fifty-two patients (55.3%) were diagnosed with reduced quality of life and 12 patients were diagnosed with depression (12.8%).

3.4. Comparison of patients with vs without erectile dysfunction

The patients presenting with different severities of ED had similar age, BMI, sleep apnea parameters and co-morbidities (Tables 1 and 2). When comparing these subgroups with the patients with preserved erectile function, the only differences found were a higher mean age and AHI in the mild and mild-to-moderate ED groups (Tables 1 and 2). The results of the ESS, WHO-5 and MDI were similar in all subgroups (Table 2).

3.5. Effects of CPAP therapy

The mean duration of follow-up was 7.0 ± 0.4 months. Overall, CPAP compliance was good with a mean usage time of 5.5 ± 0.2 h per night. Nevertheless, there was a significant proportion of patients not using their CPAP device on a regular basis (n = 31, 33% slept during <5 h per night with CPAP). Polygraphy showed that CPAP therapy was very effective in suppressing OSA (AHI: 3.0 ± 0.3/h; mean SpO_2: 94.6 ± 0.2%, lowest SpO_2: 86.6 ± 0.8%, SpO_2 < 90%: 2.7 ± 0.8% of time in bed). When looking at the duration of follow-up, CPAP compliance and the results of polygraphy under CPAP in patients with normal erectile function and those with varying degrees of ED no significant subgroup differences could be found (Supplementary Table 2). Only two patients had a slightly elevated AHI of 10–15/h under CPAP at follow-up. Both patients belonged to the mild-to-moderate ED subgroup and were later readmitted to the sleep lab for optimization of CPAP therapy.

In the patients with mild and mild-to-moderate ED, CPAP therapy had no impact on the scores of the IIEF-5 at follow-up. In contrast, there was a significant increase of these scores under CPAP in those patients presenting with moderate and severe ED at the time of study inclusion (Fig. 1).

Moreover, CPAP therapy led to significant decreases of the scores of the ESS in all subgroups investigated. Likewise, with the exception of the patients with mild-to-moderate ED, the scores of the WHO-5 increased under CPAP whereas those of the MDI decreased (Figs. 2–4).

The positive effect of CPAP therapy on ED tended to depend on good CPAP compliance (ie positive effect mainly occurred in those patients with more than 5 h of CPAP use per night), however, this was statistically not significant (r = 0,201, p = 0,053, Fig. 5). Furthermore, positive effect was more pronounced in those patients with larger increases of quality of life under CPAP (p < 0,05). In contrast, positive effect was not related to the improvements of daytime sleepiness and depression occurring after CPAP (data not shown).

Table 1
Anthropometric data and co-morbidities.

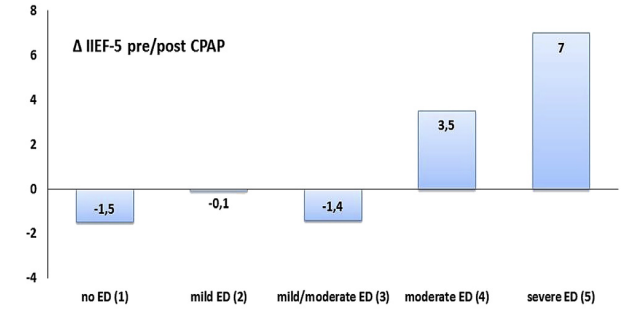
	All pts.	No ED	Mild ED	Mild-to-moderate ED	Moderate ED	Severe ED
Number of pts. (n/%)	94/100,0	30/31,9	34/36,2	18/19,1	6/6,4	6/6,4
Age (years)	51,5 ± 0,9	47,6 ± 1,5	52,3 ± 1,6*	55,7 ± 1,7**	54,0 ± 2,9	52,0 ± 4,4
BMI (kg/m^2)	34,2 ± 0,6	33,6 ± 1,2	34,8 ± 0,9	34,1 ± 1,1	33,9 ± 2,1	34,4 ± 3,1
Hypertension (n/%)	60/63,8	14/46,7	25/73,5	13/72,2	5/83,3	3/50,0
CAD (n/%)	13/13,8	1/3,3	8/23,5	1/5,6	2/33,3	1/16,7
PAD (n/%)	3/3,2	1/3,3	1/2,9	1/5,6	0	0
Diabetes (n/%)	20/21,3	5/16,7	8/23,5	5/27,8	1/16,7	1/16,7
Hyperlipidemia (n/%)	27/28,7	4/13,3	14/41,2	7/38,9	1/16,7	1/16,7
Smoking (n/%)	31/33,0	9/30,0	13/38,2	7/38,9	1/16,7	1/16,7
β-blockers (n/%)	30/31,9	10/33,3	11/32,4	5/27,8	3/50,0	1/16,7

Abbreviations: BMI = body mass index, CAD = coronary artery disease, ED = erectile dysfunction, PAD = peripheral artery disease.
*p < 0,05 / **p < 0,01 vs. patients without ED.

Table 2
Results of polysomnography and questionnaires at baseline.

	All pts.	No ED	Mild ED	Mild-to-moderate ED	Moderate ED	Severe ED
Number of pts. (n/%)	94/100,0	30/31,9	34/36,2	18/19,1	6/6,4	6/6,4
AHI (n/hour of TST)	56,0 ± 2,3	46,9 ± 3,2	65,8 ± 3,8**	57,1 ± 6,0**	49,0 ± 5,4	53,0 ± 7,4
Mean SpO_2 (%)	92,4 ± 0,3	92,2 ± 0,6	92,3 ± 0,4	92,1 ± 0,7	93,3 ± 0,5	93,7 ± 0,9
Lowest SpO_2 (%)	71,7 ± 1,4	69,7 ± 3,1	71,4 ± 2,3	73,3 ± 2,3	73,8 ± 4,7	75,2 ± 5,1
SpO_2 < 90% (% of TST)	14,7 ± 1,6	15,4 ± 3,4	16,2 ± 2,6	11,2 ± 3,4	10,5 ± 2,1	16,5 ± 6,0
IIEF-5	18,4 ± 0,6	24,1 ± 0,2	19,7 ± 0,2	14,1 ± 0,4	9,2 ± 0,4	4,0 ± 1,1
ESS	9,8 ± 0,5	9,3 ± 0,8	9,7 ± 0,9	10,3 ± 1,4	11,3 ± 1,7	10,5 ± 0,9
WHO-5	11,7 ± 0,6	11,7 ± 1,0	12,1 ± 1,1	12,4 ± 1,6	10,3 ± 2,8	8,3 ± 1,0
MDI	15,0 ± 1,1	12,7 ± 1,6	15,9 ± 1,7	15,9 ± 3,2	16,3 ± 5,4	16,5 ± 2,8

Abbreviations: AHI = apnea-hypopnea-index, ED = erectile dysfunction, ESS = Epworth Sleepiness Scale, IIEF-5 = International Index of Erectile Function, MDI = Major Depression Inventory, SpO_2 = oxygen saturation, TST = total sleep time, WHO-5 = World Health Organization Quality of Life Questionnaire.
**p < 0,01 vs. patients without ED.



Group 4 vs. groups 1 and 3 : p < 0,05

Group 5 vs. groups 1, 2 and 3 : p < 0,01

Fig. 1. Effects of CPAP therapy on erectile function.

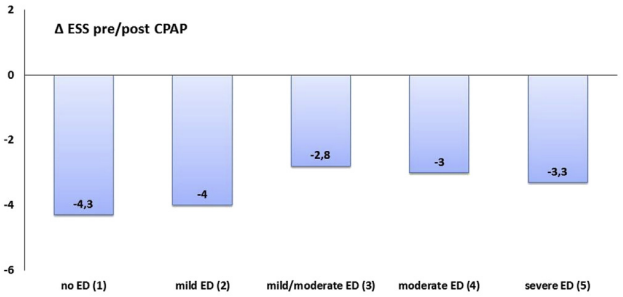
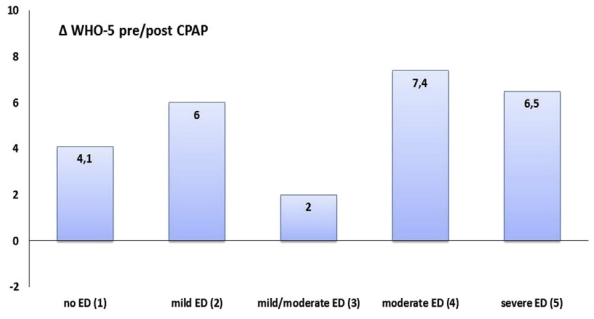
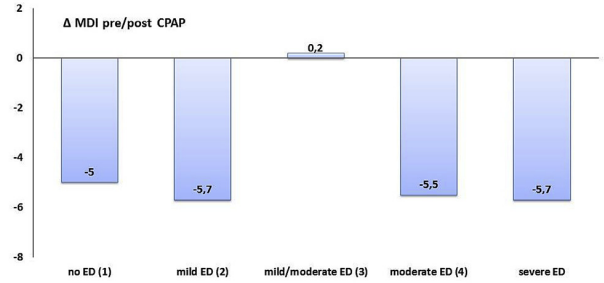


Fig. 2. Effects of CPAP therapy on daytime sleepiness.



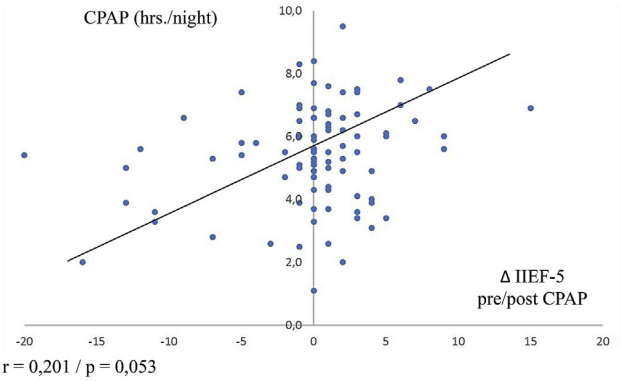
Group 3 vs. groups 2 and 4 : p < 0,05

Fig. 3. Effects of CPAP therapy on quality of life.



Group 3 vs. 2 : p < 0.05

Fig. 4. Effects of CPAP therapy on depression.



r = 0,201 / p = 0,053

Fig. 5. CPAP compliance and change of erectile function.

4. Discussion

The main results of the present study performed in men with severe OSA were that ED was highly prevalent and that long-term CPAP therapy improved erectile function in most seriously affected patients.

ED was observed in about two thirds of the patients investigated. This is in accordance with prior studies evaluating the prevalence of ED in patients with OSA [1–5]. Overall, sleep study parameters were similar in patients with varying severities of ED and those with normal erectile function, however, it must be considered that our patients were characterized by a comparable degree of sleep-disordered breathing (ie, all of them had an AHI ≥ 30/h). Somewhat unexpectedly, other characteristics such as age, BMI and co-morbidities did not differ in patients with vs. without ED as well.

After a mean follow-up period of seven months, CPAP therapy improved erectile function in those patients with the lowest IIEF-5 scores at baseline. At first sight, quite similar observations have already been reported in a preceding study by Budweiser et al. [22], however, there are major differences between these two studies.

First, Budweiser & colleagues investigated patients with the whole spectrum of OSA, ie, including those with an AHI <30/h. In contrast, we restricted study enrollment to subjects with severe OSA. Second, CPAP compliance was evaluated by asking patients if they had used their CPAP device at home and not by reading out time counters as in our study. This probably led to an over-estimation of CPAP use in the Budweiser study, as patients usually tend to report better than measured CPAP compliance [27]. Third, these authors did not perform sleep studies at follow-up. Therefore, it is unclear whether all patients had effective suppression of their OSA under CPAP therapy whereas in the present study adequate reversal of sleep-disordered breathing was ascertained by polygraphy. Fourth, Budweiser et al. employed the extended version of the IIEF (the IIEF-15). This questionnaire has other cut-off values for diagnosing ED than the IIEF-5 used in our study. Finally, and most important, the study by Budweiser et al. found no improvement of the erectile function subdomain of the IIEF-15 under CPAP. Conversely, we observed a highly significant improvement of erectile function after CPAP in those patients suffering from moderate and severe ED.

One notable finding of our study was the trend for larger improvements of erectile function in those patients exhibiting better CPAP compliance. This would have possibly been statistically significant if we had enrolled more patients with moderate or severe ED (only 12 patients belonged to these two subgroups). Furthermore, not only the presence and severity of OSA but also its duration may play an important role in the development and persistence of ED in these patients. Thus, it is conceivable that patients with long-standing OSA may have ED which is “resistant” to CPAP. This confounding factor is very difficult to quantify and was not taken into account in our study.

As previously mentioned, numerous pathways may underlie ED in OSA which can all be reversed by CPAP therapy. We can not identify the exact mechanism(s) by which CPAP exerted its beneficial effect on erectile function. Based on the available evidence we would speculate, however, that this was primarily due to the elimination of the OSA-associated hypoxia finally leading to restored endothelial-dependent vasodilation in the penile vasculature. Direct evidence from human studies lacks within this context, however, experiments performed in rodents subjected to intermittent hypoxia are in favour of this hypothesis. In rats, ED develops due to an activation of NADPH oxidase with increased production of reactive oxygen species and subsequent impairment of NO synthase activity [28]. Similarly, in mice reduced corpus spongiosum pressure and sexual activity as well as decreased endothelial NO synthase expression in the erectile tissue were observed in response to chronic intermittent hypoxia [29].

In the present study, we also evaluated changes of daytime sleepiness, quality of life and depression occurring under CPAP. As could be expected, all of these items were improved by CPAP treatment. Moreover, larger increases of quality of life were associated with greater improvements of erectile function. Similar results were reported by Goncalves & colleagues who evaluated changes of erectile function and quality of life (as judged by the SF-36 questionnaire) before and after one month of CPAP therapy in a small number of OSA patients [17]. Thus, it may be possible that better quality of life is partially responsible for the improvement of erectile function under CPAP. On the other hand, the increase in quality of life may not be the cause but rather the consequence of a more active and satisfying sexual lifestyle in CPAP-treated OSA patients.

In contrast, the improvement of erectile function occurring after CPAP was not related to its positive effects on daytime sleepiness and depression. Again, this is in line with data from the literature showing no effect of antidepressant therapy on erectile function in OSA patients despite restoration of their depression scale results [21].

5. Limitations

Our study has some limitations. First, it may be suspected that a bias was introduced by the large number of patients who were lost to follow-up or had incomplete data sets. However, this is unlikely as the characteristics of these drop-outs were quite similar when compared with the patients finally included in our study. Second, objective determinations of erectile function such as by measuring nocturnal penile tumescence were not attempted. Third, we did not perform polysomnography at follow-up. Fourth, sleep study analysis was not carried out centrally. Finally, and most important, we did not include a control group of sham-treated or even untreated patients. It might be argued that the inclusion of such a control group would have posed ethical problems as severe OSA is linked with increased mortality. On the other hand, a certain proportion of patients refuses home-based CPAP therapy and may thus have served as a suitable comparator group. We suggest that these issues should be addressed by future studies employing more sophisticated and randomized controlled designs.

6. Conclusions

In summary, ED is very frequent in men with severe OSA and can at least partly be reversed by long-term CPAP therapy in most seriously affected patients. The beneficial effect on erectile function may depend on CPAP compliance and is accompanied by improvements of quality of life. Randomized controlled trials are needed to confirm these findings.

Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.03.018.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sleep.2018.03.018.

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