Attention please: vigilance in patients with excessive daytime sleepiness

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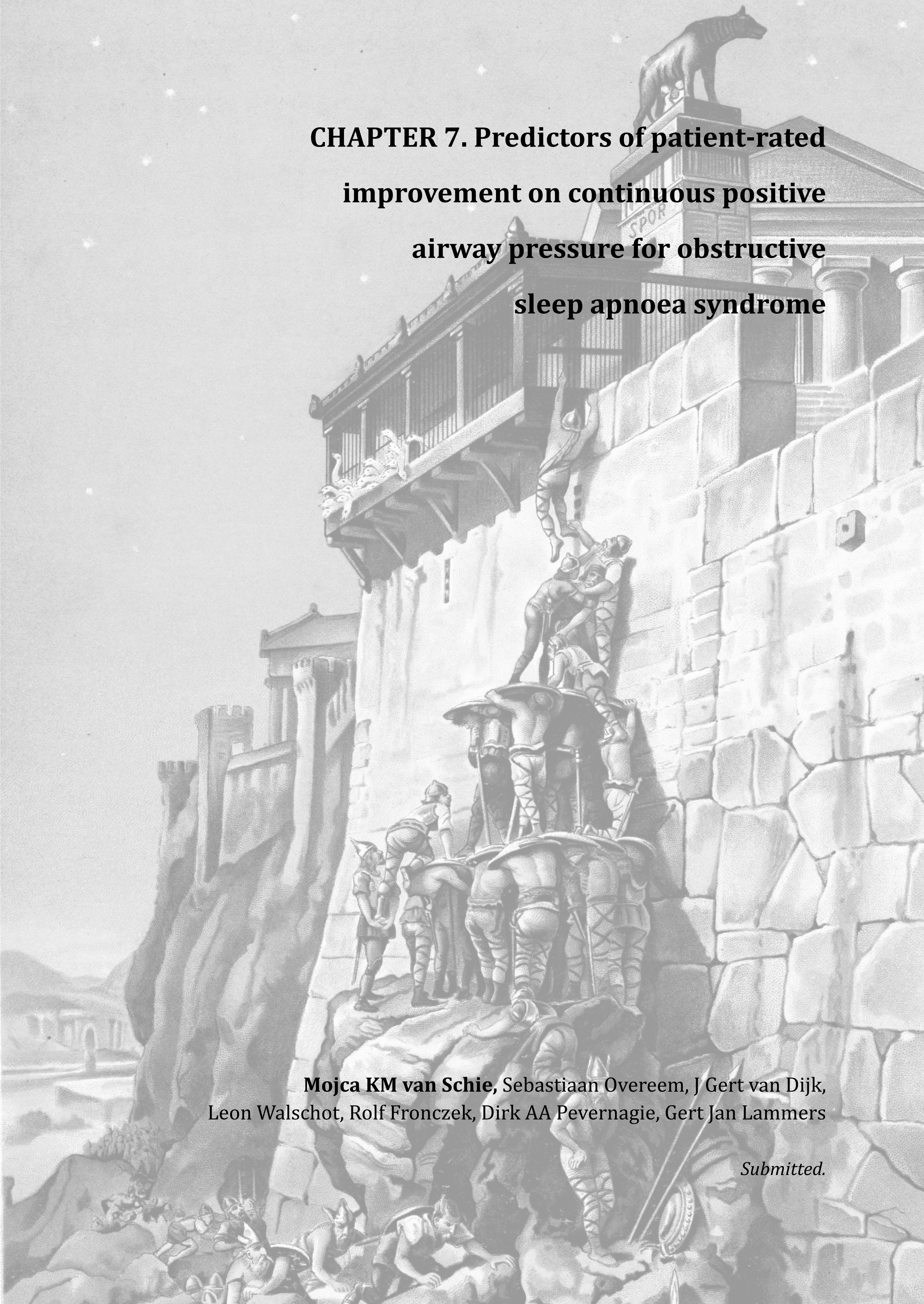

CHAPTER 7. Predictors of patient-rated improvement on continuous positive airway pressure for obstructive sleep apnoea syndrome

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Submitted.

ABSTRACT

Study Objectives

To investigate whether vigilance predicted patient-rated improvement after start of continuous positive airway pressure (CPAP) for obstructive sleep apnea syndrome (OSAS) better than parameters of breathing, sleepiness and well-being

Methods

This study comprised a prospective observational treatment-effect study of CPAP in 30 OSAS patients with an apnea-hypopnea index (AHI) >15. Vigilance, assessed through a sustained attention to response task (SART), sleepiness, measured using questionnaires, and well-being, measured with visual-analog scales, were measured during two pre-treatment visits and one after 8 weeks of CPAP. Improvement was scored on the patient-rated Clinical Global Impression of Change (PCGI-C)

Results

A linear mixed model analysis of CPAP effect indicated an improvement of all breathing indices; the AHI decreased from 41.1±24.4 to 4.1±4.3 ($p<0.001$). The Epworth Sleepiness Scale (ESS) decreased from 14.4±4.2 to 7.9±4.8 ($p<0.001$). The 100mm- visual-analog scale (VAS) of physical exhaustion decreased by 6.4 mm ($p=0.009$). No significant difference was observed in the other VAS ratings, nor in the error score on the SART. Eighty percent of patients considered themselves improved on the PCGI-C. This improvement correlated with improvement of breathing indices and the ESS.

Conclusions

The large majority of OSAS patients considered themselves improved after 8-week CPAP treatment. This improvement was best predicted by a decrease of the breathing disturbance indices. Patients' sleepiness also improved significantly. Vigilance did not predict patient-rated improvement. This study did not provide better predictors of subjective improvement after CPAP.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a sleep-related breathing disorder characterized by apneas and hypopneas during sleep, associated with desaturations and sleep disruption. These may lead to daytime symptoms impairing general well-being, including excessive daytime sleepiness (EDS), decreased vigilance, fatigue, mood disturbances, and cognitive complaints.[1]

The severity of OSAS is traditionally quantified with the apnea-hypopnea index (AHI), i.e. the number of apneas and hypopneas per hour of sleep. Continuous positive airway pressure (CPAP), the most frequently used treatment for moderate to severe OSAS, aims to reduce the AHI and consequently improve symptoms. CPAP improves symptoms of OSAS in the majority of patients, though depending on patients' adherence.[2] AHI reduction is considered an important efficacy parameter of CPAP treatment.[3,4] However, this focus on the AHI has been criticized for two main reasons. Firstly, the pathophysiological consequences of OSAS result from the severity of oxygen desaturation rather than the number of apneas or hypopneas itself, implying that the severity of the breathing disturbance will be reflected better by the oxygen desaturation index (ODI[5-8]). Secondly, improving the AHI with CPAP does not alleviate all symptoms,[9-12] indicating that some symptoms may not be a direct consequence of a reversible sleep-related breathing disturbance.

In addition to diminishing the AHI, CPAP has been described to decrease daytime sleepiness, measured by the Epworth Sleepiness Scale (ESS),[13,14] especially in a subgroup with a baseline AHI >15. CPAP in OSAS is also found to improve cognitive functions,[15] in particular attentional functions.[16] The most significant improvements were observed with tests of divided or sustained attention, more than held for classical vigilance tests involving responses to infrequently occurring stimuli.[17] Several vigilance and sustained attention tests have been used in OSAS, both to describe baseline functions and to assess efficacy of CPAP treatment. Validated tests include the Oxford Sleep Resistance (OSLER) test,[18] Psychomotor Vigilance Test (PVT[19]), Steer-Clear,[20] and Sustained Attention to Response Task (SART[21]). The SART demonstrated impaired vigilance in patients with various sleep disorders, including OSAS.[22] It has not yet been used to evaluate CPAP efficacy. It has, however, proved to correlate well with patient-rated treatment efficacy in narcolepsy patients.[23]

Efficacy of CPAP is usually quantified as an improvement of the AHI and other breathing indices, and through patients' reports. Although some correlations between decrease in AHI and self-reported daytime functioning have been described,[24] a substantial number of studies reported absent correlations between AHI, and measures of well-being or daytime functioning such as sleepiness, vigilance, mood, quality of life, or driving simulator performance, following CPAP treatment.[25]

This lack of a clear relation between improved AHI and subjective improvement is puzzling. We hypothesized that subjective improvement after CPAP treatment would be related to improvement of daytime functioning. Unfortunately, it is not obvious which parameters best reflect daytime functioning. We therefore designed this study concerning CPAP in OSAS to compare patient-rated clinical global improvement to parameters of vigilance, sleepiness, well-being, and breathing disturbances. We hypothesized that vigilance improvement might be the best candidate to reflect patient-rated improvement, since vigilance is a prerequisite for daytime functioning. Earlier studies[15-18,20] yielded contrasting findings, perhaps due to a variety of vigilance tests. We therefore decided to investigate vigilance by means of the SART, which has been shown to correlate well with patient-rated treatment efficacy in narcolepsy patients, as mentioned above.[23]

MATERIAL AND METHODS

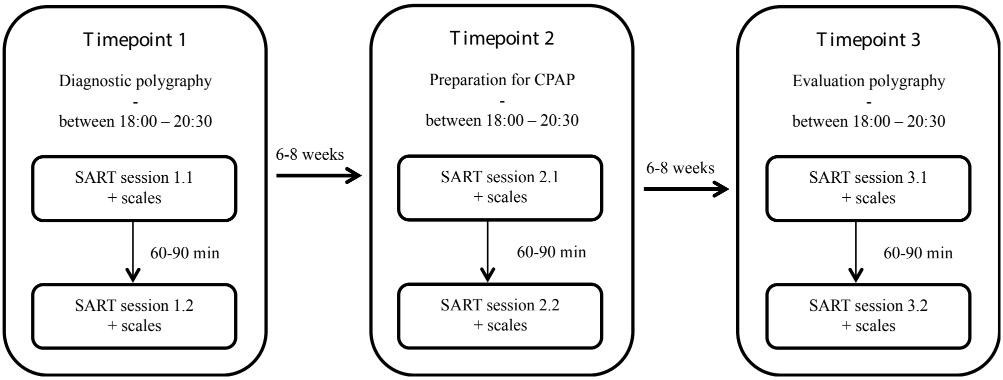
Patients

Study inclusion comprised two steps. Patients referred to the tertiary referral center Kempenhaeghe between June 2011 and June 2013 were screened for eligibility if suspected to have OSAS and aged between 18 and 70 years old. A diagnostic polygraphy/ polysomnography was scheduled. OSAS was based on the ICSD-2 criteria[26]. Those with an AHI > 15/hour were candidates for CPAP and were included in the study. Patients with significant comorbidity or coexisting sleep disorders were excluded. The study was approved by the local medical ethical committee, and written informed consent was obtained from all patients prior to the study.

Design

Data were obtained from three overnight visits in the routine work-up and treatment for obstructive sleep apnea (Figure 1). Although the study comprised therapy, this was not part of the study design. There were two pre-treatment visits with 6-8 weeks in between: the diagnostic polygraphy or polysomnography (timepoint 1) and the CPAP titration night to achieve optimal fixed pressure (timepoint 2). One visit assessed the situation after eight weeks of fixed-pressure CPAP (timepoint 3). Vigilance tests and subjective scores were taken at each timepoint. Perceived improvement with CPAP treatment was scored at timepoint 3. Patients were instructed to refrain from caffeine during all visits.

Figure 1. Study design



Diagnostic polygraphy: either polygraphy or polysomnography (see Table 1); scales: visual-analog scales.

Patient- and partner-rated Clinical Global Impression of Change

The CGI-C is a seven-point visual-analogue scale ranging from (1) 'very strong decrease of complaints' to (7) 'very strong increase of complaints'.[27] Though originally developed as a physician-rated scale, previous work by Forkmann et al indicated a moderate to good agreement of a patient-rated version of the CGI-C in comparison to the doctor-rated version.[28] As we aimed to investigate determinants of subjective improvement in well-being, we chose the patient-rated version of the CGI-C as the gold standard. Patients and their partners rated the scale (patient-version called PCGI-C from here on) at visit 3. Furthermore, patients rated the 16-point efficacy index,[27] which combines a score for the impression of change due to the treatment with a score for the inconvenience or adverse effects caused by the treatment. The efficacy index ranges from (1) 'marked improvement without side effects' to (16) 'unchanged or worse symptoms and side effects that outweigh therapeutic effect'.

Determinants

Vigilance

Vigilance was measured through measurement of sustained attention using the SART, a Go/No-Go paradigm characterized by responding to frequent Go trials and withholding responses to infrequent No-Go trials.

The SART was administered while subjects were seated in front of a computer screen in a quiet room. This 4-minute-19-second taking test comprises the numbers 1 to 9 appearing 225 times in random order on a black computer screen. Subjects had to respond to the appearance of each number by pressing a button, except for the number 3, which occurred 25 times in all. Subjects had to press the button before the next number appeared and were instructed to give equal importance to accuracy and speed in performing the task.[21] Two SART sessions with a 1,5-hour break in between were performed between 18:00 and 22:00 hours on each timepoint.

The primary outcome measure of the SART is the total error score, consisting of key presses when no key should be pressed (i.e. commission errors), and absent presses when a key should have been pressed (i.e. omission errors). The secondary outcome measure is the reaction time, the average time in milliseconds between the appearance of any number and the subject's response. Reaction times could be measured with sufficient accuracy by using a cathode ray tube screen, which was timed using a dedicated video graphics array switch to avoid delays of uncertain magnitude due to build-up of screen data.

Sleepiness

The Epworth Sleepiness Scale served as a general indication of sleepiness during the past month, measured at timepoints 1 and 3. Stanford Sleepiness Scale (SSS) measurements indicated the momentary level of sleepiness and were administered prior to each SART session at timepoints 1, 2 and 3.[29]

Well-being

Patients used seven visual-analog scales (VAS), as previously used in a sleep-restriction study,[30] prior to each SART session at all three visits, assessing the momentary level of general well-being (I feel very bad to very good), daytime alertness (sleepy to alert), stress (stressed to calm), happiness (unhappy to happy), health (sick to healthy), physical exhaustion (physically exhausted to energetic) and mental exhaustion (mentally exhausted to sharp).

Breathing disturbance indices

Apneas were defined as decrements in airflow of at least 90% from baseline for at least 10 seconds.[31] Hypopneas were defined as decrements in airflow of ≥ 50% from baseline for at least 10 seconds, accompanied by a desaturation ≥ 3% from pre-event baseline or an arousal. The sum of apneas and hypopneas per hour formed the AHI. The number of apneas per hour was calculated to obtain the apnea index (AI). The number of desaturations ≥ 3% and ≥ 4% from pre-event baseline per hour were calculated to obtain the oxygen desaturation indices, respectively ODI-3% and ODI-4%. Breathing indices were obtained at timepoint 1 and 3.

Statistical analysis

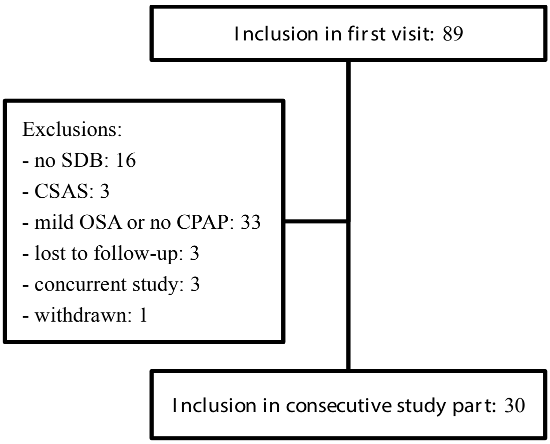
Data were analyzed using IBM® SPSS® Statistics version 23.

A linear mixed effect model was used to compare trends in parameters of vigilance, sleepiness, well-being, and breathing disturbance before and after treatment, taking into account all repeated measurements separately. Significance was set at the $p=0.01$ level to correct for multiple comparisons. Only parameters with a statistically significant change after treatment were used in the subsequent correlation analysis. For this analysis, delta scores for vigilance, sleepiness, well-being, and breathing disturbance were calculated by subtracting the average score before treatment from the score on treatment. Correlations between these delta scores, the PCGI-C scores and the efficacy index were assessed using Pearson's r or Spearman's ρ. Significance was again set at the 0.01 level to correct for multiple comparisons.

RESULTS

Ninety patients were considered eligible. Thirty fulfilled the criteria after polygraphy/ polysomnography and were included (Figure 2, Table 1).

Figure 2. Patient inclusion



SDB: sleep-disordered breathing; CSAS; central sleep apnea syndrome

CPAP compliance data of the month previous to timepoint 3 were available for 28 patients. The median of average CPAP compliance per night was 6:42 hours, and the median percentage of nights with CPAP use > 4 hours was 95%. Eighty percent of patients and 72% of partners reported that patients were much or very much improved on the PCGI-C. No patients or partners considered the patients worsened. Average pre-treatment and post-treatment values of breathing disturbance indices, parameters of sleepiness and vigilance, and VAS scores are displayed in table 1. Average pre-treatment SART error score indicated that pre-treatment vigilance was only moderately disturbed, in contrast to sleepiness and breathing disturbances.[32] Table 2 contains the results of the repeated-measurements analysis of CPAP on all outcome parameters. CPAP significantly and decreased mean AHI, AI and ODI to normal values. Simultaneously, mean ESS score decreased to a normal value. The VAS rating for physical exhaustion also decreased significantly after CPAP. No significant differences were found for SART error count or reaction time, SSS score, or the other VAS ratings.

Table 1 - Characteristics of the patient group

	Before treatment (N = 30)		**After treatment (N = 30)**	
Patient characteristics				
Mean age (years)	55 ± 8			
Sex (n)	M: 27 (90%)			
	F: 3 (10%)			
Mean BMI	31.3 ± 5.3			
Diagnostic PG/PSG (n)	PG: 11; PSG: 19*			
Test characteristics	*Mean*	*(SD)*	*Mean*	*(SD)*
Breathing disturbances				
AHI	41.1	(24.4)	4.1	(4.3)
AI	22.5	(19.7)	1.3	(2.7)
ODI-3%	29.6	(23.7)	4.3	(4.1)
ODI-4%	36.8	(24.9)	1.9	(2.6)
Sleepiness				
ESS	14.4	(4.2)	7.9	(4.8)
SSS°	4.5	(0.9)	4.8	(1.0)
Vigilance°				
SART error score	11.7	(7.1)	10.1	(6.1)
SART RT (ms)	312	(61)	308	(70)
Well-being (VAS)°				
General well-being	64.3	(19.4)	67.3	(19.0)
Daytime alertness	51.8	(19.9)	58.4	(19.6)
Stress	66.6	(22.2)	70.4	(19.6)
Happiness	71.2	(18.8)	72.8	(20.8)
Health	64.6	(21.6)	66.3	(21.5)
Physical exhaustion	55.8	(19.1)	62.2	(19.6)
Mental exhaustion	54.2	(19.7)	58.9	(19.9)
Mean of VAS	428.4	(125.9)	456.4	(127.2)

Legend: n: number; SD: standard deviation; BMI: body-mass index; PG: polygraphy; PSG: polysomnography; AHI: apnea/hypopnea index; AI: apnea index; ODI: oxygen-desaturation index; ESS: Epworth Sleepiness Scale; SSS: Stanford Sleepiness Scale; SART: Sustained Attention to Response Task; RT: reaction time; ms: milliseconds; VAS: visual-analog scales; * Two patients had to come to the clinic twice for timepoint 1 because of an unreliable polygraphy/polysomnography. The baseline breathing disturbance indices were derived from the second timepoint '1' because of the unreliability of the first. °Average of the 4 pre-treatment measurements (timepoint 1 and 2) and the 2 on-treatment measurements (timepoint 3) respectively.

Table 2– Linear Mixed Models of CPAP on all outcome parameters

Modeled parameter	**Intercept** ***Baseline condition***		**Coefficient** ***CPAP effect***	
Breathing	***Beta / S.E. / p***			
AHI	41.1 / 3.07 / 0.000	*	-37.0/ 1.99 / <0.001	*
AI	22.5 / 2.46 / 0.000	*	-21.2/ 1.60 / <0.001	*
ODI_3%	37.0 / 3.11 / 0.000	*	-32.7/ 1.99 / <0.001	*
ODI_4%	29.7 / 2.94 / 0.000	*	-27.8/ 1.92 / <0.001	*
SART	***Beta / S.E. / p***			
Error score	11.8 / 1.19 / 0.000	*	-1.7 / 0.68 / 0.015	
Reaction time	311 / 11.0 / 0.000	*	-2.8 / 6.17 / 0.656	
Sleepiness	***Beta / S.E. / p***			
ESS	14.6 / 0.69 / 0.000	*	-6.8 / 0.46 / <0.001	*
SSS	4.5 / 0.16 / 0.000	*	0.3 / 0.13 / 0.021	
VAS	***Beta / S.E. / p***			
General well-being	64.4 / 3.21 / 0.000	*	2.6 / 2.15 / 0.223	
Daytime alertness	51.7 / 3.19 / 0.000	*	6.6 / 2.66 / 0.015	
Stress	66.3 / 3.54 / 0.000	*	3.5 / 2.32 / 0.136	
Happiness	71.0 / 3.34 / 0.000	*	1.6 / 2.10 / 0.454	
Health	64.3 / 3.62 / 0.000	*	1.7 / 2.43 / 0.494	
Physical exhaustion	55.8 / 3.17 / 0.000	*	6.4 / 2.39 / 0.009	*
Mental exhaustion	53.6 / 3.34 / 0.000	*	5.0 / 2.43 / 0.040	

Legend: AHI: apnea-hypopnea index; AI: apnea index; ODI: oxygen desaturation index with either 3 or 4% cut-off value; ESS: Epworth Sleepiness Scale; SSS: Stanford Sleepiness Scale; VAS: visual-analog scales; Beta: regression coefficient derived from the linear mixed model; S.E: standard error of the regression coefficient; N.A: not available, i.e. no significant contribution to the final model; N.T: not tested in the model. Compound symmetry was chosen as a model for the covariance matrix. Asterisks flag significant LMM coefficients.

The PCGI-C score and the efficacy index were significantly correlated to all breathing disturbance indices. The better the PCGI-C score was, the more improved were the breathing disturbance indices (Table 3). Partners' CGI-C score was significantly correlated to delta-AHI, only. Delta-ESS itself was significantly correlated to delta-AHI, -AI, and -ODI-4% (not shown in the table), indicating that the lower (i.e. the better) the ESS score, the more improvement of the other outcome measures.

Table 3 – Correlations of outcome parameters with patient-rated improvement

	Patient CGI-C	Partner CGI-C	Efficacy index
AHI	r=0.59 **	r=0.58 **	r=0.51 *
AI	r=0.60 **	r=0.29	r=0.48 *
ODI-3%	r=0.59 *	r=0.45	r=0.41
ODI-4%	r=0.64 **	r-0.36	r=0.46
ESS	r=0.45	r=0.26	r=0.43
VAS			
- Physical exh.	r=-0.22	-0.31	r=-0.22

Legend: CGI-C: clinical global impression of change; AHI: apnea-hypopnea index; AI: apnea index; ODI: oxygen desaturation index with either 3 or 4% cut-off value; ESS: Epworth Sleepiness Scale; exh: exhaustion. Asterisks flag significant correlation coefficients with *: p≤0.01, **: p≤0.001. The outcome parameters used in this correlation analysis are the outcome parameters for which a statistically significant change following CPAP treatment was found with the Linear Mixed Models analysis shown in table 2.

DISCUSSION

We investigated changes in vigilance, sleepiness, well-being, and indices of breathing disturbance after 8-week CPAP treatment in OSAS patients, as well as the correlation between these changes and patient-rated improvement on the PCGI-C. In contrast to our hypothesis, there was no significant change in vigilance as assessed with the SART, possibly because SART performance was only moderately disturbed in this study at baseline. In other words, vigilance as assessed with the SART was not a sensitive indicator of baseline impairment. However, other parameters did show patient-rated improvement. We observed a substantial improvement in breathing disturbance indices, implicating that obstructive sleep apnea as causal factor was well controlled. In addition, we observed a substantial improvement of excessive daytime sleepiness measured by the ESS, and a small improvement in the VAS subscale of physical exhaustion. Eighty percent of patients reported themselves much or very much improved on PCGI-C. This improvement correlated well with the improved breathing disturbance indices but only moderately and not statistically significant to ESS. It did not correlate to the VAS of physical exhaustion either. This study therefore showed that changes of AHI and other parameters assessing breathing disturbance best reflected patient-rated improvement.

The correlation coefficients of the correlations between the PCGI-C and the breathing indices were all large, whereas those between PCGI-C and sleepiness were moderate. These results, as well as the correlations observed between sleepiness on the one hand with breathing disturbance indices on the other hand, contrast with previous studies in which breathing disturbance indices, especially AHI, did not correlate with subjective estimates of daytime functioning.[3,8,17,25,33] A possibly contributing factor might be that our patient group was preselected on the criterion AHI > 15, appeared to be relatively severely affected in terms of AHI, and that CPAP adherence was high. Moreover, patients with comorbid sleep disorders were excluded. There have been some indications in previous studies that the treatment effect of CPAP differs between OSAS severity groups based on AHI, with more improvement on sleepiness but less improvement on vigilance for groups with AHI > 30 as compared to groups with lower AHI (range varying across studies, mostly 5-10 or 5-15), for which the opposite yields. [3,4,34] This could apply to our study as well. It might also explain the inconsistency of the literature regarding sustained attention in OSAS: Some studies assessing Steer-Clear performance found a significant difference in obstacle hit between OSAS patients and controls,[35] while others did not or did so only in specific OSAS severity groups based on AHI.[4] A treatment-related improvement of Steer-Clear performance was found in some studies. PVT results also differed across studies, some showing improvement following CPAP,[3,36] while others did not. One recent publication by Guaita et al. did not find a change in SART performance, but pre-treatment error count was already relatively low, as in our study.[37]

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Study limitations

This was an observational treatment-effect study without a placebo treatment group. Therefore, the relevance of small improvements remains uncertain. The large effect size of the improvements of breathing disturbance indices and ESS score is, however, in the same range as was found in the CPAP treatment group in placebo-controlled CPAP treatment-effect studies.[24] The strong correlation between the improved objective breathing disturbance indices and our patient-rated gold standard is reassuring: it excludes the possibility that patients only found themselves improved as a consequence of medical attention. Diurnal influences could have affected our results, since vigilance and sleepiness measurements have only been taken during evening hours. Although these tests were administered at similar times across visits to minimize the consequences of time-of-day performance fluctuations, recent work in narcolepsy showed the possibility of a treatment-induced time-of-day effect with worst performance in the evening.[38] If a similar mechanism would apply to OSAS patients and CPAP as well, our study could have missed a relevant improvement of vigilance in the morning. Another limitation of this study concerns the use of non-validated VAS instead of validated quality of life measurements, although a momentary rating of well-being prior to each SART session would not have been feasible or meaningful with validated quality of life measurements. Nevertheless, discriminative validity of these VAS remains unknown.

Conclusions

The majority of OSAS patients considered themselves improved after 8-week CPAP treatment. This improvement was best predicted by a large and clinically relevant decrease of the breathing disturbance indices AHI, AI, and ODI-3% and ODI-4%. Patients' sleepiness also improved significantly. Vigilance did not significantly improve and, as such, did not predict patient-rated improvement. This study therefore did not provide better predictors of subjective improvement after CPAP.

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