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ABSTRACT

Aim : Central sleep apnoea syndrome (CSA) with Cheyne-Stokes respiration (CSR) has an important influence on prognosis of congestive heart failure (CHF). Nocturnal Continuous Positive Airway Pressure (CPAP) has been found to improve transplant-free survival. Adaptive Servo-Ventilation (ASV) is a novel positive pressure mode that provides servo-controlled bi-level pressure support. The present study compared the compliance with and efficacy of ASV to CPAP, in patients with CSA-CSR and CHF, using Apnoea Hypopnoea Index (AHI), quality of life and LVEF over 6 months.

Methods and results : 25 patients (age: 28-80y, NYHA: II-IV) with stable CHF and CSA-CSR were randomised to either CPAP or ASV. At inclusion, both groups were comparable for NYHA class, LVEF, medical treatment, BMI and CSA-CSR. Both ASV and CPAP decreased the AHI, but noticeably, only ASV completely corrected the CSA-CSR, with AHI below 10/h. At 3 months, compliance was comparable between ASV and CPAP, however, at 6 months compliance with CPAP was significantly less than with ASV. At 6 months, the improvement in quality of life was higher with ASV and only ASV induced a significant increase in LVEF.

Conclusion : These results suggest that patients with CSA-CSR might receive greater benefit from treatment with ASV than with CPAP.

INTRODUCTION

Cheyne-Stokes respiration (CSR) is a distinct pattern of periodic breathing with alternating crescendo-decrescendo sequences of hyperventilation and apnoea, often found in congestive heart failure. [1]The detrimental consequence of Central Sleep Apnoea syndrome (CSA) with CSR (CSA-CSR) on the outcome of congestive heart failure (CHF) patients has been known for a long time.[2][3] This effect appears to be independent of other known risk factors, such as Left Ventricular Ejection Fraction (LVEF) or peak oxygen consumption. Haemodynamic improvement after pharmacological therapy for CHF is often associated with a significant decrease in CSA-CSR. However, persistent CSA-CSR, despite optimal pharmacological therapy, should be treated more aggressively. Its treatment with nocturnal Continuous Positive Airway Pressure (CPAP) was first described in 1990.[4] CPAP, when it alleviates CSA-CSR, reduces sympathetic nervous system activity and improves LVEF.[5] The effect of CPAP over a prolonged period has been found to improve ejection fraction and combined mortality-cardiac transplantation rate in a monocentric randomized study.[6] However, CPAP did not always normalize the Sleep Apnoea Syndrome (SAS). Adaptive servo-ventilation (ASV, AutosetCS ®, ResMed Corp, San Diego, CA) is a novel therapy that provides a positive expiratory airway pressure and an inspiratory pressure support which is servo-controlled, based on the detection of CSR, with a backup respiratory rate. In a study with a randomized cross over design, ASV was shown to be effective in controlling central apnoeas and in improving sleep quality better than CPAP or nasal oxygen.[7] In a one-month randomized parallel trial versus placebo, ASV was recently reported to induce a significant improvement in daytime sleepiness and also in plasma brain natriuretic factor and catecholamine urinary excretion, both markers of CHF prognosis,[8] whereas no change was observed in patients with the placebo, which was subtherapeutic ASV.[9] With the aim of comparing ASV with CPAP in the treatment of CSA-CSR in heart failure patients on a long term basis, we have performed a 6 month, randomized, prospective, parallel comparison of therapeutic ASV *versus* CPAP, and assessed compliance, Apnoea-Hypopnoea Index (AHI), daytime sleepiness, quality of life and LVEF after 6 months of either treatment.

METHODS

Study subjects

This study was a prospective, parallel, randomized, multi-centre trial. Patients between 18 and 80 years old, with stable CHF and newly diagnosed for CSA-CSR by nocturnal polygraphy (Embletta®, Flaga, distributed by Resmed SA, Lyon, France), with an AHI > 15/h, were invited to participate in this study. CHF was defined by medical history of heart failure, a LVEF of 45 percent or less at rest, assignment to New York Heart Association (NYHA) functional class II, III or IV, and the absence, within the previous month, of exacerbations of heart failure while receiving stable optimal pharmacological therapy at the highest tolerable doses.

Sleep studies, daytime sleepiness, respiratory function and cardiovascular assessment

Patients underwent a baseline overnight polysomnographic sleep study in a sleep laboratory. Sleep stages and arousals were scored according to standard criteria [10] and an AHI was calculated.[11] A nasal cannula evaluates the nasal flow together with an oral thermistor. Two channel-Respiratory Inductance Plethysmography (RIP), respectively chest and abdominal RIP was also used to distinguish obstructive from central events, based on the absence of thoraco-abdominal movements in case of central events. Oxyhaemoglobin saturation was monitored by oximetry. CSR was defined by occurrence of crescendo-decrescendo periodic ventilation, and CSA by an AHI > 15/h with more than 80% of central apnoea-hypopnoea. The desaturation index was calculated as the number of dips >3% from the baseline, per hour of sleep.

Daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS) and the Maintenance of Wakefulness Test (MWT) performed the day after the overnight sleep study.[12] Patients sat in a comfortable chair, in the dark, and were asked to resist sleep. Five 30 minute-long tests were performed (8:00, 10:00, 12:00, 16:00 and 18:00). Sleep onset was defined as the time from “lights off” to the first of three consecutive epochs of stage 1 non-REM sleep or one epoch of any other sleep stage. Once sleep onset was identified, the patient was awakened to prevent consolidated sleep improving his performance on the subsequent test. The mean latency of the five tests was calculated.

Quality Of Life (QOL) was evaluated by the *Minnesota Living with Heart Failure Questionnaire* [13] which is a self-administered test of 21 questions specifically assessing the limitations commonly associated with heart failure, the answer to each question raging from 0 to 5, the lower the score, the better the quality of life. LVEF was measured by conventional radionuclide isotopic technique.

Intervention

After their baseline polysomnography, patients underwent the therapeutic trial. All patients were naïve to nocturnal ventilation. Adaptation was performed during one night in lab- polysomnography using a CPAP device, in order to determine the effective CPAP pressure (Peff), and to check blood pressure (BP) tolerance to nocturnal ventilation and mask leaks. The ventilation was started with a nasal mask that was switched to a facial mask if leaks were > 0.4 l/sec. Airway pressure was manually increased from 4 cm H_2O to the Peff, with a maximum of 12 cm H_2O. The Peff was chosen as the pressure abolishing or significantly decreasing the CSR. The titration was performed with BP monitoring: BP was checked just before and 5 minutes after any increase in CPAP pressure. In case of a BP drop of greater than 20% from baseline following an increase in CPAP, pressure was decreased by 1 cm H_2O, BP checked, and the titration interrupted if BP did not return to the previous value within 5 minutes.

On the next day, patients were randomly assigned to either CPAP set at the Peff, or to ASV set to its default settings (expiratory pressure 5 cm H_2O, inspiratory pressure support between 3 and 10 cm H_2O, back-up respiratory rate 15 breaths per minute).

Nocturnal ventilation was provided at day zero (D0) by a non-profit home care company (ADEP Assistance), whose nurses checked BP at rest and after 15 minutes of machine use on awake patients. They came back to check tolerance to and compliance with treatment on the following day (D1), on D7 and then every month over the 6 month-period of the study. Compliance was measured as the machine use (h/night) given by the in-built counter.
Efficacy of treatment on CSA-CSR evaluated by polysomnography and QOL were assessed at 3 months. Measurements at inclusion and 6 months included QOL, polysomnography, MWT, ESS and LVEF.
The study complied with the Declaration of Helsinki and was approved by a locally appointed ethics committee. All patients gave their informed consent to participate in the study.

Statistics

Data are presented as mean (standard deviation), unless otherwise stated. Unpaired *t* tests were used for normally distributed data and Mann–Whitney U tests were used for non-normally distributed data, correlations were tested using the Z test (Statview program, version 5.0, Abacus concept, Cary, NC, USA). Significance was considered for $p < 0.05$.
Regarding compliance, comparisons were performed after exclusion of the patient who underwent heart transplantation in the ASV group, and the two patients who deceased in the CPAP group. The value “zero” was assigned to compliance of the two patients in the ASV group and of the three patients in the CPAP group who dropped out.

RESULTS

Patients

320 patients were screened between April 2001 and November 2003. 32 were eligible regarding inclusion criteria and 25 patients (28-80y, NYHA: II-IV) were recruited. The remaining seven declined to participate in the study. Both randomisation groups were comparable in terms of clinical presentation, LVEF (range 18-44%), SAS and sleepiness (tables 1 and 2). Atrial fibrillation was present in 5 and 6 patients respectively in the ASV and the CPAP group. 92% of the overall population of the study were treated with diuretics, 68% with angiotensin converting enzyme inhibitors, 72% with beta-blockers and 76% with antiplatelets and/or anticoagulants. Medical treatment was comparable in both groups (table 1).

Twelve patients were allocated to the ASV group, and thirteen to the CPAP group. Eight patients dropped out of the study, 3 in the ASV group and 5 in the CPAP group. In the ASV group, one patient underwent heart transplantation (after 3 months) and two chose to discontinue ASV, respectively after 4 and 5 months. In the CPAP group, three patients discontinued CPAP (one at 2 weeks after initiation of treatment, one after one month and one after 4 months) and two deceased, one from septic shock at one-month of treatment and one from carcinoma at 3 months. In the CPAP group, mean Peff was 8.0 (1.8) cm H_2O (5.0 minimum – 10.0 maximum).

Table 1

Baseline characteristics of both study groups regarding NYHA stages, causes of heart failure, left ventricular ejection fraction, and treatments

	ASV group (n=12)	CPAP group (n=13)
Age, yr	64.2 (15.5)	60.3 (11.5)
NYHA stages, mean (SD)	2.9 (0.6)	3.0 (0.1)
Causes of heart failure		
coronary heart disease	7	8
valvulopathy	3	2
others	2	3
Left ventricular ejection fraction, mean % (SD)	29 (9)	30 (9)
Treatments		
Diuretics	12	11
ACE inhibitors	8	8
Beta-blockers	9	9
Platelet-inhibitor and anti-coagulants	11	8

Data are provided as number of patients in each group, except the isotopic left ventricular ejection fraction given as mean % (SD). Both groups were comparable regarding all these parameters.

Table 2

Baseline general characteristics of the study groups

	ASV Mean (SD) (n=12, male)	CPAP Mean (SD) (n=13, male)
Body mass index, kg/m^2	25.2 (3.3)	28.8 (6.3)
Apnea/hypopnoea index, per hour	47 (18.6)	40.5 (13.9)
Oxygen desaturation index,	45.7 (19.4)	34.7 (17.8)
Epworth sleepiness score	8.6 (4.9)	7.4 (3.9)
Minnesota questionnaire	54.4 (26.5)	43.8 (22.3)

Definition of abbreviations: ASV = adaptive servo-ventilation; CPAP = continuous positive airway pressure

Effects on sleep apnoea syndrome and daytime sleepiness

In both groups nocturnal ventilation induced a significant decrease in AHI (fig. 1, panel A), however the decrease in AHI obtained with ASV was significantly greater than with CPAP, both at 3 and 6 months (fig. 1, panel B). In the CPAP group, three patients had an AHI ≥ 20/h at 6 months, but they did not exhibit any particular clinical characteristics. No correlation was found between the Peff level and the AHI at 6 months, suggesting that lack of efficacy was not due to insufficient level of CPAP. Noticeably, only ASV completely corrected the CSA-CSR with normalization of AHI (fig. 1 panel A).
Nocturnal ventilation induced a non-significant decrease in the ESS [-3.0 (5.7) in the ASV-, and -1.3 (3.2) in the CPAP-group] as well as a non-significant increase in MWT [1.1 (6.0) minutes in the ASV-, and 5.8 (6.9) minutes in the CPAP-group]. However, and in line with a previous report,[9] those patients were not, or only a little, sleepy at baseline, with ESS 8.0 (4.4) and MWT 18.5 (8.5) minutes.

Compliance with treatment

Overall compliance with treatment was 4.7 (2.6) h/night at 3 months, and 4.3 (3.1) h/night at 6 months. In contrast to ASV, compliance with CPAP significantly decreased over time (fig. 2) and therefore compliance at 6 months was higher with ASV than with CPAP.

Effects on cardiac function and on quality of life

Only 7 patients treated with ASV, and 6 patients treated with CPAP, underwent LVEF measurements at 6 months. Despite this small number, a significant difference was found as ASV induced a significant increase in LVEF whereas CPAP had no effect (fig.3).
The QOL was improved by either mode of nocturnal ventilation, as shown by the positive difference between the initial value of the score minus the value at the considered time-point, either 3 or 6 months. However, the improvement in QOL was significantly higher with ASV than with CPAP after 6 months of treatment (fig. 4, panel A). A positive correlation was found between compliance with treatment measured at 6 months, and the improvement in QOL (fig. 4, panel B).

Discussion

The present study was undertaken to compare compliance with and efficacy of ASV to CPAP over a prolonged period of time, namely 6 months. This study demonstrates that patients with CSR and symptomatic CHF treated by either ASV or CPAP have good compliance to nocturnal ventilation over 6 months, but that the compliance to treatment is higher with ASV compared to CPAP. We also show that nocturnal ventilation improves both SAS and QOL, with ASV having a greater effect compared to CPAP. In addition, in this study, only ASV induced a significant gain in LVEF over 6 months.

According to previous studies,[7] [9] ASV was effective in correcting CSA-CSR, and was more effective than CPAP. Additionally, CSA-CSR was always corrected with ASV, in contrast to CPAP. A previous study had demonstrated that ASV was effective in correcting CSA-CSR and improving sleep, and that it was more effective than oxygen or CPAP.[7] This partial response to CPAP is in line with some previous studies.[14] [5] Remarkably, some patients who responded to CPAP after 3 months of treatment did not respond at 6 months, whereas the efficacy of ASV was consistent over 6 months. The method used in this study to apply CPAP was somewhat different from other studies, in which the target pressure was 10 to 12.5 cm H_2O [6] and was not based on a titration night. Here, the Peff for each patient was the result of both the haemodynamic tolerance to CPAP and the efficacy of CPAP on CSA-CSR, leading to a lower mean pressure [8.0 (1.8) cm H_2O]. Taking into account the haemodynamic tolerance of CPAP might be important as a potentially detrimental effect of CPAP has been underlined in an early report.[15] Indeed, a reduction in cardiac output under CPAP has been described in patient with post-capillary wedge pressure < 12 cm H_2O.[16] Conversely, Bradley et al. reported an increase in cardiac output and stroke volume using a low level (5 cm H_2O) of CPAP.[17] Accordingly, Baratz et al. found an increase in cardiac output in 7 out of 13 patients with acute heart failure using several CPAP levels.[18] Naughton et al. showed that stroke volume index and cardiac index that significantly decreased under CPAP (which was up to 10 cm H_2O) applied to healthy subjects, did not change in patients with CHF.[19] Altogether, these results suggest that the effect of CPAP depends on the level of pressure and the initial haemodynamic status of the patient.

Compliance with treatment was in the range of what is usually reported when using CPAP to treat obstructive SAS (OSAS). Adherence to treatment was also in the range of that usually reported in the treatment of conventional OSAS with CPAP, where the drop-out rate is from 5 [20] to 37%.[21] In the current study, 3 patients in the CPAP-group (23%) and 2 (17%) in the ASV-group discontinued the study secondary to nasal ventilation intolerance. The lack of adherence might be linked to absence of daytime sleepiness, evidenced by ESS below 11, and normal MWT values at inclusion, in line with previous studies that have suggested low CPAP acceptance in non-sleepy patients with OSAS.[22][23] In patients who continued nocturnal ventilation over the study duration, overall compliance with treatment was good. Interestingly, compliance with CPAP significantly decreased over time, and became significantly lower than that with ASV at 6 months. The better compliance with ASV might be due to better comfort observed with bi-level ventilation, which may result from the lowering of the pressure at expiration, as suggested by some previous reports on the use of bi-level in OSAS. [24] The variations of pressure support which is anti-cyclic to the CSR might also be a source of increased comfort. Interestingly the compliance at six months was correlated with the improvement in QOL, suggesting that compliance is a consequence of subjective benefits experienced by the patient from his treatment, according to previous observations.[22][23] The compliance may also reflect the efficacy of treatment, in line with Pepperell et al., who showed superior compliance with therapeutic ASV than with subtherapeutic ASV.[9]

The correction of CSA-CSR did not improved daytime sleepiness. However, our patients were not or only moderately, sleepy at baseline and therefore a striking effect was not expected, in line with

previous studies in non-sleepy patients.[22][23] Hanly et al. have reported more pronounced daytime sleepiness in CHF patients, but the measurement of sleepiness was based on multiple sleep latency tests which measure the propensity to get to sleep, and not the capability to resist sleep, like MWT.[25] Accordingly, Pepperell et al., recently studied the effect of ASV upon daytime sleepiness as the capability to resist sleep, by performing Osler tests, and showed a significant improvement, which was not found however on the ESS.

In the present study, CPAP did not improve LVEF, in contrast to previous studies conducted both in the treatment of CSA-CSR [6] and in the treatment of OSAS.[26] This could be due to the small number of patients in this study. Another hypothesis is that the lower mean CPAP pressure applied to our patients resulted in limited haemodynamic benefits of CPAP. On the other hand, using higher levels of CPAP might have detrimental consequences, as discussed above. A final hypothesis is based on the decrease in compliance with treatment observed over time under CPAP, which may negatively influence the usually beneficial effect of CPAP on LVEF. This absence of effect of CPAP on LVEF contrasts with the significant increase in LVEF observed with ASV. The effect of ASV on LVEF is in line with the results of Pepperell et al., who demonstrated a significant decrease in plasma brain natriuretic peptide and urinary metadrenaline excretion after 1 month of treatment.[9]

The acute beneficial effects of CPAP on the cardiovascular system in patients with CHF are well described, and are thought to explain the improvement of physiological outcomes over periods of 1 to 6 months, previously reported.[6] [27] Indeed, in CHF patients, positive airway pressure has positive effects on cardiac haemodynamics, as it increases intrathoracic pressure and augments stroke volume and cardiac output.[17] CPAP also reduces left ventricular preload and afterload by decreasing left ventricular transmural pressures.[28] However, the reduction in preload might be detrimental under certain conditions (see above).[15] It has been previously suggested that atrial fibrillation should be envisaged as a potential detrimental factor in further reducing LV preload during positive pressure application, however in the present study 5 patients in the CPAP group, and 6 in the ASV group had atrial fibrillation, and this did not interfere with the nocturnal ventilation. The reduction in preload is expected to be lower with ASV than with CPAP, as pressure support varies between inspiration and expiration, and varies from one cycle to another. However, these safety data should be obtained in further studies. Additionally, ASV, as a bilevel ventilatory mode, might have greater beneficial effect on PaO_2 compared to CPAP. Indeed, a greater increase in PaO_2 had been observed with conventional bi-level compared to CPAP,[16] [29] thus contributing to further decrease in sympathetic nervous system activity during sleep.

Another important finding of this study is the greater improvement obtained with ASV than with CPAP in QOL, along with increase in LVEF. This improvement was more pronounced than that observed in some studies which looked at other treatments for CHF. For example, a meta-analysis on cardiac resynchronization therapy showed a mean difference in the Minnesota score of 7.6 points [CI, 3.8 to 11.5 points], [30] whereas the difference in the present study was twice this value. Improvement in fatigue and exercise capacity with treatment of CSA-CSR after nocturnal ventilation have previously been reported [31] as well as an improvement in inspiratory muscle strength [32] and both could contribute to improve QOL. Interestingly, compliance with treatment evaluated at 6 months was correlated with improvement in QOL, whereas it was not correlated to initial AHI, initial LVEF nor initial sleepiness. This improvement in QOL was noted despite a lack of significant effect on daytime sleepiness.

The present trial has limitations, the first one being the small number of subjects. However, despite this small number, significant differences were noted between ASV and CPAP, consistent with previous results on ASV [7] [9] and with complete correction of CSA-CSR obtained with such a

ventilation mode. Blinding was also not possible, however study personnel involved in polysomnography readings and LVEF measurements were blinded to the treatment assigned to patients.

On the other hand, only a few randomised studies compare two ventilation modes in treating SAS. [33] In CSA-CSR, only one study compared CPAP on a long term basis to another mode (bilevel pressure support), and showed equal effectiveness of both modes.[34] In summary, our study showed that both CPAP and ASV decrease AHI, but that ASV induced a greater decrease in AHI than CPAP, with a consistent normalization of AHI. Compliance to treatment significantly decreased over time with CPAP, whereas it remained stable with ASV. This might contribute to the increase in LVEF, and to improvement in QOL observed with ASV. These results suggest that patients might receive greater benefit from treatment of CSA-CSR with ASV than with CPAP.

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FIGURE LEGENDS

Figure 1

Effect of nocturnal ventilation on apnoea-hypopnoea index (AHI / h of sleep). Panel A shows the individual AHI in both groups at baseline and after 3 and 6 months of treatment with either ASV (left part of the figure) or CPAP (right part of the figure). Panel B shows the difference between baseline AHI and AHI measured at 3 and 6 months. ASV induced a greater decrease in AHI than CPAP. Data are shown as mean± SD, * indicates a significant difference.

Figure 2

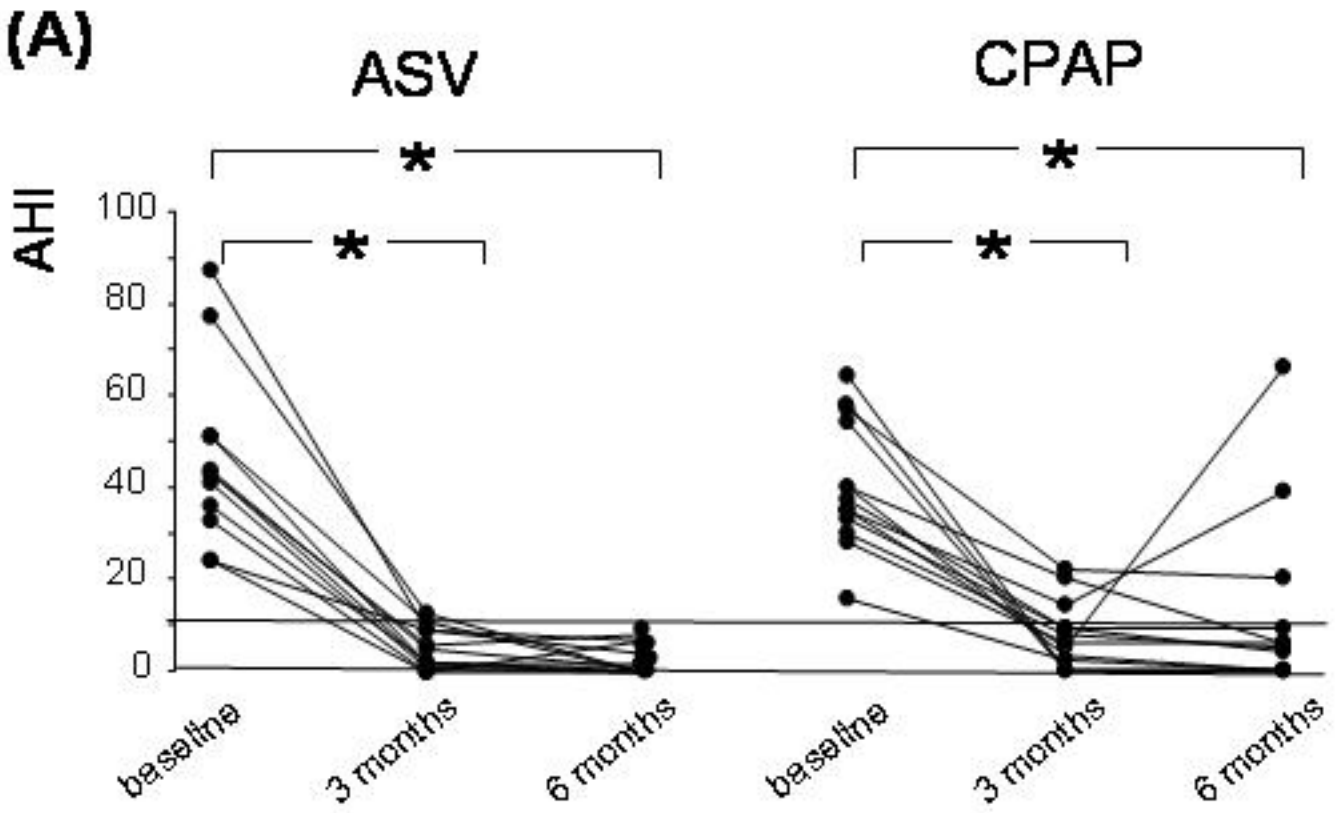
Compliance (h/night) with nocturnal ventilation in both groups, at 3 and at 6 months treated with either ASV (left part of the figure) or CPAP (right part of the figure). One patient died, and one discontinued nocturnal ventilation in the CPAP before the third month, explaining why two points are reported as zero as early as 3 months. Compliance with ASV is significantly better with ASV than with CPAP at 6 months. Additionally a significant decrease in compliance was observed with CPAP between 3 and 6 months. Data are shown as mean± SD, * indicates a significant difference.

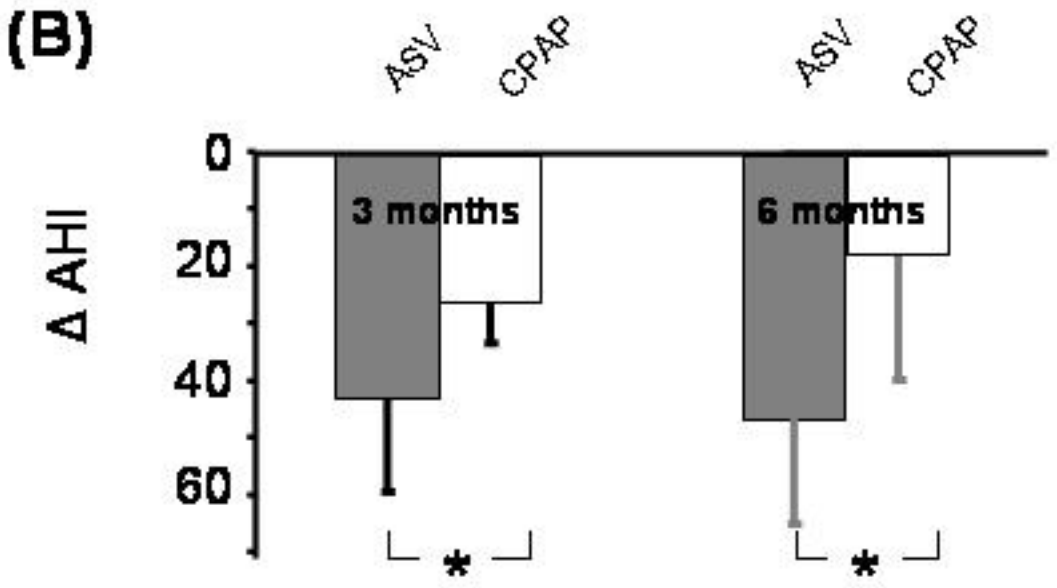
Figure 3

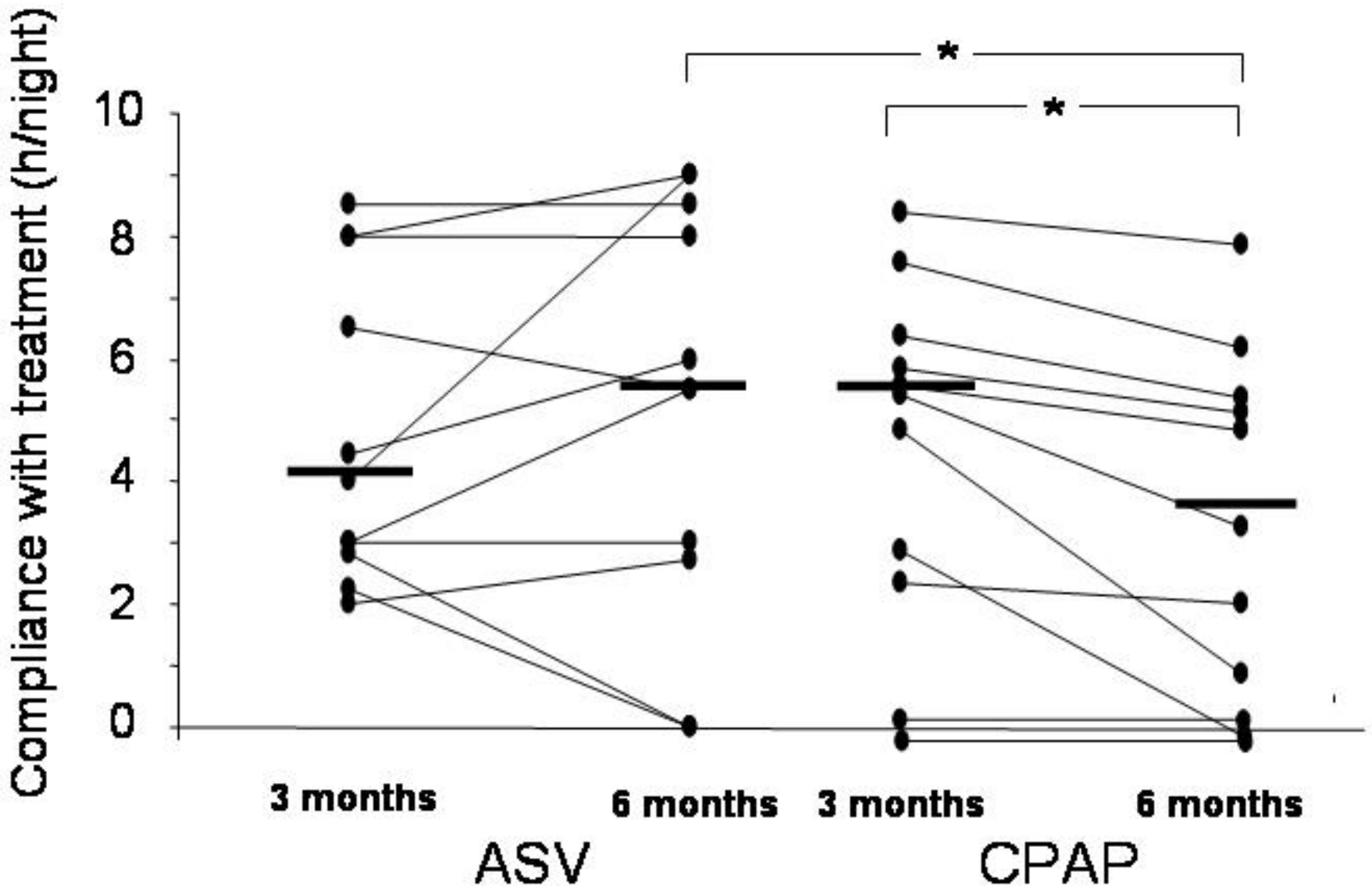
Changes in LVEF (%) obtained with either ASV (white rectangle) or CPAP (grey rectangle). Only ASV induced a significant increase in LVEF. Results are presented as mean ± SD * indicates a significant difference.

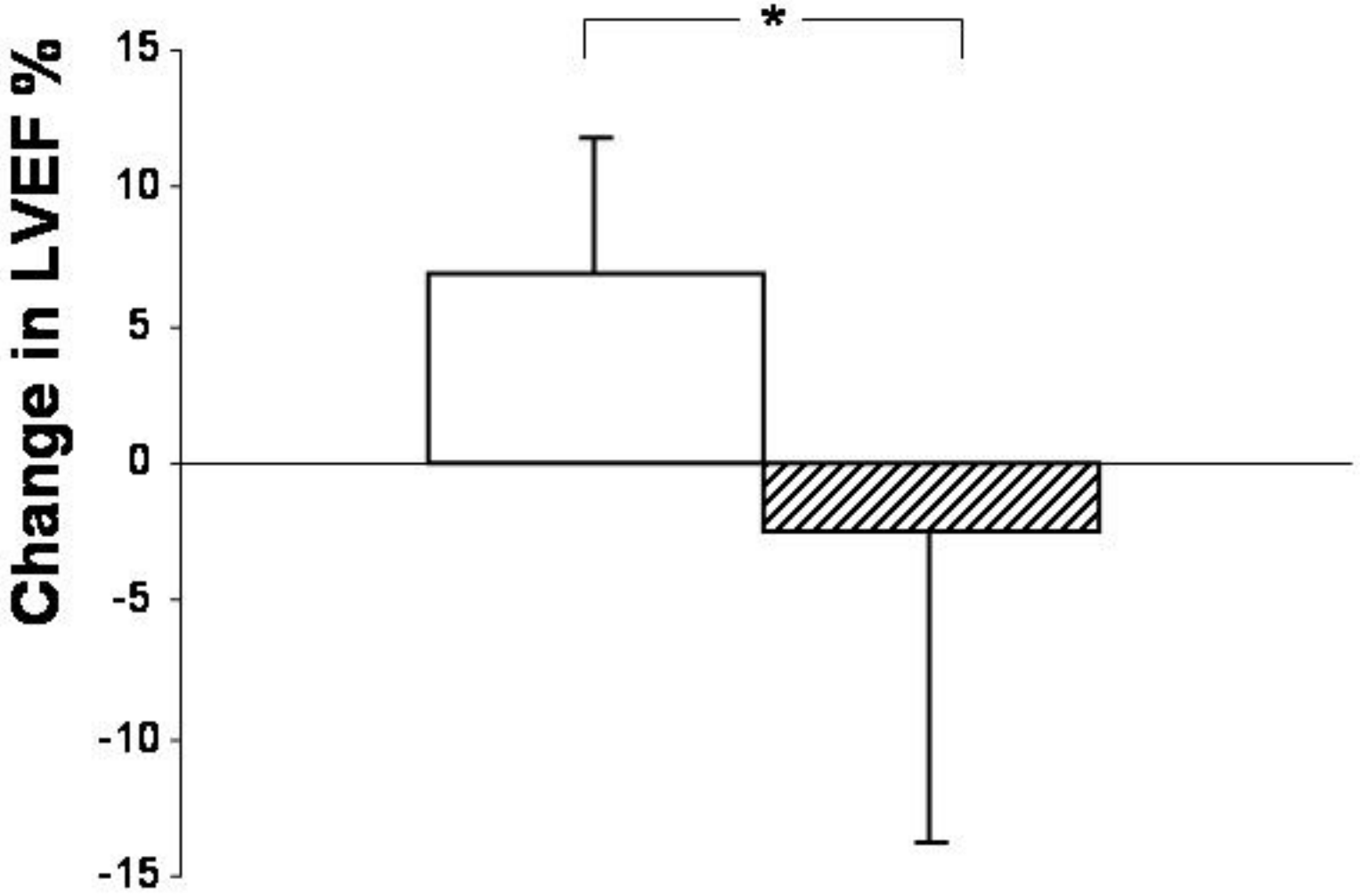
Figure 4

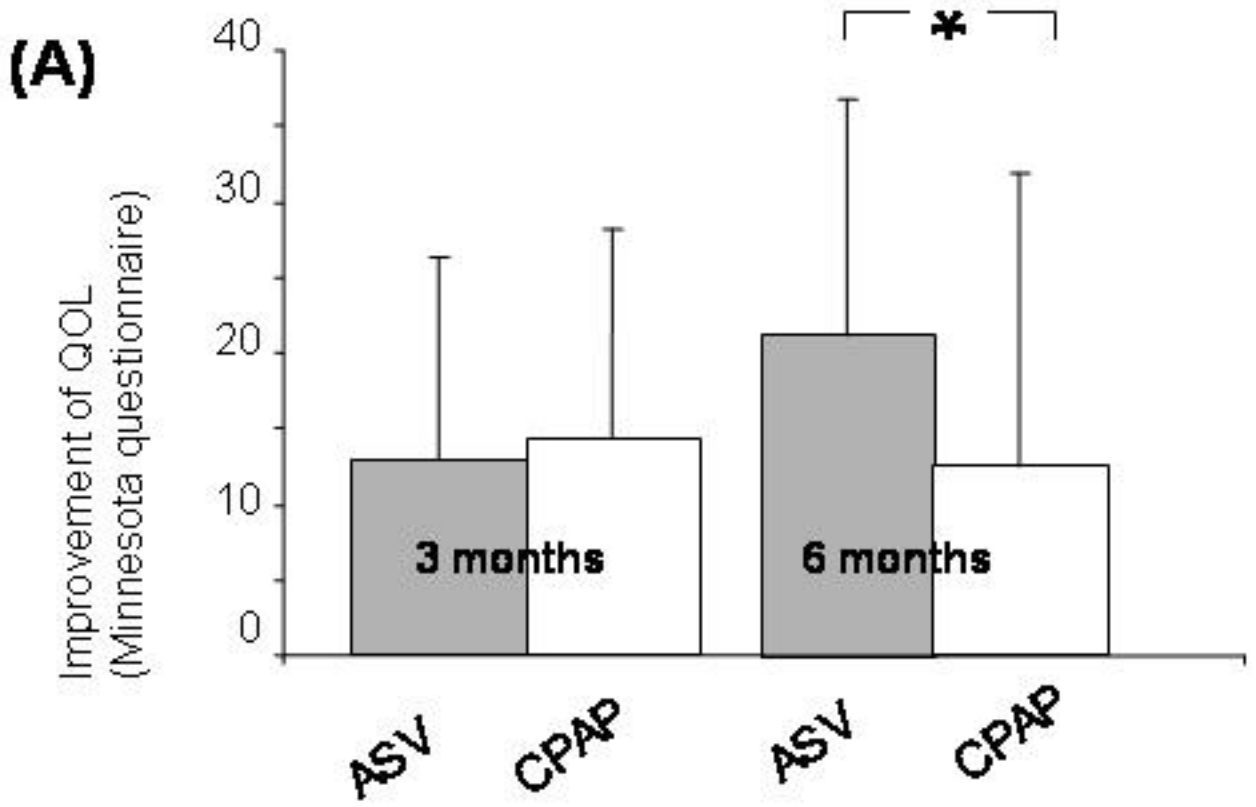
Panel A shows the evolution of quality of life measured by the *Minnesota Living with Heart Failure Questionnaire.* The figure shows the improvement of quality of life expressed by the positive difference between the baseline score minus the score at the considered time point, either 3 or 6 months. Both ASV and CPAP induced a significant improvement in quality of life at 3 months, but the improvement observed after 6 months was significantly greater with ASV than with CPAP. Data are shown as mean± SD, * indicates a significant difference. Panel B shows the significant positive correlation between compliance with treatment measured at 6 months, and the improvement in QOL.

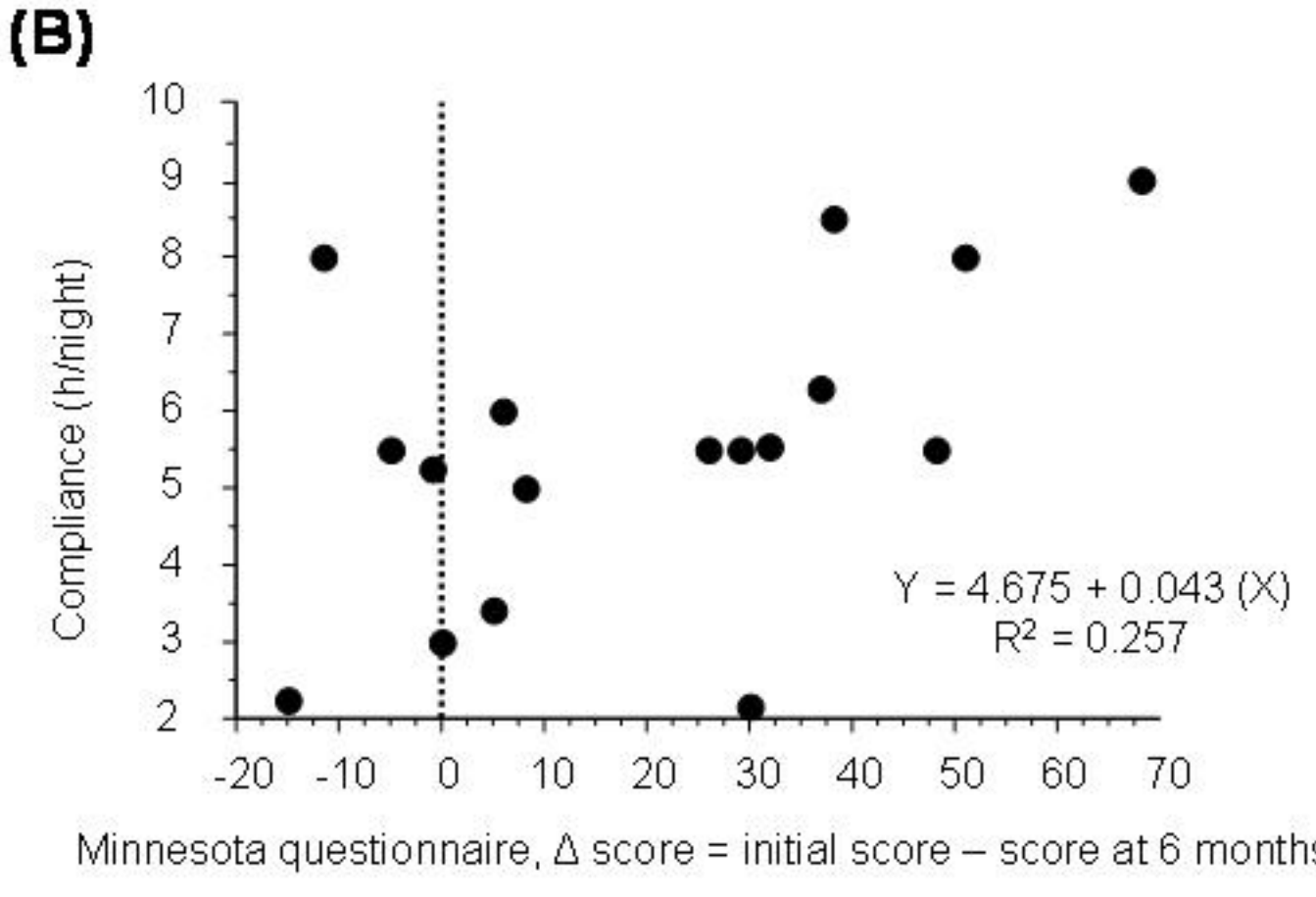

(A)
ASV
CPAP
AHI
100
80
60
40
20
0
*
*
*
*
baseline
3 months
6 months
baseline
3 months
6 months


(B)
ASV
CPAP
ASV
CPAP
Δ AHI
0
20
40
60
3 months
6 months
*
*


Compliance with treatment (h/night)
10
8
6
4
2
0
*
*
3 months
6 months
3 months
6 months
ASV
CPAP


*
Change in LVEF %
15
10
5
0
-5
-10
-15


(A)
*
40
30
20
10
0
Improvement of QOL
(Minnesota questionnaire)
3 months
6 months
ASV
CPAP
ASV
CPAP


(B)
10
9
8
7
6
5
4
3
2
Compliance (h/night)
Y = 4.675 + 0.043 (X)
R² = 0.257
-20
-10
0
10
20
30
40
50
60
70
Minnesota questionnaire, Δ score = initial score – score at 6 months