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Early gain in body mass with continuous positive airway pressure therapy for obstructive sleep apnea

Early body mass gain with CPAP therapy

Introduction

Obesity contributes to the development and severity of obstructive sleep apnea (OSA). Conversely, OSA appears to contribute, in a form of vicious cycle, to the development and severity of obesity [1, 2, 3]. Obstructive sleep apnea confers risk factors for obesity including glucose intolerance and insulin resistance [4, 5, 6], increased levels of appetite-stimulating neuropeptide ghrelin [7], and decreased physical activity [8].

If sleep apnea causes physiological changes that accelerate gain in body mass, then treatment of sleep apnea might slow or reverse development of obesity. Some clinicians believe therapy of OSA with continuous positive airway pressures (CPAP) leads to weight loss [9, 10]. A recent study reported by Redenius et al. [10] set out to prove the hypothesis that CPAP therapy reverses obesity. However, in their retrospective study of 183 patients, not only was there no change in body mass index (BMI) after 1 year of treatment (0.1±0.1 kg/m²), but also the 63 patients who used CPAP for >7 h/night gained in body mass (0.6±0.2 kg/m²) [10].

On review of the studies published to date, the normal course of change in body mass in patients treated for sleep apnea remains undefined. Studies demonstrate increased body mass [10, 11], decreased body mass [9], and no change in body mass [10, 12, 13, 14, 15, 16, 17, 18]. Importantly, two studies of CPAP therapy demonstrated, by different techniques, a reduction in visceral fat mass without a change in body mass. After 6 months of CPAP therapy, Chin et al. [15] demonstrated by computerized tomography a reduction of visceral fat in patients with or without changes in body mass, and a reduction of subcutaneous fat only in patients who lost body mass. After 31 weeks of CPAP therapy, Trenell et al. [18] found, by magnetic resonance imaging, a similar reduction of visceral fat but no change in body mass.

In our clinic population, we had the impression that body mass increased consistently after 4 weeks of CPAP therapy. Three small studies have previously addressed effects of relatively short-term CPAP treatment on body mass. Engleman et al. [13] studied 13 subjects with sleep apnea before and after 21–35 days of placebo or CPAP treatment and found a trend toward increased BMI with treatment (35.8±3 to 36.3±3 kg/m², p=0.08). Another study found no difference after 4 weeks of CPAP treatment (35.7±5.6 to 34.7±6, p=0.8, n=34) [17]. Chin et al. [15] also reported no change in weight after 1 month of CPAP therapy.

To test the hypothesis that physiological changes associated with treatment of OSA might include a relatively rapid increase in body mass, we retrospectively studied body mass change after 1 month and 6 months of CPAP therapy of OSA, and searched for physiological correlates that might indicate mechanisms for an observed, short-term increase in body mass.

Methods

Subjects: We reviewed the records from one physician (RB) of 218 consecutive patients with obstructive sleep apnea treated with CPAP. Criteria for inclusion in the study were as follows: new diagnosis of obstructive sleep apnea, treatment with CPAP, return visit with body mass recorded between 2 and 8 weeks after titration, and absence of left ventricular failure and pregnancy.

Physiological measurement: Patients were weighed each visit on the same, digital scale (Model #8821321134, Vogel & Halke GmbH, Hamburg, Germany). Baseline body mass was recorded after the evening meal on the evening of CPAP titration. CPAP treatment at home was undertaken within 7 days of titration. Arterial blood pressure was measured in the right arm of a seated patient with an aneroid gauge (ADC, Hauppauge, NY), brachial cuff,

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Tab. 1 Baseline data

	Mean	SD	Minimum	Maximum
All *n*=152				
Age (years)	55	14	18	85
BMI (kg/m^{-2})	35.3	7.3	22.9	55.3
AHI (events/h)	38.4	35.9	3.5	166.7
Men *n*=108				
Age (years)	53	14	18	85
BMI (kg/m^2)	34.5	7.0	22.9	54.3
AHI (events/h)	41.0	35.9	4.6	147.6
Women *n*=44				
Age (years)	58	12	27	81
BMI (kg/m^2)	37.1	7.5	24.9	55.3
AHI (events/h)	32.0	35.4	3.5	166.6

SD standard deviation.

and standard technique [19]. The Epworth Sleepiness Scale (ESS) was recorded at each visit. Data were downloaded from positive airway pressure generators using device-specific software to analyze use from all devices with this capability.

Diagnostic methods: Sleep evaluation included history, examination, ESS [20], and polysomnography. Montage for polysomnography included 6-lead/4-channel electroencephalogram (EEG), electro-oculogram, mentalis surface electromyography (SEMG), anterior tibialis SEMG, electrocardiography, nasal/buccal airflow by thermocouple, thoracic and abdominal effort by piezo-belt transduction, intercostal SEMG, and oxyhemoglobin saturation by pulse oximetry. Studies were performed from 2004 to 2007 (prior to new AASM guidelines). Manual scoring followed rules of Rechschafen and Kales [21], and nasal pressure transducers were not used. Hypopnea was defined as a 30% reduction in amplitude of airflow for >10 s and associated with a 3% reduction in oxyhemoglobin saturation.

Statistical analysis: Data were analyzed at baseline and 4 weeks for all patients for whom CPAP was prescribed. The Kolmogorov-Smirnov test was used to determine normal distribution with *p* values for normality and equal variance set at 0.05. Comparison of data between men and women were made using the t-test for normally distributed data, and the Mann-Whitney rank sum test for data that did not meet criteria for normality. Comparisons of results of measurements between baseline and 4 weeks for 152 subjects and subgroups were made using paired t-tests for normally distributed data, and Wilcoxin signed rank test were used for data that did not meet criteria for normality. Bonferroni correction was made for multiple comparisons.

A comparison of body mass among three time points was analyzed in patients who returned at 6 months and reported CPAP use. We used one-way analysis of variance with repeated measures and Friedman repeated measures of analysis of variance on ranks. Post-hoc comparisons were made with Tukey's test. Correlations were sought using Spearman rank order correlation. All tests were performed using SigmaPlot version 11.0.0.77 (Systat Software, Inc., Chicago, IL).

Methods used in this study were approved by the Institutional Review Board of the University of Toledo and found to be in accordance with ethical standards of the institution and the Declaration of Helsinki.

Results

After a review of the charts for 218 subjects, 66 subjects did not meet the criteria for inclusion; 46 refused CPAP therapy, 12 had a previous diagnosis of OSA and recent CPAP use, three had left ventricular failure, three did not have a recorded body mass at follow-up, two had a body mass greater than scale capacity (180 kg).

Baseline age, BMI, and AHI for 152 subjects are presented in **Tab. 1**. There was no difference between respective values for men and women.

Body mass, cardiovascular data, and symptomatic daytime sleepiness estimated by the ESS at baseline (the time of CPAP titration) and 1 month (29±11 days; mean±SD) after CPAP initiation, are presented in **Tab. 2**. Median and mean body mass increased after 1 month of CPAP therapy in all subjects, men, and women. Gain in body mass occurred in 119 of 152 subjects (78%) including 88 of 108 (81%) men and 32 of 44 (73%) women. As a group, subjects on CPAP gained 1.4±2.5 kg (mean±SD). Body mass of men had a positive skew (tail to higher mass) of 0.8. This skew affected normality of the group including both men and women, and, as noted in the methods, nonparametric statistics were used to analyze changes in body mass in these groups that included men that did not meet the test for normality. After 4 weeks of CPAP therapy, women gained less body mass than men, whether expressed in kg (p<0.01) or as a percentage of body mass (p=0.01). As expected, women had lower body mass than men, but did not differ from men in BMI. To allow a graphical representation of the range and distribution of BMI of subjects, the change in BMI as determined by Wilcoxin signed rank test is presented in **Fig. 1** as respective values for median with percentiles of distribution.

After confirmation that CPAP therapy was associated with an early increase in body weight, we looked for correlates of weight gain. After 4 weeks of treatment, patients were symptomatically less sleepy as measured by ESS (**Tab. 2**), but no correlation between improvement in ESS and change in body mass was noted.

Although blood pressure and heart rate tended to be lower with treatment (not statistically significant), there was no correlation between change in body mass and baseline or change in mean arterial pressure (MAP), systolic pressure, diastolic pressure, HR, or rate-pressure product (RPP). Interestingly, we found no change in RPP, but men showed a trend toward decreased systolic pressure (uncorrected and insignificant p=0.015) without change in HR, while women exhibited a trend toward decreased HR (uncorrected p=0.18) without a change in systolic pressure.

The presence or absence of diabetes or impaired glucose tolerance did not in-

Abstract · Zusammenfassung

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Early gain in body mass with continuous positive airway pressure therapy for obstructive sleep apnea. Early body mass gain with CPAP therapy

Abstract

Study objectives. Many clinicians believe that continuous positive airway pressure (CPAP) therapy of obstructive sleep apnea (OSA) is associated with a decrease in body mass, but to date, studies generally suggest long-term stability in body mass after 1 year. We have seen body mass increase after 4 weeks of treatment with CPAP in most patients with OSA. In this study, we test the hypothesis that therapy of OSA with CPAP produces a short-term gain in body mass, and look for physiological correlates to suggest an underlying mechanism.

Methods. Retrospective analysis of 218 consecutive patients treated for sleep apnea at a community-based sleep center.

Results. A total of 152 patients met the criteria for study conclusion. After 1 month of CPAP treatment, 119 subjects (78%) gained mass, including 81% of men and 73% of women. As a group, subjects on CPAP gained 1.4±2.5 kg (mean±SD). The Epworth Sleepiness Scale was reduced after 1 month of CPAP therapy. There was no correlation between gain in body mass and measured parameters. A subgroup of 71 patients remained on therapy. They demonstrated a gain in mass at 4 weeks, which did not persist at 6 months.

Conclusions. CPAP treatment of OSA is associated with gain in body mass at 1 month but not 6 months of therapy. The nature of this gain in mass remains unknown. We believe the gain is due to increased vascular volume, and might represent an early marker of physiological benefit of CPAP. This article includes a review of potential mechanisms for early increase in body mass with CPAP.

Keywords

Sleep apnea · Obstructive · Continuous positive airway pressure · Weight gain · Obesity · Hypertension · Body mass index

Anfängliche Gewichtszunahme bei kontinuierlicher Positivdruck-Therapie wegen obstruktiver Schlafapnoe. Anfängliche Gewichtszunahme bei CPAP-Therapie

Zusammenfassung

Fragestellung. Viele klinisch tätige Ärzte gehen davon aus, dass eine kontinuierliche Positivdruck (CPAP)-Therapie bei obstruktiver Schlafapnoe (OSA) mit Gewichtsabnahme einhergeht, allerdings legen Studien bis heute eine Langzeitstabilität des Gewichts nach einem Jahr nahe. Wir haben bei den meisten Patienten mit OSA nach 4 Wochen CPAP-Therapie eine Gewichtszunahme beobachtet. In dieser Studie prüfen wir die Hypothese, dass die CPAP-Therapie einer OSA mit einer kurzfristigen Gewichtszunahme einhergeht, und versuchen, physiologische Korrelate für mögliche zugrunde liegende Pathomechanismus zu finden.

Methoden. Retrospektive Untersuchung von 218 konsekutiven Patienten, die gegen Schlafapnoe in einem kommunalen Schlafzentrum behandelt wurden.

Ergebnisse. Den Einschlusskriterien der Studie entsprachen 152 Patienten. Nach einer einmonatigen CPAP-Behandlung war bei 119 (78%; 81% der Männern und 73% der Frauen), eine Gewichtszunahme erfolgt (1,4±2,5 kg, Mittelwert ± Standardabweichung: 1,4±2,5 kg). Die Epworth-Schläfrigkeitsskala war nach einem Monat der CPAP-Therapie reduziert. Es gab keine Korrelation zwischen der Körpergewichtszunahme und den gemessenen Parametern. Eine Untergruppe von 71 Patienten führte die Therapie fort. Sie demonstrierten Gewichtszunahme nach 4 Wochen, die sich nicht über 6 Monate hielt.

Schlussfolgerungen. Die CPAP-Behandlung einer OSA ging mit einer Gewichtszunahme innerhalb des ersten Monats einher, die sich nicht über 6 Monate hielt. Die Ursache dafür bleibt unklar. Wir glauben, dass die Gewichtszunahme durch eine Vergrößerung des Gefäßvolumens verursacht wird und dies ein frühes Merkmal für eine physiologische Kompensation sein könnte. Die Diskussion beinhaltet eine Übersicht über die möglichen Mechanismen für die frühe Gewichtszunahme bei der Anwendung von CPAP.

Schlüsselwörter

Schlafapnoe · Obstruktiv · Kontinuierliche Positivdruck-Behandlung · Gewichtszunahme · Fettleibigkeit · Bluthochdruck · Körpermassenindex

Tab. 2 Baseline data

	Baseline		1 Month	
	Mean	SD	Mean	SD
All *n*=152				
Body mass (kg)	108.6	25.2	109.9[a]	25.4
BP sys (mm Hg)	134.1	15.4	132.7	16.0
BP dias (mm Hg)	82.0	10.0	80.6	10.7
MAP (mm Hg)	99.4	10.2	98.0	11.0
Heart rate (bpm)	72.9	11.7	72.1	12.9
ESS (*n*=150)	11.6	5.2	7.2[a]	4.6
Men *n*=108				
Body mass (kg)	111.9	25.5	113.5[a]	25.7
BP sys (mm Hg)	134.9	15.0	131.9	15.8
BP dias (mm Hg)	82.7	9.6	80.8	10.6
MAP (mm Hg)	100.1	9.8	97.8	10.9
Heart rate (bpm)	71.7	11.0	71.9	13.6
ESS	11.9	5.2	7.0[a]	4.3
Women *n*=44				
Body mass (kg)	100.4	22.8	101.1[a]	22.7
BP sys (mm Hg)	132.4	16.1	134.7	16.6
BP dias (mm Hg)	80.4	10.6	80.0	11.2
MAP (mm Hg)	97.7	11.3	98.2	11.4
Heart rate (bpm)	75.6	13.0	72.5	11.4
ESS	11.0	5.3	7.7[a]	5.3

[a]p<0.01 compared to baseline.**SD** standard deviation, **BP sys** systolic blood pressure, **BP dias** diastolic blood pressure, **MAP** mean arterial pressure, **ESS** Epworth Sleepiness Scale.

fluence results. Congestive heart failure was not present in this population. AHI, nights of reported CPAP use (range 4–66), mean hours of daily CPAP use (5.9±1.6, mean±SD, range 1.9–9.2, *n*=57), did not correlate with change in body mass after 4 weeks of therapy. Initial BMI and body mass did not correlate with the subsequent change in BMI or body mass.

To test for persistence of the observed early gain in body mass, we analyzed data for 71 subjects who reported CPAP therapy for 6 months (193±86 days, mean±SD). Again, an overall increase in body mass was demonstrated at 4 weeks (**Fig. 2**). Body mass at 6 months, however, was not different from body mass at initiation of CPAP therapy and not different from body mass at 1 month (**Fig. 2**). In our subjects, early body mass gain with initiation of CPAP therapy for OSA does not seem to persist, and the rate of body weight gain appears to decrease after the first visit. Again, in this analysis, men gained more body mass at 1 month than women. In this smaller group of women (*n*=22), body mass did not change significantly after 1 month on CPAP therapy, but trends in the first 4 weeks were similar to the larger group of women (*n*=44). Analysis of BMI produced similar results.

Discussion

This is the first report to demonstrate a statistically significant gain in body mass 1 month after initiation of CPAP therapy (**Tab. 2** and **Fig. 1**). This gain does not statistically persist (**Fig. 2**). Our findings are comparable to a trend toward increased weight during the first 4 weeks of CPAP therapy noted by Engelman et al.[13]. Although the latter study (*n*=13) and two other studies (*n*=34, [17]; *n*=21 [15]) found no statistically significant change in weight after 1 month of CPAP therapy, they might have been underpowered. Our data, which suggest that short-term weight gain does not persist, are compatible with a number of longer studies [10, 12, 13, 14, 15, 16, 17, 18].

Our analysis of retrospective data supports the hypothesis that CPAP therapy of OSA results in short-term gain in body mass. The use of retrospective data, however, has significant drawbacks and severely limits conclusions. In this context, we have tried to approach our statistical analysis as conservatively as possible. This study did not allow control of menstrual status, phase of menstrual cycle, circadian rhythm in blood pressure, diet, physical activity, or medication.

In view of these limitations, it might not be surprising that analysis did not identify a physiological correlate to observed weight gain. If CPAP treatment of OSA decreases basal metabolic rate and 24-h energy expenditure, as described by Stenlof et al. [22] after 3 months of therapy, then we might hypothesize that early weight gain is due to a more rapid increase in fat mass in patients already obese. In our subjects, caloric excess would need to be about 500 Kcal/day to achieve the observed gain in weight after 1 month. A previous study by Ryan et al. [12] demonstrated, however, that subjects with OSA had no change in energy expenditure or post-prandial thermogenesis following 12 weeks of CPAP therapy. Furthermore, with the rapidity of weight gain seen in some of our subjects as early as 4 days, we have the impression that increase in body mass does not simply represent ongoing gain in fat mass gain. The level of obesity as suggested by initial weight or BMI does not correlate with subsequent, early weight gain on CPAP therapy. Furthermore, as noted above, CPAP therapy for 6 months or more is associated with a decrease in visceral fat mass, regardless of change in body mass [15, 18].

A rapid gain in body mass could occur with increased food consumption, and increased mass of gut content. A recent publication speculated that a decrease in leptin, traditionally considered an appetite-suppressing neuropeptide, might stimulate eating behavior and weight gain with CPAP therapy [10]. After 1 month of CPAP therapy, Chin et al. [15] demonstrated serum leptin levels decreased 24% without a significant change in BMI in 10 patients. In the same study, 4 days of therapy resulted in a reduction in leptin of 17%, which was not different from that seen at 1 month. On the other hand, as little as 2 days of therapy with CPAP was sufficient to reduce levels of the appetite-stimulant, ghrelin [7], which would be expected to reduce appetite and

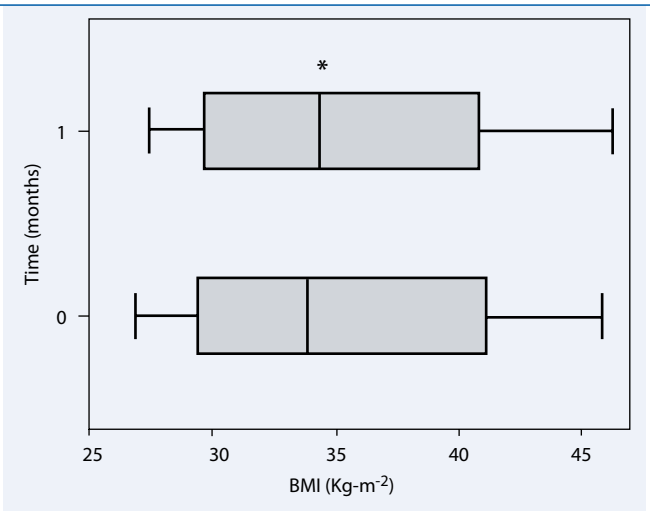

Fig. 1 ▲ Change in body mass index 1 month after initiation of CPAP therapy for OSA. Data is expressed as the median confidence intervals of 25%–75% (*box*) and 10%–90% (*bars*). *Asterisk* different from Baseline, $p<0.05$

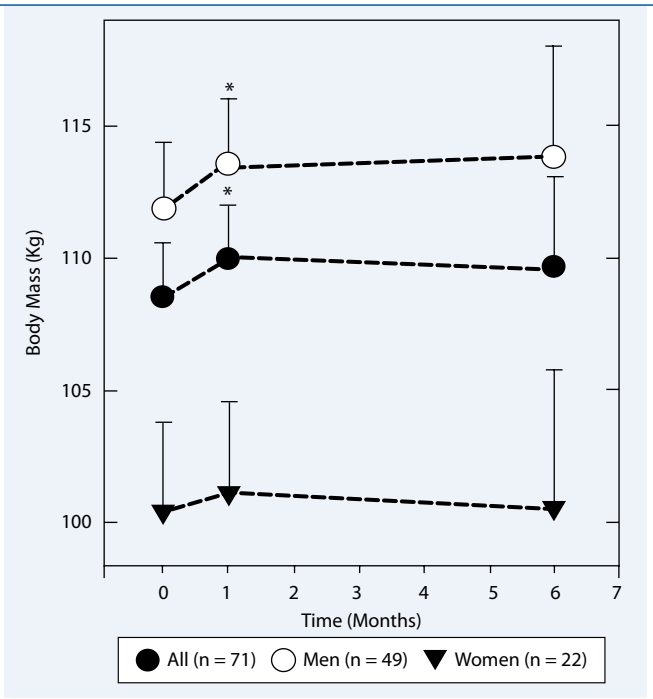

Fig. 2 ▲ Change in body mass 1 month and 6 months after initiation of CPAP therapy for OSA

lead to weight loss. The role of leptin and other neuropeptides in weight control has proven far more complex than originally thought, and conclusions based on observed changes in plasma levels should be avoided [23].

We suspect that part, if not all, of the weight gain is due to increased vascular volume and hydration. Increase in vascular volume might be due to improved endothelial function, decreased sympathetic nervous system tone, and decreased urinary output associated with a decrease in sleep fragmentation. Growth hormone increases within 2 days of CPAP therapy of OSA, at least in men [24], and mediates increases in vascular volume [25]. In addition, endothelin is a vasoconstrictive substance, which is elevated in severe OSA and improves with 4 h of CPAP treatment [26].

Decrease in nocturia has been well established, but its effects on weight have not. Patients with sleep apnea have increased nocturnal sodium excretion and urine production, which reverses with CPAP therapy [27, 28] and is associated with increased plasma volume [28]. Non-REM sleep is associated with increases in plasma renin activity. CPAP therapy of OSA has improved sleep architecture and non-REM sleep consolidation, doubled plasma renin activity, and increased plasma concentration of aldosterone by 50% [28]. Obstructive sleep apnea is also associated with increases in brain-type atrial natriuretic peptide (ANP) [29, 30]. ANP is reduced with CPAP treatment [31, 32, 33, 34]. All changes can increase vascular volume.

Follenius et al. [28] found CPAP therapy of obstructive sleep apnea for 1 night was associated with a decrease in urine production by half (504 to 269 ml) and an increase in plasma volume by 12.7%. If we estimate plasma volume at 3 l, this change in urine output should result in an increase in morning body mass of 0.4 kg after only 1 night of CPAP therapy.

CPAP therapy of OSA is known to decrease sympathetic nervous system activity [22, 35, 36], and might also mediate increased vascular volume through a decrease in vasoconstrictive sympathetic nervous system activity. Physiologically, we would expect this improvement to occur relatively early after initiation of treatment. Indeed, after 1 month of compliance-monitored CPAP, Waravdekar et al. [37] found a 23% reduction of daytime sympathetic tone by peroneal microneurography in four OSA patients, although measured burst activity was still 59% higher than the control group after treatment.

In this context, we found a trend toward decreased MAP after 1 month of CPAP therapy in men. A trend to lower MAP was also seen in 1-month trials of continuous positive airway pressure by both Engelman et al. [13] and Campos-Rodriguez et al. [17]. None of these trends were significant, but given the limitations of the studies, effects of CPAP treatment on MAP warrants further evaluation.

Our data also suggest men and women might have different cardiovascular responses to CPAP; men showed a trend toward lower systolic pressure and no change in heart rate, whereas women demonstrated a trend toward lower heart rate with no change in systolic pressure. Differences between men and women could be associated with relative differences in responses of sympathetic nervous system and parasympathetic nervous system to CPAP treatment. Electrocardiographic R-R variability might be used to evaluate these changes, and fast Fourier transform and analysis of the ECG leads is now easily performed in most polysomnographic laboratories. As previously reported, treatment of OSA with CPAP was associated with a several-fold reduction in modified low-frequency to high-frequency power (simplistically a measure of contribution sympathetic to parasympathet-

ic tone to modulation of heart rate) and a three-fold increase in average gain relating to respiration to RR changes (simplistically, a measure of parasympathetic or vagal tone) [38].

This report demonstrates an increase in body mass after 1 month of CPAP treatment of OSA, which does not persist after 6 months of treatment. Short-term change in body mass might be multifactorial, but we suspect an increase in vascular volume occurs soon after initiation of CPAP therapy due to improved endothelial function, decreased sympathetic nervous system tone, and decreased excretion of urine and sodium associated with multiple endocrine changes. As visceral adiposity decrease after 3–6 months of CPAP therapy [15, 18], an increase in vascular volume could persist in the absence of a persistent increase in body mass. As short-term gain in body mass might represent an integrated measure of beneficial cardiovascular responses to CPAP therapy, carefully controlled prospective studies should be undertaken to confirm these findings and to assess the time course and relative contributions of associated physiological changes.

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