ORIGINAL ARTICLE

# Echocardiographic Changes with Positive Airway Pressure Therapy in Obesity Hypoventilation Syndrome

## Long-Term Pickwick Randomized Controlled Clinical Trial

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## Abstract

**Rationale:** Obesity hypoventilation syndrome (OHS) has been associated with cardiac dysfunction. However, randomized trials assessing the impact of long-term noninvasive ventilation (NIV) or continuous positive airway pressure (CPAP) on cardiac structure and function assessed by echocardiography are lacking.

**Objectives:** In a prespecified secondary analysis of the largest multicenter randomized controlled trial of OHS (Pickwick Project; $N = 221$ patients with OHS and coexistent severe obstructive sleep apnea), we compared the effectiveness of three years of NIV and CPAP on structural and functional echocardiographic changes.

**Methods:** At baseline and annually during three sequential years, patients underwent transthoracic two-dimensional and Doppler echocardiography. Echocardiographers at each site were blinded to the treatment allocation. Statistical analysis was performed using a linear mixed-effects model with a treatment group and repeated measures interaction to determine the differential effect between CPAP and NIV.

**Measurements and Main Results:** A total of 196 patients were analyzed: 102 were treated with CPAP and 94 were treated with NIV. Systolic pulmonary artery pressure decreased from 40.5 ± 1.47 mm Hg at baseline to 35.3 ± 1.33 mm Hg at three years with CPAP, and from 41.5 ± 1.56 mm Hg to 35.5 ± 1.42 with NIV ($P < 0.0001$ for longitudinal intragroup changes for both treatment arms). However, there were no significant differences between groups. NIV and CPAP therapies similarly improved left ventricular diastolic dysfunction and reduced left atrial diameter. Both NIV and CPAP improved respiratory function and dyspnea.

**Conclusions:** In patients with OHS who have concomitant severe obstructive sleep apnea, long-term treatment with NIV and CPAP led to similar degrees of improvement in pulmonary hypertension and left ventricular diastolic dysfunction.

Clinical trial registered with www.clinicaltrials.gov (NCT01405976).

**Keywords:** sleep apnea; pulmonary hypertension; hypercapnia; diastolic dysfunction; noninvasive ventilation; continuous positive airway pressure

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## At a Glance Commentary

**Scientific Knowledge on the Subject:** This is the first randomized controlled trial that compares long-term changes in cardiac structure and function in patients with obesity hypoventilation syndrome treated with either noninvasive ventilation or continuous positive airway pressure.

**What This Study Adds to the Field:** Both noninvasive ventilation and continuous positive airway pressure improved pulmonary hypertension and left ventricular diastolic dysfunction without any significant difference between treatment modalities.

Obesity hypoventilation syndrome (OHS) is characterized by a combination of obesity, daytime hypercapnia, and sleep-disordered breathing in the absence of an alternative cause of hypoventilation. Concomitant obstructive sleep apnea (OSA) is present in about 90% of patients with OHS, with 73% of patients having severe OSA (1).

Positive airway pressure (PAP) therapy during sleep is the main treatment option for patients with OHS. The most common PAP modalities are noninvasive ventilation (NIV) and continuous PAP (CPAP). CPAP prevents upper airway obstructive events but, in contrast to NIV, it is not designed to augment ventilation (2). In patients with OHS, however, both NIV and CPAP have been shown to be similar in improving daytime symptoms, quality of life, sleep quality, and daytime and nocturnal gas exchange, as well as spirometric and polysomnographic parameters in medium-term randomized controlled trials (3–8) and a long-term clinical trial (7–9).

Patients with OHS have a higher frequency of cardiovascular morbidity, hypertension, diabetes, and dyslipidemia than equally obese patients with eucapnic OSA (10–12). Untreated OHS is associated with increased mortality, partially related to cardiovascular morbidity (13). Some observational studies have reported a high prevalence of pulmonary hypertension and right ventricular dysfunction in patients with OHS (14–18). Medium-term analysis in the Pickwick randomized clinical trial showed a reduction in pulmonary hypertension and left ventricular hypertrophy with two months of NIV therapy but not with CPAP (19). Whether these medium-term beneficial effects on echocardiographic assessment of pulmonary artery pressure and left ventricular hypertrophy persist after longer periods of treatment remains unclear.

The Pickwick randomized controlled trial was designed to determine the comparative medium-term effectiveness of NIV, CPAP, and lifestyle modification (control group) after two months of follow-up as well as the long-term effectiveness between NIV and CPAP during three years of follow-up with the *a priori* hypothesis that NIV may have better outcomes than CPAP because NIV has a wider physiologic spectrum of treating breathing disorders during sleep than CPAP (1, 4, 9, 19–22). Echocardiographic parameters were one of the prespecified secondary outcomes of the Pickwick study. Therefore, we examined the long-term impact of PAP therapy on echocardiographic parameters in patients with OHS to test the hypothesis that long-term treatment with NIV will lead to a greater improvement in pulmonary hypertension and left ventricular function compared with CPAP. Some of the results of these studies have been previously reported in the form of an abstract (23).

## Methods

### Trial Design

We performed a multicenter, open-label, randomized clinical trial with two parallel groups conducted at 16 clinical sites in Spain.

### Participants

From May 2009 to March 2013, we sequentially screened patients between 15 and 80 years of age who were referred for pulmonary consultations due to suspected OHS or OSA at 16 tertiary hospitals in Spain (*see* online supplement). OHS was defined as obesity with a body mass index $\geq$30 kg/m$^2$; stable hypercapnic respiratory failure ($Pa_{CO_2} \geq 45$ mm Hg, pH $\geq$ 7.35, and no clinical exacerbation during the previous 2 mo); no significant spirometric evidence of chronic obstructive pulmonary disease ($FEV_1$ had to be above 70% of predicted in cases in which the $FEV_1$/FVC ratio was below 70); and no evidence of neuromuscular, chest wall, or metabolic disease to explain hypercapnia. Other inclusion criteria were as follows: *1*) severe OSA (apnea-hypopnea index [AHI] $\geq$ 30 events/h), *2*) an absence of narcolepsy or restless legs syndrome, and *3*) a correctly executed 30-minute CPAP or NIV treatment test (*see* online supplement). The exclusion criteria were as follows: *1*) a psychophysical inability to complete questionnaires, *2*) severe chronic debilitating illness, *3*) severe chronic nasal obstruction, and *4*) a lack of informed consent.

A complete list of Spanish Sleep Network members may be found before the beginning of the References.

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Data sharing statement: Additional related documents, such as study protocol, statistical analysis plan, and informed consent form, will be available upon request from the Pickwick Project principal investigator (J.F.M.). Deidentified patients' data can be requested by researchers for use in independent scientific research and will be provided following review, approval of the research proposal (including statistical analysis plan), and completion of a data-sharing agreement with the Pickwick Project Publications Committee. Investigator data requests can be made any time from one to two years after the publication of this trial. Requests should be sent to the corresponding author.

The Pickwick Project consisted of two parallel randomized clinical trials conducted in two phases (20) (*see* online supplement). The study was approved by the 16 centers' ethics committees, and written informed consent was obtained from all patients.

### Interventions

Ambulatory OHS patients with severe OSA (AHI $\geq$ 30) were initially randomized by an electronic database without a preset allocation rate (simple randomization) into NIV, CPAP, or control group for two months (first phase). After this period, patients included in the control group (i.e., lifestyle changes) were rerandomized to NIV or CPAP by a simple randomization owing to prespecified ethical reasons. All patients randomized to NIV or CPAP were followed for three years (second phase). Both arms (CPAP and NIV) were treated with lifestyle recommendation (*see* online supplement). Oxygen therapy was added if baseline daytime ($Pa_{O_2}$ < 55 mm Hg) or nocturnal hypoxemia (mean oxygen saturation as measured by pulse oximetry signal during the titration polysomnography $\leq$ 88%) was detected during PAP adjustment (22).

***CPAP titration.*** Patients were instructed to use at-home fixed CPAP during the entire sleep period based on a conventional CPAP titration polysomnogram (*see* online supplement).

***NIV.*** Patients were instructed to use NIV treatment during the entire sleep period. The ventilator mode was set at a bilevel PAP with assured volume (*see* online supplement).

### Masking Strategy

The study was open-label for both the investigators and the patients. However, the treating clinicians (routine care team) were unaware of the research study (*see* online supplement). Echocardiographers at each center were blinded to the allocated treatment arm.

### Outcomes

Patients were evaluated on five occasions during three years: at baseline, at 2 months, and every year until completing three years of follow-up (*see* Table E1 in the online supplement). Evaluations at the second month were performed before rerandomization of the control group to CPAP or NIV; therefore, they were not considered for this analysis (1) (Figure 1).

At baseline and during each annual visit we assessed anthropometric data, arterial blood gases (ABGs) on room air, sphygmomanometric blood pressure (24) (*see* online supplement), spirometry (25), 6-minute-walk distance (6MWD) test (26), dyspnea by the Medical Research Council scale, and conventional transthoracic echocardiogram. Objective adherence to CPAP and NIV was obtained using internal device hourly counters. During all visits, we encouraged treatment adherence and made adjustments to supplemental oxygen therapy or PAP settings and masks if the patients required them.

***Echocardiogram.*** All two-dimensional (2D) and Doppler echocardiograms were recorded using available echocardiographic equipment in each center (*see* online supplement). Left ventricle size and wall thickness were measured according to international guidelines (27). All these parameters were derived from 2D-guided motion mode imaging or from linear measurements obtained from 2D images. Left ventricle ejection fraction was calculated from end-diastolic and end-systolic volume estimates, using volumetric measurements. Left ventricle mass was estimated by linear method with the cube formula ($0.8 \times 1.04 \times [(IVS + LVDD + LVPW)^3 - LVDD^3] + 0.6$ g), where LVDD is the diastolic diameter of left ventricle (internal diameter), LVPW is the left ventricle posterior wall thickness, and IVS is the interventricular septum thickness, all measured at end-diastole in the long-axis parasternal view using either 2D-guided motion mode or linear measurements from 2D echocardiographic images. Left ventricle mass index was obtained by dividing the left ventricle mass by the body surface area according to Dubois's formula. To assess left ventricle diastolic function, we obtained peak early wave (E) and peak atrial wave (A) mitral valve in-flow velocities, as well as their ratio (E/A ratio), deceleration time, and the anteroposterior diameter of the left atrium measured in the parasternal long-axis view. Systolic pulmonary artery pressure was assessed from the maximum velocity of tricuspid regurgitation signal (continuous-wave Doppler) by the addition of right atrial pressure, estimated from inferior cava vein and its collapsibility. Right ventricular systolic function was evaluated using the right ventricle index of myocardial performance (global myocardial function index).

### Statistical Analysis

Intention-to-treat analysis was performed. Baseline bivariate analysis was performed by *t* test (or equivalent nonparametric) or $\chi^2$ test, depending on quantitative or categorical variables, respectively. Linear mixed-effects models were used to analyze longitudinal outcomes derived from the echocardiogram, ABGs, spirometry, 6MWD test, blood pressure, and body weight during three years of follow-up. The models included center and subject as random effects and visit, treatment (CPAP and NIV), and the interaction of visit and treatment as fixed effects. The visit was considered as a categorical factor (28). Because randomization was performed in two phases with more probability of arm imbalances, all models were adjusted for potentially unbalanced covariates with a *P* value less than 0.1 in the baseline bivariate analysis (i.e., age, sex, smoking habits, and FVC). Dyspnea on the Medical Research Council scale was categorized as $\geq$2 for clinically significant and <2 for not clinically significant. Clinically significant dyspnea was compared between arms by a mixed-effects logistic regression. Similar analysis was used to assess the evolution of the prevalence of pulmonary hypertension and diastolic dysfunction.

Exploratory *post hoc* analysis of subgroup assessment was performed based on the presence of pulmonary hypertension at baseline (systolic pulmonary artery pressure $\geq$ 40 mm Hg was chosen based on the anthropometric characteristics of our population [29]) and according to the presence of left ventricle diastolic dysfunction at baseline (E/A ratio $\leq$ 1%). Moreover, we performed an adherence subgroup analysis. Adherence to CPAP or NIV was categorized in two groups using mean daily use $\leq$4 hours per day as low adherence versus >4 hours per day as high adherence (9) (*see* online supplement). Data management and statistical analyses were performed using SPSS software (IBM SPSS Statistics, Version 22.0; IBM Corp.) and Stata software (Stata Statistical Software, Release 13; StataCorp LP).

## Results

### Study Participants

Of the 363 patients who met inclusion criteria, 142 were excluded (91 had AHI < 30 events/h). Of the remaining patients, 115 were allocated to the CPAP arm and 100 to the NIV arm (*see* Figure 1). For the echocardiogram analysis, 102 patients were available in the CPAP group

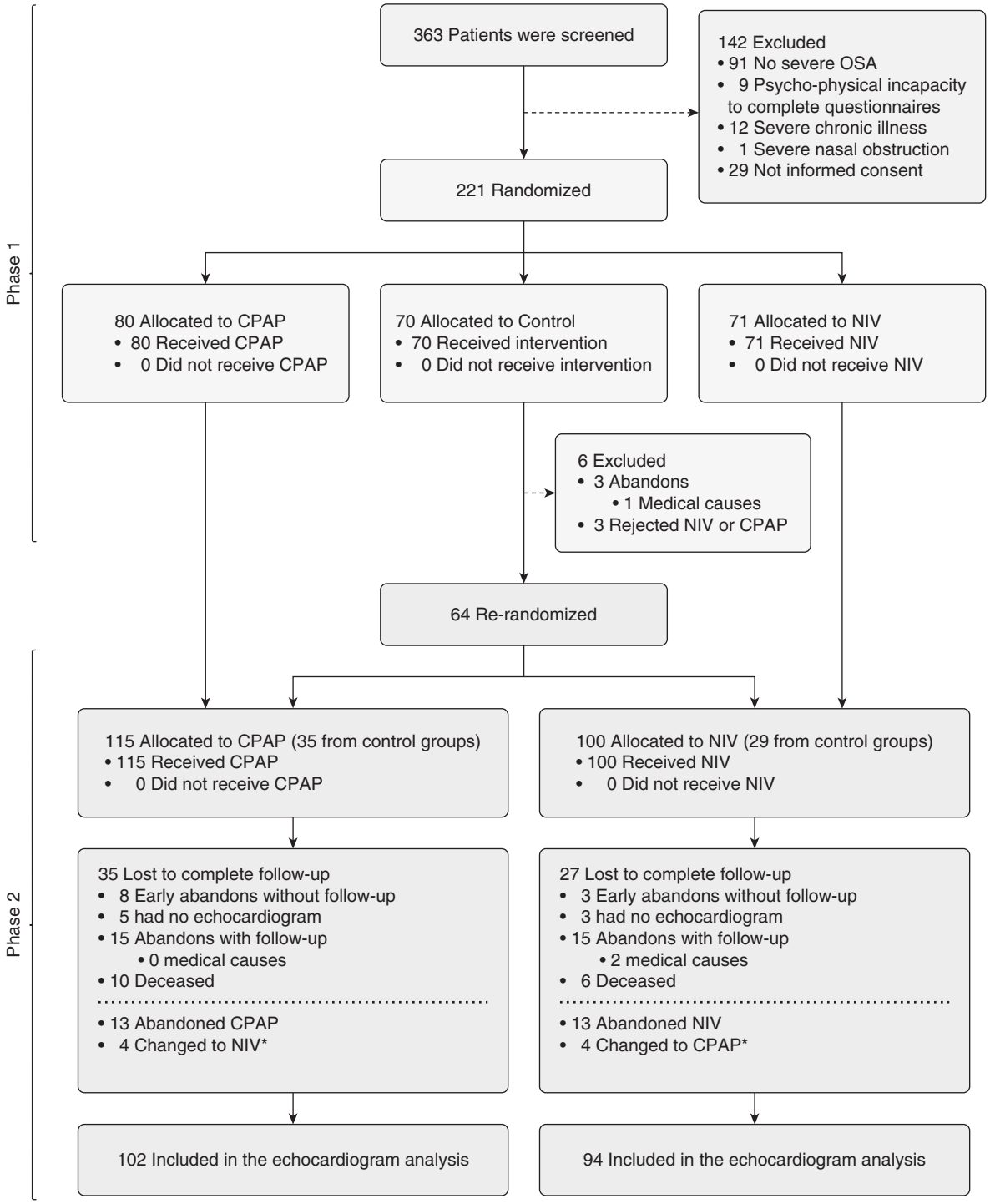


**Figure 1.** Flow chart of the study protocol. Of 363 selected patients, 142 were excluded and 221 were randomized. After the first 2 months of treatment (first phase), patients included in the control group (i.e., lifestyle changes) were rerandomized to continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) to be followed for a minimum of 3 years (second phase). A total of 215 patients were randomized to either CPAP ($n = 115$) or NIV ($n = 100$). From the 115 patients included in the CPAP arm, 8 abandoned the study early without follow-up and 5 did not complete an echocardiogram. The remainder ($n = 102$) were available for the primary analysis. From the 100 patients included in the NIV arm, 3 abandoned the study early without follow-up and 3 did not complete an echocardiogram. The remainder ($n = 94$) were available for the primary analysis. *Patients who changed treatment after randomization (i.e., from CPAP to NIV or vice versa) were analyzed in the original arm according to the intention-to-treat principle. OSA = obstructive sleep apnea.

and 94 in the NIV group. Table 1 summarizes baseline characteristics of the two groups.

The median (interquartile range [IQR]) follow-up was 3.00 (2.92–3.17) years for the CPAP group and 3.00 (2.92–3.08) years for the NIV group. The median (IQR) treatment adherence for CPAP was 6.0 (3.10–7.10) hours per day. The median (IQR) treatment adherence for NIV was 6.0 (0.81–7.33) hours per day. The trial was stopped when the last enrolled patient completed three years of follow-up. Due to technical difficulties, 8 patients (4%) did not complete an echocardiogram and 69 patients (33%) had at least one echocardiographic parameter unavailable. We were unable to obtain an appropriate measure of pulmonary artery pressure in 29 out of 196 (15%) of patients with echocardiogram.

### Echocardiogram Outcomes

Systolic pulmonary artery pressure was reduced significantly with both PAP modalities, but without group differences (Figure 2 and *see* Table E2). The proportion of patients with pulmonary hypertension decreased significantly in both groups but with a slight advantage for NIV (*see* Table E3 and Figure E2). There were no significant changes in the right ventricular systolic function as assessed by the global myocardial function index in either group (*see* Figure 2 and Table E2). E/A ratio, deceleration time, and anteroposterior diameter of the left atrium parameters improved significantly with PAP, indicating improvement in left ventricle diastolic function without differences between CPAP and NIV (Figure 3 and E3 and Tables E2 and E3). There were no significant longitudinal changes in left ventricle posterior wall thickness and left ventricle ejection fraction with either PAP modality (Figure 4). Similarly, there were no significant longitudinal changes with either PAP modality in parameters of left ventricle hypertrophy, such as interventricular septal thickness, left ventricular posterior wall thickness, left ventricle mass, and left ventricle mass index (Figure 5 and Table E2).

### Other Outcomes

Both systolic and diastolic blood pressure improved significantly with PAP but without group differences (*see* Table E4 and Figure E4). Table E5 and Figure E5 illustrate longitudinal changes of the ABG

**Table 1.** Baseline Characteristics

| | CPAP ($n = 102$) | NIV ($n = 94$) | *P* Value |
|---|---|---|---|
| Age, yr | 60 (49–71) | 65 (56.8–72) | 0.076 |
| Sex, F, % | 51.0 | 63.8 | 0.069 |
| Smokers, % | 31.4 | 19.1 | 0.0499 |
| Smoking*, pack-years | 25 (15.3–40) | 36.3 (28.8–42.1) | 0.339 |
| Drinkers†, % | 14.7 | 23.4 | 0.120 |
| Alcohol*, gr | 30 (14.5–46.8) | 28 (15–47.8) | 0.935 |
| BMI, kg/m$^2$ | 42.5 (38.1–49.1) | 43.1 (38.2–48) | 0.686 |
| Neck circumference, cm | 45 (41–48) | 44 (42–47) | 0.588 |
| ESS, mean (SD) | 10.5 (5.2) | 11.3 (5) | 0.298 |
| FOSQ, mean (SD) | 74.1 (21.5) | 74.9 (21.3) | 0.793 |
| SF 36–physical | 35.6 (28.5–45.4) | 36.7 (27.6–45) | 0.925 |
| SF 36–mental | 46 (31.9–53.1) | 45.3 (32.5–53.3) | 0.825 |
| VAWS | 49.2 (32.7–66.7) | 50 (37.5–58.3) | 0.764 |
| Dyspnea MRC scale $\geq$ 2, % | 57.0 | 47.7 | 0.204 |
| Hypertension, % | 65.7 | 71.3 | 0.400 |
| Systolic BP, mm Hg | 138 (130–141) | 138 (130–150) | 0.957 |
| Diastolic BP, mm Hg | 80 (70–90) | 80 (70–90) | 0.307 |
| Diabetes, % | 32.4 | 41.5 | 0.185 |
| Antidiabetic medications, % | 30.4 | 40.4 | 0.142 |
| Dyslipidemia, % | 39.2 | 47.9 | 0.222 |
| Treatment of dyslipidemia, % | 33.3 | 40.4 | 0.304 |
| Stroke, % | 8.8 | 5.3 | 0.341 |
| Ischemic heart disease, % | 8.8 | 8.5 | 0.938 |
| Arrhythmia, % | 4.9 | 10.6 | 0.131 |
| Chronic heart failure, % | 4.9 | 5.3 | 0.895 |
| Leg arteriopathy, % | 10.8 | 18.1 | 0.144 |
| Pulmonary hypertension, % | 6.9 | 8.5 | 0.665 |
| At least 1 CVM, % | 32.4 | 33.0 | 0.926 |
| pH | 7.4 (7.38–7.43) | 7.4 (7.38–7.41) | 0.486 |
| $Pa_{O_2}$, mm Hg | 60 (55–67) | 61 (56.8–67) | 0.576 |
| $Pa_{CO_2}$, mm Hg | 49 (47–52) | 50 (47.6–54) | 0.373 |
| Bicarbonate, mmol/L | 29.5 (27.9–32) | 29.8 (27.8–31.1) | 0.670 |
| $FEV_1$ % predicted | 77 (64–90) | 77 (66.5–89) | 0.635 |
| FVC, % predicted, mean (SD) | 82.9 (21.1) | 76.7 (20.6) | 0.0386 |
| 6MWD, m | 377.5 (285.8–448.5) | 380 (256–453) | 0.706 |
| Polysomnographic parameters‡ | | | |
| TST, h, mean (SD) | 5.3 (1.4) | 5.2 (1.2) | 0.599 |
| Sleep efficiency | 72.8 (58.1–85.4) | 72.9 (60.8–85) | 0.918 |
| Non-REM 1 and 2, % | 84.9 (73.9–91.7) | 85.3 (72.7–92.2) | 0.785 |
| Non-REM 3, % | 5.3 (0.6–13.5) | 3.5 (0–16.3) | 0.382 |
| REM sleep, % | 7 (3.3–14.2) | 9.7 (3.6–14.4) | 0.660 |
| Arousal index | 59.5 (31.9–85) | 52 (33.2–75.4) | 0.470 |
| AHI | 69 (43.1–93) | 69.3 (48.8–97) | 0.372 |
| ODI, mean (SD) | 70.7 (30.9) | 68.1 (31.2) | 0.572 |
| $Sp_{O_2}$ during sleep, mean | 86 (80.4–89.8) | 85 (82–88) | 0.525 |
| TST with $Sp_{O_2} < 90\%$, % | 75.5 (48.5–94.5) | 78.7 (51.5–95.6) | 0.881 |
| Oxygen therapy§, % | 26.5 | 20.2 | 0.302 |
| Oxygen therapy flow*, L/min | 1.5 (1.0–2.0) | 1.8 (1.0–2.0) | 0.779 |
| Erythrocytes, *n*/ml, mean (SD) | 5 (0.6) | 4.9 (0.6) | 0.351 |
| Fasting blood glucose, mg/dl | 105.5 (90.8–128.8) | 107 (93–141.5) | 0.352 |
| Triglycerides, mg/dl | 130.5 (110–172.8) | 138 (103–188) | 0.796 |
| Cholesterol, mg/dl, mean (SD) | 187.4 (38.2) | 185 (34) | 0.642 |
| HDL, mg/dl | 43 (38–51) | 45 (40–55) | 0.202 |
| LDL, mg/dl | 110 (94.8–132) | 111.5 (94–134) | 0.964 |
| Creatinine, mg/dl | 0.8 (0.6–1) | 0.8 (0.7–1) | 0.615 |
| C-reactive protein, mg/L | 1.9 (0.6–8.1) | 1.7 (0.8–6.3) | 0.658 |

*Definition of abbreviations* 6MWD = 6-minute-walk distance; AHI = apnea–hypopnea index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; CVM = cardiovascular morbidity; ESS = Epworth sleepiness scale; FOSQ = Functional Outcomes Sleep Questionnaire; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MRC = Medical Research Council; NIV = noninvasive ventilation; ODI = 3% oxygen desaturation index; SF 36 = Short Form 36 Health Survey; $Sp_{O_2}$ = oxygen saturation as measured by pulse oximetry; TST = total sleep time; VAWS = visual analogical well-being scale.

Data presented as median (interquartile range) unless otherwise specified.

*Includes only patients who reported to be active smokers or drinkers, or those with oxygen therapy.

†Men who drink >30 g or women who drink >20 g of alcohol per day.

‡Polysomnography was performed in baseline conditions without CPAP, NIV, or oxygen therapy in place.

§Oxygen therapy was prescribed during the baseline visit.

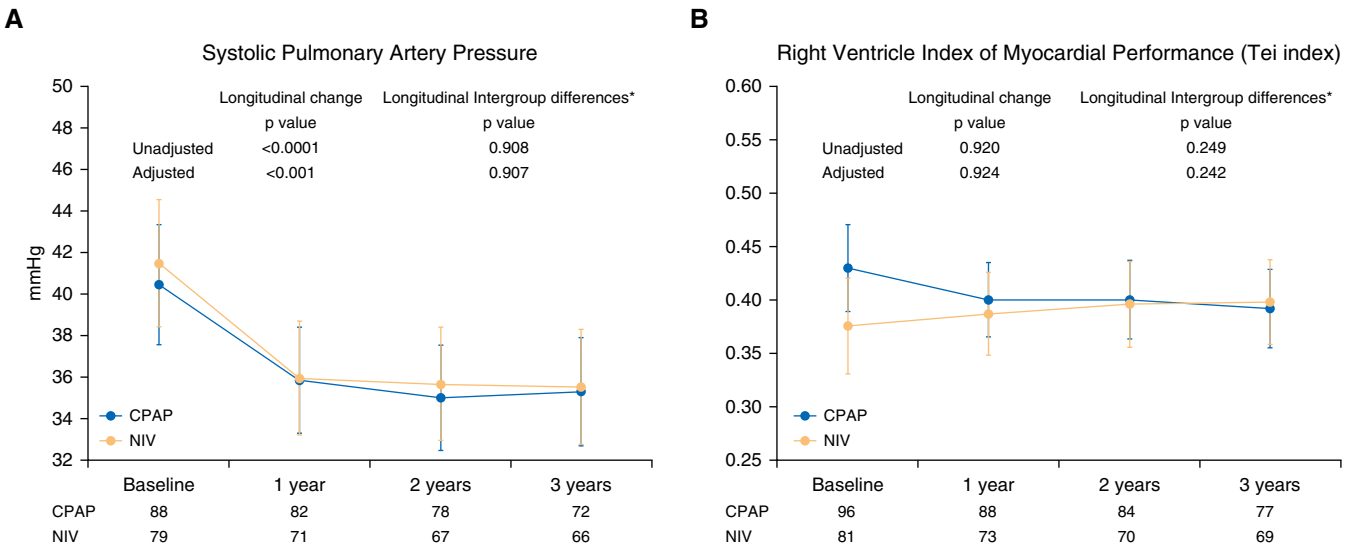


**Figure 2.** Adjusted longitudinal changes of systolic pulmonary artery pressure and right ventricular systolic function during follow-up (mean and 95% confidence interval). *P* values correspond to unadjusted and adjusted (age, sex, smoking status, and FVC) longitudinal changes for systolic pulmonary artery pressure and right ventricle index of myocardial performance (Tei index) and for the intergroup continuous positive airway pressure and noninvasive ventilation comparison from a linear mixed-effects regression model. (*A*) Systolic pulmonary artery pressure changes and (*B*) Tei index changes. *Interaction between treatment intervention group and time. CPAP = continuous positive airway pressure; NIV = noninvasive ventilation; Tei = global myocardial function.

parameters with CPAP and NIV. $Pa_{CO_2}$, bicarbonate, pH, and $Pa_{O_2}$ improved significantly with both treatments, without group differences. Both $FEV_1$ and FVC improved with PAP but without significant group differences. The 6MWD test did not improve with either PAP modality (*see* Table E5 and Figure E6). Weight was reduced similarly in both CPAP and NIV arms in the unadjusted and adjusted models (*see* Table E4 and Figure E7).

The prevalence of clinically significant dyspnea decreased significantly in both arms but without differences between them. In the CPAP group, the proportion of patients with dyspnea decreased from 54% at baseline to 36% at 1 year and to 33% at 3 years. Similarly, in the NIV group, dyspnea decreased from 63% at baseline to 29% at 1 year, and to 27% at 3 years (*see* Figure E8 and Table E6).

Table E7 summarizes CPAP and NIV settings. Both NIV and CPAP groups experienced a statistically significant reduction in the need for daytime supplemental oxygen therapy, without significant differences between them (from 26% at baseline to 15% at 3 years for CPAP, and from 20% at baseline to 12% at 3 years for NIV).

### Subgroup Analysis

Pulmonary hypertension and left ventricular diastolic dysfunction improved significantly more in patients who had evidence of these abnormalities at baseline (*see* online supplement; Tables E8, E9, E11, and E12 and Figures E9 and E10). The 6MWD test improved significantly in patients with pulmonary hypertension at baseline (*see* Table E10). We did not find a statistically significant difference in any echocardiographic parameters based on subgroup of high or low PAP adherence (*see* online supplement and Tables E13–E15).

## Discussion

The Pickwick study is the largest randomized clinical trial to date comparing long-term results of NIV and CPAP in patients with OHS. Moreover, our study is the only clinical trial that systematically compared the effect of PAP intervention on structural and functional echocardiographic changes. The main results are that PAP therapy led to a significant improvement in systolic pulmonary artery pressure and left ventricle diastolic dysfunction, without differences between NIV and CPAP. Importantly, the improvement in systolic pulmonary artery pressure and left ventricle diastolic dysfunction were more robust in patients who had these abnormalities at baseline. PAP therapy significantly improved respiratory functional parameters and dyspnea as well, without differences between NIV and CPAP.

Prevalence of pulmonary hypertension in patients with OHS differs among studies, mostly due to different patient populations and methods of assessment of pulmonary artery pressures (15–19, 30–32). Using transthoracic echocardiogram, the prevalence of pulmonary hypertension has been reported between 52% and 88% (18, 19, 31, 32). From a pathophysiologic standpoint, a variety of phenomena can increase the risk of pulmonary hypertension in patients with OHS, including frequent and profound intermittent hypoxemia during sleep, swings in intrathoracic pressure caused by recurrent upper airway obstruction, hypercapnia, and acidosis (33–35). These physiologic perturbations during sleep can result in pulmonary vasoconstriction and vascular endothelial remodeling, leading to development of pulmonary hypertension (36). In patients with eucapnic OSA, 12 weeks of CPAP therapy has been shown to reduce pulmonary artery pressures (37, 38), but there are insufficient data on the effects of NIV or CPAP in patients with OHS. Three small clinical series did not observe statistically significant improvement in systolic pulmonary artery pressure after

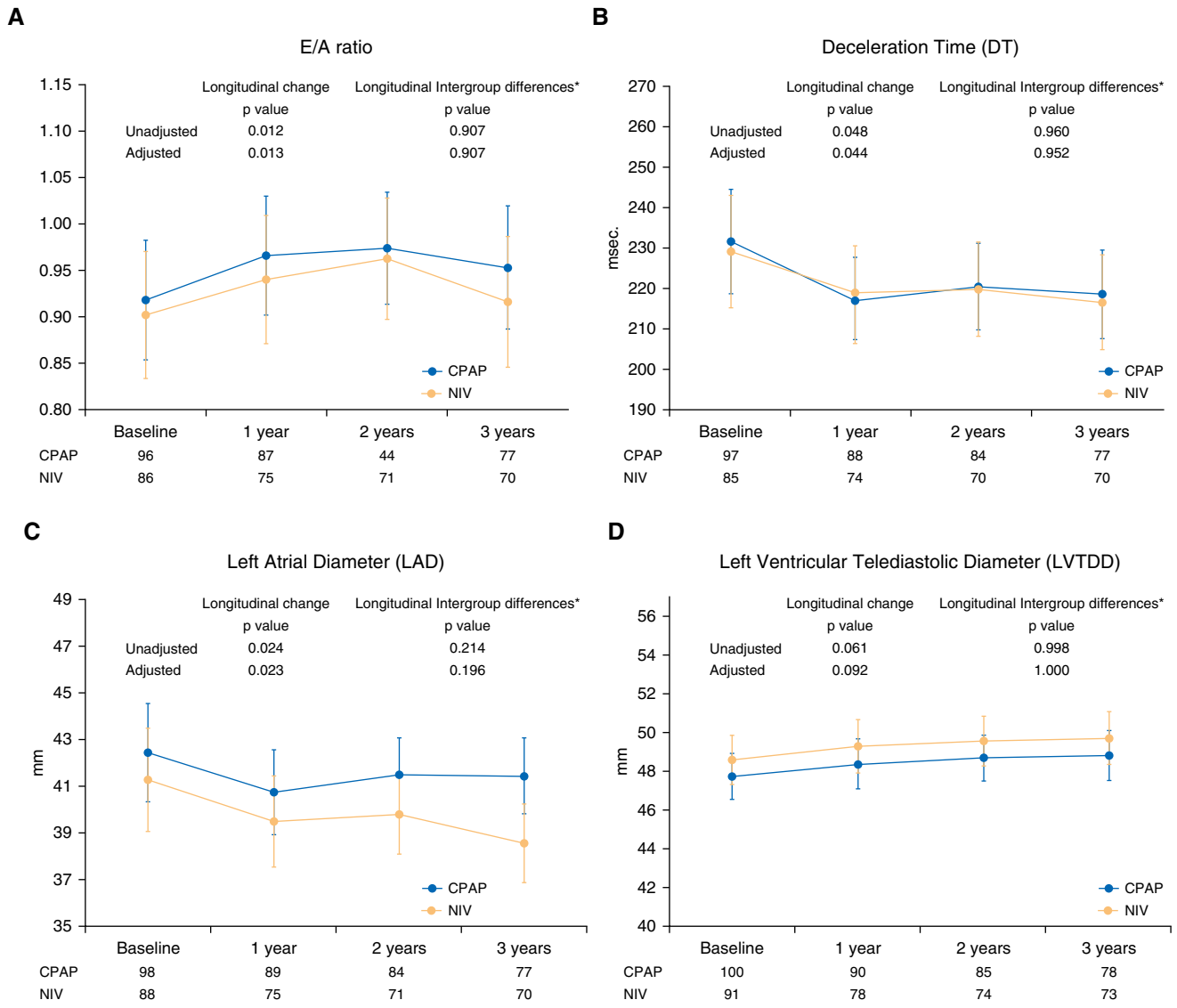


**Figure 3.** Adjusted longitudinal changes of diastolic function parameters (mean and 95% confidence interval). *P* values correspond to unadjusted and adjusted (age, sex smoking status, and FVC) longitudinal changes for each one of diastolic function parameters and for the intergroup continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) comparison from a linear mixed-effects regression model. (*A*) E wave to A wave ratio changes, (*B*) deceleration time changes, (*C*) left atrial diameter changes, and (*D*) left ventricular telediastolic diameter changes. *Interaction between treatment intervention group (CPAP or NIV) and time. E/A = E wave to A wave ratio.

3 months (30, 39) or 6 months (14) of NIV therapy, except in patients with echocardiographically confirmed right ventricular overload at baseline (14, 30). In our largest randomized trial, two months of treatment with NIV led to greater improvement in certain respiratory functional parameters, systolic pulmonary artery pressure, and left ventricular hypertrophy than CPAP and control groups. The median (IQR) change for NIV was −3.4 (−5.4 to −1.5) mm Hg, for CPAP it was 0.02 (−1.7 to 1.7) mm Hg, and for the control group it was −0.44 (−2.7 to 1.9) mm Hg (1, 19). However, in the present long-term analysis of the same cohort, we did not observe sustained benefit with NIV over CPAP on any of these parameters. It is important to note that the patients in the long-term analysis are not exactly the same as the patients reported in the analysis at two months because after two months of therapy the control group was rerandomized to the CPAP and NIV groups to be followed for at least three years (1). It is possible that the addition of these patients to the CPAP and NIV arms led to the mentioned differences between medium-term and long-term results. Another explanation is that the beneficial effects of CPAP therapy may take longer to take effect when compared with NIV. Therefore, at 2 months, NIV appeared superior but not after 3 years. Others have also described that the beneficial effects of CPAP may take longer than NIV (6).

Whether the improvement with PAP in pulmonary hypertension has any clinical relevance remains unknown. To put our findings into context, in patients with group 1 pulmonary hypertension, sildenafil reduces the mean pulmonary artery pressure

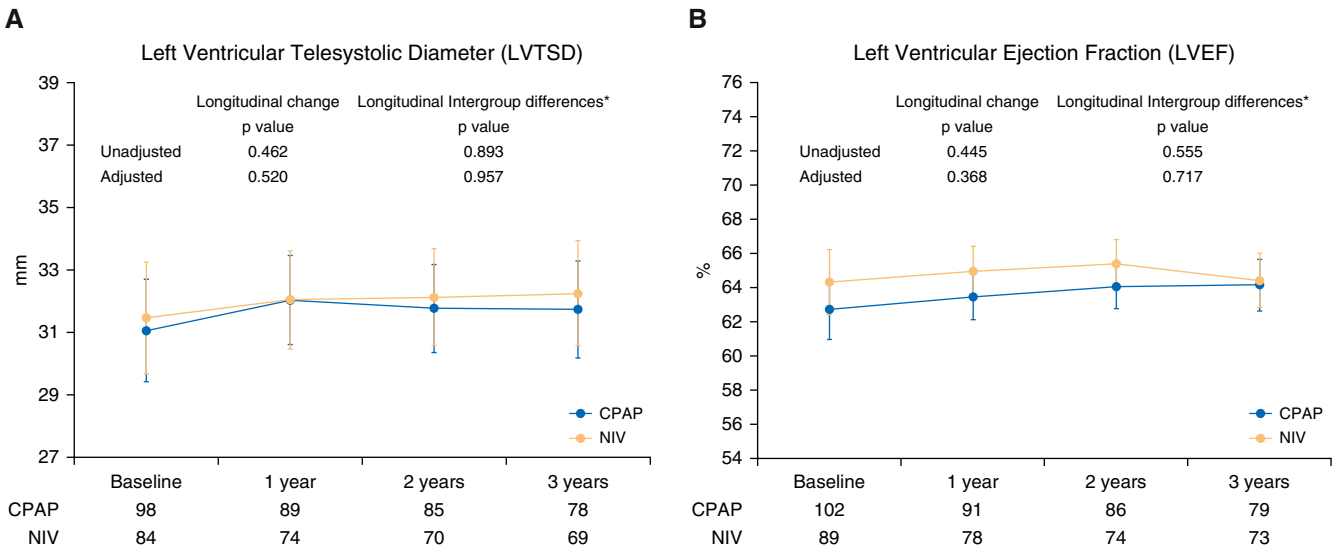


**Figure 4.** Adjusted longitudinal changes of left ventricular systolic function parameters (mean and 95% confidence interval). *P* values correspond to unadjusted and adjusted (age, sex smoking status, and FVC) longitudinal changes for each systolic function parameter and for the intergroup continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) comparison from a linear mixed-effects regression model. (*A*) Left ventricular telesystolic diameter changes and (*B*) left ventricular ejection fraction changes. *Interaction between treatment intervention group (CPAP or NIV) and time.

by 2.1 mm Hg (40). In our study, the degree of improvement observed in the systolic pulmonary artery pressure with either NIV or CPAP (∼6 mm Hg) was greater than the improvement observed with sildenafil, despite the fact that the systolic PAP was not extremely elevated at baseline. However, in the subgroup that had evidence of pulmonary hypertension at baseline (i.e., 87 patients with systolic pulmonary artery pressure ⩾ 40 mm Hg), there was a greater improvement in pulmonary hypertension with both NIV and CPAP (∼11 mm Hg) (*see* Table E8 and Figure E9). The 6MWD test was unchanged during follow-up in the entire cohort. However, in patients with pulmonary hypertension at baseline, the longitudinal improvement in 6MWD was statistically significant (*see* Table E10). This may indicate that either improvements in 6MWD may only become evident in patients with pulmonary hypertension at baseline who experience an improvement in pulmonary hypertension with PAP therapy or that the 6MWD test is less sensitive to detect improvement in pulmonary artery pressures in patients with OHS given that it remained unchanged despite a clinically significant improvement in gas exchange and spirometry.

Left ventricle diastolic dysfunction has been frequently observed in patients with OSA (27, 41–45). A case-control study of 50 patients with OHS reported a higher degree of left ventricle diastolic dysfunction measured by the E/A ratio compared with matched obese control subjects (46). In patients with OHS, the prevalence of left ventricle diastolic dysfunction has been estimated between 60% and 67% (19, 47, 48), very similar to the prevalence of 68% observed in our study. Although obesity, hypertension, and OSA are important risk factors for developing left ventricle diastolic dysfunction, OHS appears to confer additional risk. Patients with OHS have two times higher odds of having an abnormal left atrial diameter (⩾40 mm) than patients with eucapnic OSA (49). From a pathophysiologic standpoint, large swings in intrathoracic pressure due to intermittent upper airway obstruction, increased sympathetic activity, and the activation to the renin–aldosterone–angiotensin system may result in cardiac remodeling, left ventricle hypertrophy and dysfunction, and an abnormal left ventricle morphology (50). By treating some of these underlying physiologic alterations, PAP therapy during sleep can potentially lead to improving left ventricle diastolic dysfunction. However, there is very limited research in this area. Only one prospective observational study assessed changes in E/A ratio, deceleration time, and left atrial diameter after six months of NIV treatment (14). Although the magnitude of improvement in these parameters was similar to what we observed in the present study, it did not reach statistical significance likely due to a small sample size of 24 patients. In our previous assessment, after two months of PAP treatment, the E/A ratio had a significant longitudinal improvement with NIV but the difference with the control group did not reach statistical significance. The median (IQR) change for NIV was 0.07 (0.01–0.13), for CPAP it was 0.06 (−0.02 to 0.13), and for the control group it was −0.002 (−0.07 to 0.07) (19). In several studies (51), the anteroposterior diameter of the left atrium and the diastolic indices have been significantly associated with all-cause mortality, leading us to surmise that improvement or even stabilization of left ventricular diastolic dysfunction can have a significant long-term clinical impact.

High level of adherence to NIV and CPAP therapy is associated with improvement in $Pa_{CO_2}$ (1, 52) and reductions in hospital resource utilization and mortality (9). In our study, adherence to PAP treatment was relatively high and similar to what has been described in long-term observational cohorts. However, echocardiographic outcomes were similar in the high-adherence and low-adherence subgroups. There may be relevant factors other than adherence to NIV or CPAP therapy that led to improvement in echocardiographic outcomes (i.e., pulmonary hypertension at baseline).

Although we observed a mean weight loss of approximately 3% to 4% (∼4 kg), it is

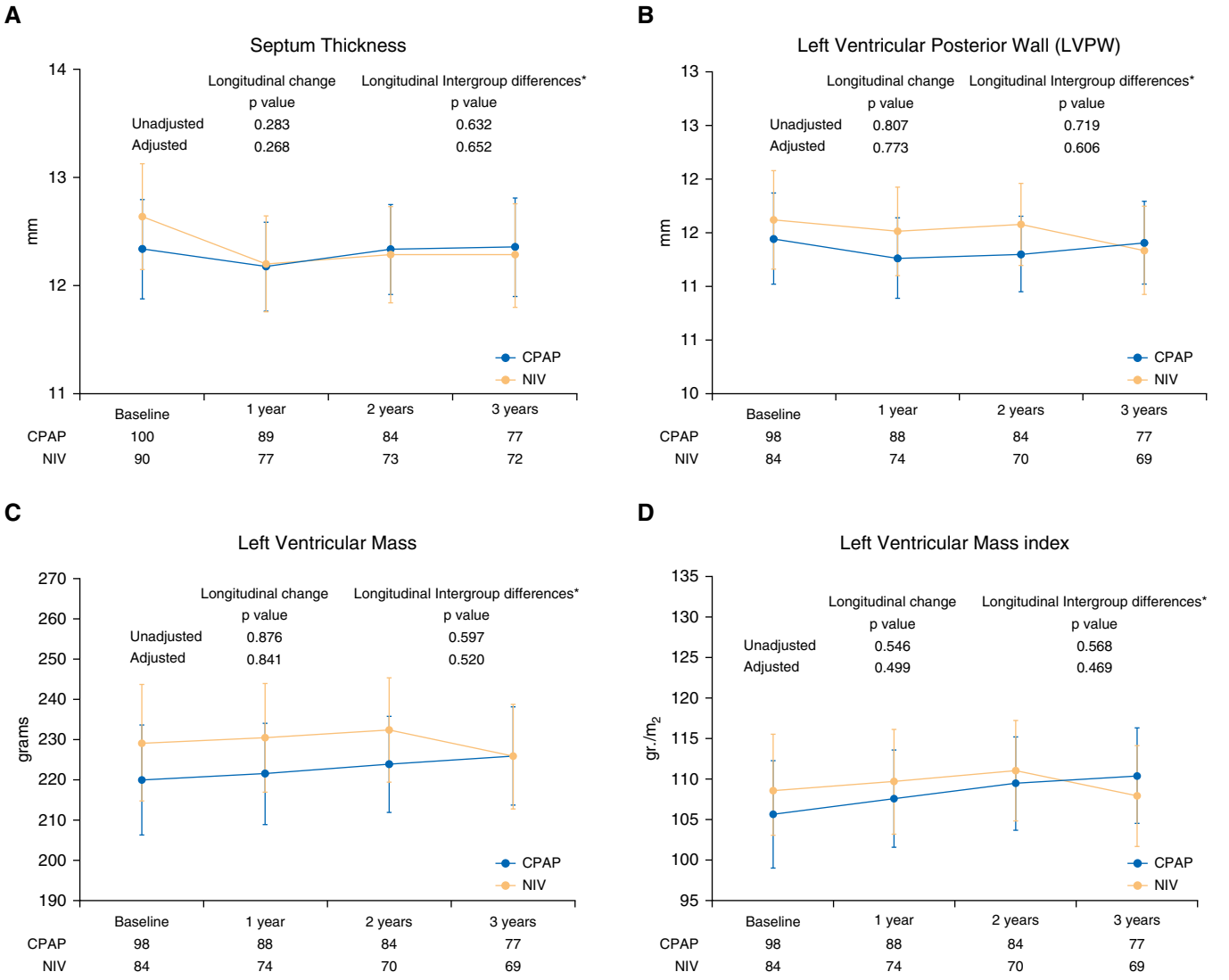


**Figure 5.** Adjusted longitudinal changes of left ventricular mass parameters (mean and 95% confidence interval). *P* values correspond to unadjusted and adjusted (age, sex, smoking status, and FVC) longitudinal changes for each left ventricular mass parameter and for the intergroup continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) comparison from a linear mixed-effects regression model. (*A*) Septum thickness changes, (*B*) left ventricular posterior wall changes, (*C*) left ventricular mass changes, and (*D*) left ventricular mass index changes. *Interaction between treatment intervention group (CPAP or NIV) and time.

unlikely that this level of weight loss led to improvements in gas exchange and dyspnea. It is important to point out that we did not implement intensive lifestyle modification. Our lifestyle modification consisted of recommending to all patients to decrease their caloric intake to 1,000 calories per day and to maintain adequate sleep hygiene and lifestyle habits. We have no objective data as to whether the participants followed any of these recommendations.

Our study has several limitations. Sample size calculation had not been performed *a priori* for the secondary outcomes, except for $Pa_{CO_2}$ (1). Consequently, the echocardiographic analysis should be interpreted with caution. We did not have a control group; therefore, we do not know if the observed longitudinal improvements also would occur in the control group. Alternatively, if we had an untreated longitudinal group, the magnitude of improvement could have been even greater if the untreated group continued to deteriorate over the three years. It is difficult to overcome this limitation because it would be unethical to withhold PAP therapy from symptomatic patients for a longitudinal study of three years duration. Our cohort was limited to patients with OHS who also have concomitant severe OSA (73% of the total OHS population) (1). Patients and investigators were not blinded to treatment allocation. However, the cardiologists who performed the echocardiograms were unaware of the treatment allocation. Different echocardiographic equipment and technicians may have increased interobserver variability, although it should have affected the two arms similarly. Although we acknowledge the inherent limitations of echocardiography for accurate diagnosis of pulmonary

hypertension, it is important to point out that it is a practical and readily available noninvasive tool used routinely in clinical practice, and it can be repeated multiple times in a longitudinal study. Performing multiple right heart catheterizations in such a large cohort of patients in a clinical trial would have not been pragmatic. We could have used better methods to assess diastolic function, such as the tissue Doppler data of the mitral annulus (mitral annular early diastolic velocity) and its ratio between early mitral inflow velocity and mitral annular early diastolic velocity that have already been generalized in the practice of ordinary echocardiography, but that was not the case in 2007 when the study was designed. This may be especially important in patients with atrial fibrillation (7.6% of the total population), although the estimation of filling pressure from transmitral Doppler flow remains meaningful (53). Changes in $\dot{Q}$ can influence echocardiographic measurement of systolic pulmonary artery pressure. Although we do not have a measure of $\dot{Q}$, several recent studies have reported a good correlation between estimated pulmonary artery pressure by echocardiography without adjusting for $\dot{Q}$ and measured pulmonary artery pressures using the gold standard of right heart catheterization (54–56). Our external validity may be limited because the study was exclusively performed in Spain and patients from other ethnic or racial backgrounds may have different characteristics that may influence the results. Unfortunately, we do not have specific information about medication other than if medications were prescribed for hypertension, dyslipidemia, or diabetes, and the number of medications. Therefore, we do not know if changes in specific drugs had any influence on the echocardiographic parameters, but it is likely the effect would be applied equally to both the CPAP and NIV groups.

## Conclusions

In patients with OHS and concomitant severe OSA, long-term PAP therapy improves systolic pulmonary artery pressure and left ventricle diastolic dysfunction, without differences between NIV and CPAP modalities. Our study suggests that echocardiograms may offer valuable clinical information in the management of patients with OHS and severe OSA treated with PAP therapy. ■

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