

ORIGINAL ARTICLE

Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome

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ABSTRACT

Rationale Despite a significant association between obesity hypoventilation syndrome (OHS) and cardiac dysfunction, no randomised trials have assessed the impact of non-invasive ventilation (NIV) or CPAP on cardiac structure and function assessed by echocardiography.

Objectives We performed a secondary analysis of the data from the largest multicentre randomised controlled trial of OHS (Pickwick project, n=221) to determine the comparative efficacy of 2 months of NIV (n=71), CPAP (n=80) and lifestyle modification (control group, n=70) on structural and functional echocardiographic changes.

Methods Conventional transthoracic two-dimensional and Doppler echocardiograms were obtained at baseline and after 2 months. Echocardiographers at each site were blinded to the treatment arms. Statistical analysis was performed using intention-to-treat analysis.

Results At baseline, 55% of patients had pulmonary hypertension and 51% had evidence of left ventricular hypertrophy. Treatment with NIV, but not CPAP, lowered systolic pulmonary artery pressure (−3.4 mm Hg, 95% CI −5.3 to −1.5; adjusted P=0.025 vs control and P=0.033 vs CPAP). The degree of improvement in systolic pulmonary artery pressure was greater in patients treated with NIV who had pulmonary hypertension at baseline (−6.4 mm Hg, 95% CI −9 to −3.8). Only NIV therapy decreased left ventricular hypertrophy with a significant reduction in left ventricular mass index (−5.7 g/m²; 95% CI −11.0 to −4.4). After adjusted analysis, NIV was superior to control group in improving left ventricular mass index (P=0.015). Only treatment with NIV led to a significant improvement in 6 min walk distance (32 m; 95% CI 19 to 46).

Conclusion In patients with OHS, medium-term treatment with NIV is more effective than CPAP and lifestyle modification in improving pulmonary hypertension, left ventricular hypertrophy and functional outcomes. Long-term studies are needed to confirm these results.

Trial registration number Pre-results, NCT01405976 (<https://clinicaltrials.gov/>).

Key messages

What is the key question?

- No randomised trials have assessed the impact of non-invasive ventilation (NIV) or CPAP on cardiac structure and function assessed by echocardiography in patients with obesity hypoventilation syndrome (OHS).

What is the bottom line?

- Both NIV and CPAP improve clinical symptoms, polysomnographic parameters and daytime PaCO₂ in OHS. Whether NIV is more effective than CPAP in improving the cardiovascular burden imposed by OHS requires further investigation.

Why read on?

- This is the first randomised controlled trial that evaluates changes in cardiac structure and function with NIV, CPAP and control. NIV, but not CPAP, improves pulmonary hypertension and left ventricular hypertrophy.

INTRODUCTION

Obesity hypoventilation syndrome (OHS) is defined by a combination of obesity, daytime hypercapnia and sleep-disordered breathing in the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation. Approximately 90% of patients with OHS have concomitant obstructive sleep apnoea (OSA), with 73% having severe OSA.¹ Although the exact prevalence of OHS in the community is unknown, it is likely to increase in parallel with the rise in severe obesity (body mass index or BMI ≥40 kg/m² and ≥50 kg/m²).² In fact, the prevalence of OHS among patients with OSA and a BMI ≥40 kg/m² is alarmingly high at 20%–30%.³

Positive airway pressure (PAP) therapy is the cornerstone intervention in patients with OHS. PAP therapy can be administered as non-invasive ventilation (NIV) or as CPAP. Both NIV and CPAP improve



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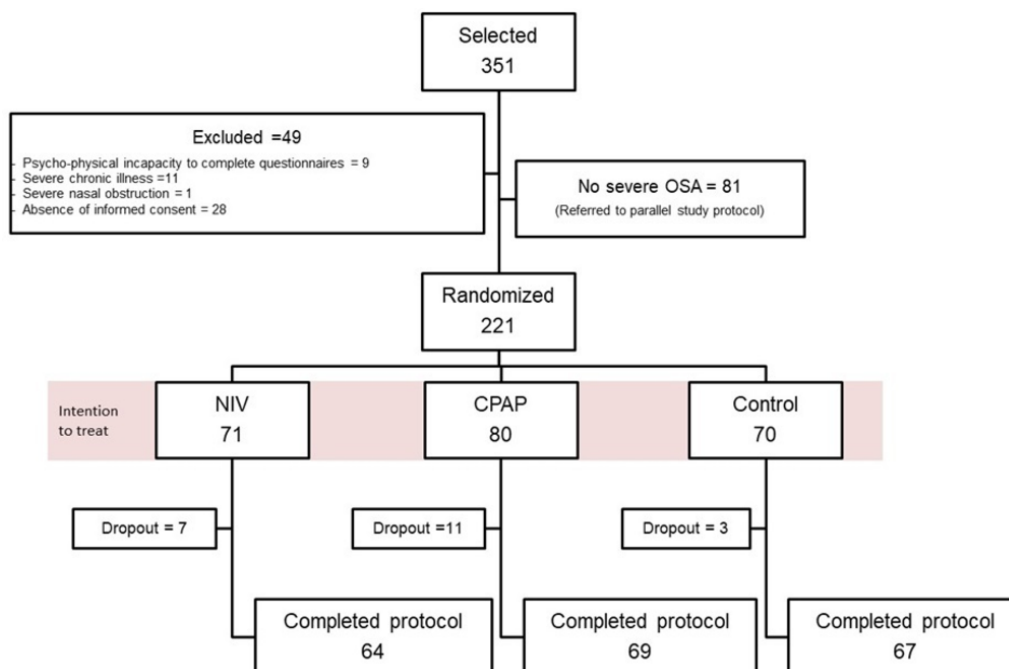


Figure 1 Flow chart of the study protocol. Of the 351 selected patients, 49 were excluded and 221 with severe OSA (AHI \geq 30) were randomised to NIV, CPAP or control groups. Eighty-one patients without severe OSA were referred to a parallel randomised controlled trial. AHI, Apnoea Hypopnoea Index; NIV, non-invasive ventilation; OSA, obstructive sleep apnoea.

daytime symptoms, quality of life, sleep quality, and daytime and nocturnal gas exchange.^{1,4–7} Moreover, PAP therapy lowers intrathoracic pressure swings and sympathetic activity.⁸ Several randomised controlled trials have shown clinical, spirometric and polysomnographic improvements with both PAP treatment modalities.^{1,4,5,7} However, there may be some respiratory functional advantages with NIV.¹

Compared with patients with eucapnic OSA, patients with OHS have a higher prevalence of cardiovascular morbidity, hypertension, diabetes and dyslipidaemia.^{9–11} Moreover, the high mortality observed in patients with untreated OHS has been partly attributed to cardiovascular morbidity.¹² Although a few small observational studies have reported a high prevalence of pulmonary hypertension and right ventricular dysfunction in patients with OHS,^{13–17} randomised controlled trials assessing the impact of NIV or CPAP on cardiac outcomes have not been performed.

Given the very limited information on the effect of PAP therapy on cardiac function and structure in patients with OHS, we aimed to assess the impact of the two most commonly prescribed PAP treatment modalities in OHS (ie, NIV and CPAP) on commonly reported echocardiographic parameters as a hypothesis generating model. We analysed data from the largest multicentre randomised controlled trial with three open parallel groups. This study was designed to determine the comparative efficacy of NIV, CPAP and lifestyle modification (control group) after 2 months of follow-up (Pickwick Study) including a priori echocardiographic assessments as a secondary objective.^{1,6,18}

METHODS

Patients

From May 2009 to March 2013, we screened consecutive patients between 15 years and 80 years old who were referred for pulmonary consultation for suspected OHS or OSA in 16 tertiary care hospitals in Spain. For the initial medium-term

outcomes of this study (see online supplementary material) we enrolled subjects who had OHS with severe OSA (Apnoea Hypopnoea Index \geq 30 events/h).¹ OHS was defined as (1) obesity with BMI \geq 30 kg/m² plus stable hypercapnic respiratory failure during wakefulness (PaCO₂ \geq 45 mm Hg, pH \geq 7.35), (2) no clinical worsening during the previous 2 months and (3) no evidence of relevant COPD (FEV₁ $>$ 70% of predicted when FEV₁/FVC $>$ 70), neuromuscular, chest wall or metabolic disease. Other inclusion criteria were an absence of narcolepsy or restless legs syndrome, and a correctly executed 30 min CPAP/NIV treatment test (see online supplementary material). The exclusion criteria were: (1) a psychophysical inability to complete questionnaires, (2) severe chronic debilitating illness, (3) severe chronic nasal obstruction and (4) lack of informed consent. The study was approved by the ethics committees of the 16 centres and written informed consent was obtained from all patients.

Interventions

All participants underwent conventional inlaboratory polysomnography (PSG) and an analysis of arterial blood gases (ABGs). All patients were ambulatory and were randomised by an electronic database (simple randomisation) into the NIV, CPAP or control groups (figure 1).

Control group: lifestyle modification

The lifestyle modification consisted of a 1000-calorie diet and maintenance of adequate sleep hygiene (see online supplementary material). Oxygen therapy was added if baseline daytime or nocturnal hypoxaemia was detected.¹⁸

CPAP

In addition to lifestyle modification and oxygen (if required),¹⁸ patients were instructed to use home CPAP therapy at a fixed pressure during the entire sleep period based on the results of

a conventional CPAP titration study (see online supplementary material).

Non-invasive ventilation

In addition to lifestyle modification and oxygen (if required),¹⁸ patients were instructed to use NIV treatment during the entire sleep period. The ventilator mode was set at a bilevel PAP with assured volume. More information about the setting, daytime and polysomnographic adjustments, ventilators and masks used are available in the online supplementary material.

Follow-up and outcomes

At baseline we evaluated: ABG while breathing room air (see online supplementary material), anthropometric data, comorbidities, smoking and alcohol intake habits, level of dyspnoea (defined as a score of ≥ 2 points in the Medical Research Council Scale), 6 min walk distance (6-MWD), PSG and conventional transthoracic echocardiogram. At 2 months, we evaluated: ABG while breathing room air, anthropometric data, level of dyspnoea, 6-MWD, Epworth Sleepiness Scale (ESS), blood pressure, PSG, spirometry and conventional transthoracic echocardiogram. Objective adherence to NIV or CPAP was also assessed at 2 months. Dropout definition is described in the online supplementary material.

Polysomnography

We performed PSG at baseline, for PAP titration (only for the NIV and CPAP groups), and after 2 months of treatment (with NIV and CPAP in place and without treatment for the control group) using standard protocols (see online supplementary material). Oxygen treatment was not applied during any of the polysomnographic studies.

Echocardiogram

Echocardiographers at each centre were blinded to the allocated treatment arm. All two-dimensional (2D) and Doppler echocardiograms were recorded using available echocardiographic equipment in each centre (see online supplementary material). Left ventricle (LV) size and wall thickness were measured according to European guidelines.¹⁹ All these parameters were derived from 2D-guided M-mode imaging or from linear measurements obtained from 2D images. LV ejection fraction (LVEF) was calculated from end-diastolic and end-systolic volume estimates, using volumetric measurements. LV mass was estimated by linear method with Cube's formula ($0.8 \times 1.04 \times ((\text{IVS} + \text{LVID} + \text{PWT})^3 - \text{LVID}^3) + 0.6\text{g}$), where LVID is the internal dimension of LV, PWT is the posterior wall thickness and IVS is the interventricular septum thickness, all measured at end-diastole in the parasternal long-axis view using either 2D-guided M-mode or linear measurements from 2D echocardiographic images. LV mass index was obtained dividing the LV mass by the body surface area according to Du Bois's formula. To assess LV diastolic function, we obtained peak early (E), peak atrial (A) mitral valve inflow velocities, as well as their ratio (E/A), isovolumic relaxation time (IVRT), deceleration time (DT) and the anteroposterior diameter of the left atrium measured in the parasternal long-axis view. Pulmonary artery systolic 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 (TEI Index). We considered a systolic pulmonary artery

pressure $\geq 40\text{ mm Hg}$ as evidence of pulmonary hypertension. LV hypertrophy was present if the LV mass index was $\geq 115\text{ g/m}^2$ in men and $\geq 95\text{ g/m}^2$ in women.²⁰

Statistical analysis

Intention-to-treat analysis was performed. Missing values (drop-outs included) were imputed following a multiple imputation method with iterative multivariable regression because the missing data had characteristics compatible with a missing at random pattern. We compared baseline characteristics of patients with OHS randomised to NIV, CPAP or control by analysis of variance (ANOVA) or using the χ^2 test for categorical variables; if the overall significance was <0.05 , we then performed comparison by pairs. Intragroup changes from baseline to 2 months were assessed using paired t tests or equivalent non-parametrical test for continuous variables. The observed effects in the three arms of the study (intergroup differences) were compared using ANOVA. When the overall comparison was statistically significant ($p < 0.05$), paired comparisons of groups were performed by analysis of covariance (ANCOVA) taking into account the baseline value of the variable analysed, age, gender, BMI, presence of hypertension and diabetes, systolic and diastolic blood pressures and Oxygen Desaturation Index (henceforth 'basic adjustment').

In the NIV group we further analysed the change in systolic pulmonary artery pressure and 6-MWD according to the presence of pulmonary hypertension at baseline (systolic pulmonary artery pressure $\geq 40\text{ mm Hg}$) using t test. We also compared the change in LV mass index and 6-MWD according to the presence of LV hypertrophy at baseline (LV mass index $\geq 115\text{ g/m}^2$ male, $\geq 95\text{ g/m}^2$ female). In the NIV group we also compared the percentage of patients with pulmonary hypertension and LV hypertrophy at baseline and after 2 months of therapy using the χ^2 test. Correlations among changes with treatment in systolic pulmonary artery pressure, LV mass index and anthropometric, clinical and respiratory functional variables were carried out by Pearson's test.

Data management and statistical analyses were performed using SPSS software V.22.0 (IBM SPSS Statistics, Armonk, New York, USA).

RESULTS

Of the 351 patients who met inclusion criteria, 49 were excluded and 81 had mild-moderate OSA (figure 1). Dropout rates were similar in patients randomised to NIV, CPAP or lifestyle modification. Table 1 summarises baseline patient characteristics according to treatment allocation ($n=221$). Patients were of middle age and generally severely obese, and there was a slight female preponderance. Comorbidities such as hypertension, diabetes and cardiovascular disorders were equally prevalent among the three groups. Patients randomised to CPAP were slightly younger than patients randomised to NIV ($p < 0.01$).

Due to technical difficulties, some echocardiographic variables were unavailable in 11% of the cohort. As described in the methods, missing values were imputed. Table 2 describes baseline echocardiographic measurements and the prevalence of abnormal echocardiographic parameters.²⁰ The prevalence of structural and functional abnormalities was high across all subjects: 55% of patients had high systolic pulmonary artery pressure ($\geq 40\text{ mm Hg}$) and 51% had evidence of LV hypertrophy based on an LV mass index of $\geq 115\text{ g/m}^2$ in men and $\geq 95\text{ g/m}^2$ in women.

Table 3 summarises baseline and echocardiographic changes according to treatment allocation. Compared with the control

Non-invasive ventilation

Table 1 Baseline patient characteristics according to treatment allocation

	NIV n=71	CPAP n=80	Control n=70
Gender, male, %	35	52	44
Age, years, X (SD)	64 (11)	57 (13)*	60 (13)
BMI, kg/m ² , X (SD)	43 (6.7)	45 (7.6)	44 (7)
Active drinker, %	21	13	23
Active smoker, %	17	29	27
ESS, X (SD)	11 (5.1)	11 (4.8)	11 (5.3)
Dyspnoea MRC Scale \geq 2, %	48	37	56
Hypertension, %	76	65	62
SBP, mm Hg, X (SD)	136 (15)	140 (17)	136 (16)
DBP, mm Hg, X (SD)	77 (12)	80 (12)	79 (12)
Diabetes, %	41	33	37
Dyslipidaemia, %	49	40	41
Ischaemic heart disease, %	8.5	11	10
Arrhythmia, %	13	2.5	10
Chronic heart failure, %	18	13	16
Stroke, %	5.6	6.3	13
Leg arteriopathy, %	4.2	3.8	10
Pulmonary hypertension, % [†]	7	6.3	13
At least one CVM, %	34	31	39
pH, X (SD)	7.41 (0.03)	7.40 (0.04)	7.39 (0.04)
PaO ₂ , mm Hg, X (SD)	62 (8.7)	63 (9.8)	61 (8.2)
PaCO ₂ , mm Hg, X (SD)	51 (4.3)	50 (4.5)	51 (4.2)
Bicarbonate, mmol/l, X (SD)	30 (3.4)	30 (4)	30 (3.2)
FEV ₁ , %, X (SD)	76 (17)	79 (20)	80 (20)
FVC, %, X (SD)	78 (19)	80 (20)	82 (20)
6-MWD, metres, X (SD)	340 (132)	358 (131)	338 (112)
Sleep efficiency, %, X (SD)	71 (15)	72 (16)	70 (17)
Light sleep, %, X (SD)	82 (14)	82 (13)	83 (12)
Deep sleep, %, X (SD)	8.5 (10.0)	9.2 (10.2)	8.5 (9.2)
REM sleep, %, X (SD)	9.1 (6.8)	9.3 (8.0)	8.6 (6.2)
Arousal index, X (SD)	54 (29)	61 (36)	58 (29)
AHI, X (SD)	68 (29)	71 (30)	69 (30)
ODI, X (SD)	63 (31)	72 (35)	68 (31)
SpO ₂ , %, X (SD)	85 (5.8)	85 (6.4)	84 (6.5)
SpO ₂ <90%, X (SD)	69 (29)	67 (30)	72 (26)
Oxygen therapy, %	24	20	29
Compliance, hours/day	5.3 (2.3)	5.3 (2.1)	--

*P<0.05 NIV versus CPAP

[†]=diagnosis prior to study entry

AHI, Apnoea Hypopnoea Index; BMI, body mass index; CVM, cardiovascular morbidity; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; MRC, Medical Research Council; NIV, non-invasive ventilation; ODI, 3% Oxygen Desaturation Index; PaCO₂, arterial pressure of CO₂; PaO₂, oxygen arterial pressure; REM, rapid eyes movement; SBP, systolic blood pressure; SpO₂, oxygen saturation by pulse oximetry; X, mean; 6-MWD, 6 min walk distance.

group, NIV significantly lowered systolic pulmonary artery pressure and decreased LV hypertrophy (ie, septum thickness, LV posterior wall, LV mass and LV mass index) and these differences remained significant despite basic adjustment. Moreover, NIV led to a significant reduction in systolic pulmonary artery pressure

Table 2 Baseline echocardiographic measurements and prevalence of abnormal echocardiographic parameters

	Mean (SD) (n= 221)
Systolic PAP, mm Hg	41 (12)
PAP \geq 40 mm Hg, %	55
TEI Index	0.41 (0.12)
TEI Index \geq 0.43, %	43
EA ratio	0.93 (0.34)
EA ratio \leq 1, %	64
IVRT, ms	97 (29)
IVRT \geq 89 ms, %	61
DT, ms	220 (64)
DT \geq 220 ms, %	49
LAD, mm	40 (10)
LAD \geq 40 mm male, \geq 38 mm female, %	68
LVTDD, mm	49 (7.4)
LVTDD \geq 59 mm male, \geq 53 mm female, %	14
LVTSD, mm	31 (7.2)
LVTSD \geq 40 mm male, \geq 35 mm female, %	16
LVEF, %	64 (9)
LVEF \leq 53, %	7.2
LV septum, mm	13 (2.4)
LV septum \geq 9 mm, %	95
LVPW, mm	12 (2.2)
LVPW \geq 9 mm, %	92
LV mass, gr	224 (64)
LV mass \geq 224 g male, \geq 164 g female, %	69
LV mass index, g/m ²	106 (31)
LV mass index \geq 115 g/m ² male, \geq 95 g/m ² female, %	51

LV, left ventricle; DT, deceleration time; EA, E and A waves; IVRT, isovolumic relaxation time; LAD, left atrial diameter; LVTSD, left ventricular telesystolic diameter; LVTDD, left ventricular telediastolic diameter; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; PAP, pulmonary arterial pressure; TEI, global myocardial function.

and septum thickness when compared with CPAP in adjusted analysis. CPAP, however, reduced the DT when compared with controls without other echocardiographic benefits. Table s1 summarises the changes in ABG, spirometry, 6-MWD, weight, blood pressure, ESS and polysomnographic parameters. NIV and CPAP treatment were more effective than lifestyle modification (control group) in improving ESS and polysomnographic parameters. NIV, however, was more effective than CPAP in improving FEV₁ and 6-MWD. There were no significant inter-group differences in the degree of weight loss (see online supplementary material).

Figure s2 illustrates improvement of the systolic pulmonary artery pressure and 6-MWD in the NIV group according to the presence of pulmonary hypertension at baseline. The improvement in both parameters occurred mainly in the subgroup of patients with pulmonary hypertension at baseline. Figure s2 also shows the improvement in LV mass index and 6-MWD in the NIV group according to the presence of LV hypertrophy at baseline. The improvement in LV mass index and 6-MWD in the NIV group was not statistically different between those with or without LV hypertrophy at baseline. In the NIV group, the prevalence of pulmonary hypertension was reduced from 62% to 42%

Table 3 Baseline changes in echocardiographic parameters based on treatment allocation

	Baseline, mean (SD)			Intragroup differences, mean (95% CI)			P value of intergroup differences	
	NIV n=71	CPAP n=80	Control n=70	NIV	CPAP	Control	Unadjusted	Adjusted
Systolic PAP, mm Hg	41 (9.2)	38 (12)	41 (10)	−3.4 (−5.3 to −1.5)***	0.02 (−1.7 to 1.7)	−0.44 (−2.7 to 1.9)	0.021† 0.008‡	0.040† 0.033‡
TEI Index, %	0.43 (0.19)	0.43 (0.23)	0.38 (0.19)	−0.04 (−0.1 to 0.02)	−0.02 (−0.07 to 0.03)	−0.01 (−0.05 to 0.03)	NS	--
EA ratio	0.88 (0.33)	0.94 (0.26)	0.99 (0.42)	0.07 (0.01 to 0.13)*	0.06 (−0.02 to 0.13)	−0.002 (−0.07 to 0.07)	NS	--
IVRT, ms	96 (27)	96.0 (29)	101 (32)	0.42 (−9.7 to 11)	−0.45 (−9.2 to 8.3)	11 (−0.8 to 22)	NS	--
DT, ms	232 (71)	218 (63)	212 (58)	−1.3 (−18 to 16)	−13 (−31 to 4)	15 (0.3 to 30)*	0.015§	0.021§
LAD, mm	40 (10)	40 (11)	41 (10)	−0.77 (−2.6 to 1.1)	0.02 (−1.6 to 1.7)	−0.4 (−2 to 1.2)	NS	--
LVTDD, mm	49 (6.5)	50 (8.1)	49 (7.3)	0.25 (−1.2 to 1.7)	−0.57 (−1.8 to 0.63)	0.42 (−0.73 to 1.6)	NS	--
LVTSD, mm	31 (7.1)	31 (8.1)	30 (6.1)	0.86 (−0.86 to 2.6)	−0.29 (−1.9 to 1.3)	0.84 (−0.45 to 2.1)	NS	--
LVEF, %	66 (7.6)	62 (11)	63 (7.9)	−1.9 (−4.1 to 0.23)	1.6 (−0.6 to 3.8)	0.49 (−1.2 to 2.1)	0.027‡	NS
Septum, mm	13 (2.1)	12 (2.4)	13 (2.6)	−0.52 (−0.96 to −0.08)*	0.29 (−0.08 to 0.67)	0.15 (−0.16 to 0.46)	0.003† 0.017‡	0.033† 0.031‡
LVPW, mm	12 (2)	11 (2)	12 (2.5)	−0.38 (−0.76 to 0)*	0.29 (−0.35 to 0.41)	0.20 (−0.20 to 0.60)	0.042†	0.011†
LV mass, g	225 (52)	211 (63)	237 (73)	−13 (−24 to −2.1)*	5.5 (−5.1 to 16)	8 (−3.1 to 19)	0.016† 0.008‡	0.006† NS
LV mass index, g/m ²	108 (27)	98 (29)	102 (37)	−5.7 (−11 to −4.4)**	2.9 (−2.1 to 8)	3.5 (−1.5 to 8.6)	0.017† 0.014‡	0.013† NS

P values of intragroup differences (2 months - baseline): * <0.05 ; ** <0.01 ; and *** <0.001

P values of intergroup differences unadjusted or adjusted by basic adjustment (baseline values of the variable analysed and age, gender, BMI, systolic and diastolic blood pressures, hypertension, diabetes presence and Oxygen Desaturation Index). † NIV and control; ‡ NIV and CPAP and § CPAP and control.

LV, left ventricle; DT, deceleration time; EA, E and A waves; IVRT, isovolumic relaxation time; LAD, left atrial diameter; LVTSD, left ventricular telesystolic diameter; LVTDD, left ventricular telediastolic diameter; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall; NIV, non-invasive ventilation; NS, non significant; PAP, pulmonary arterial pressure; TEI, global myocardial function.

($p<0.01$) and the prevalence of LV hypertrophy from 61% to 53% (non significant). Table s2 provides the correlation among changes with treatment in systolic pulmonary artery pressure, LV mass index and anthropometric, polysomnographic, clinical and respiratory functional variables included in table s1. Improvement in systolic pulmonary artery pressure was associated with improvement in PaCO₂ and FEV₁ while the improvement in LV mass index was associated with improvement in 6-MWD.

DISCUSSION

The Pickwick Study is the largest randomised clinical trial to date comparing NIV, CPAP and lifestyle modification in patients with OHS. Moreover, our study is the only clinical trial that systematically compared the effect of the abovementioned interventions on structural and functional echocardiographic changes. The main results can be summarised as follows: (1) more than half of the patients with OHS had echocardiographic evidence of pulmonary hypertension and LV hypertrophy; (2) NIV was more effective in improving LV hypertrophy parameters compared with control; and (3) only NIV therapy led to a significant reduction in pulmonary artery pressure. Only patients treated with NIV experienced a significant improvement in their 6-MWD.

Pulmonary hypertension is the most recognised haemodynamic disorder in patients with OHS but its prevalence has varied in different studies, likely due different patient populations and

methods of measurement.^{13–17} Notably, only 19 out of 221 patients (8.5%) in our cohort were diagnosed with pulmonary hypertension prior to enrolment, suggesting a significant underdiagnosis of this important comorbidity. The high prevalence of pulmonary hypertension observed in our cohort is in line with prior studies using similar echocardiographic criteria.^{13–17} In contrast, the prevalence LV hypertrophy was higher in our cohort than prior studies. In a small case series of 30 patients with OHS, Castro-Añón *et al* did not find any evidence of LV hypertrophy.¹³ In a case-control study of 50 patients with OHS and 50 matched obese controls, Russo *et al* reported a higher degree of LV diastolic dysfunction measured by the E/A ratio compared with matched obese controls.²¹ Notably, the E/A ratio in their OHS group were similar to the present study.

In a small clinical series of 30 patients with OHS who were treated with 6 months of NIV, the LV mass decreased by 12.3 g. However, this clinically significant reduction in LV mass was not statistically significant, likely due to the small sample size.¹³ In the current study, we report a significant reduction in LV mass after 2 months of NIV therapy (−13 g). This degree of reduction in LV mass was accompanied by a significant reduction in LV mass index (5.7 g/m²). This is clinically relevant given that LV hypertrophy as measured by echocardiogram is a marker of cardiac end-organ damage and an established surrogate end point for cardiovascular morbidity and mortality.²² Moreover,

reduction of LV hypertrophy has been associated with a lower incidence of cardiovascular events in patients with hypertension. The reduction in LV mass index observed with NIV therapy in our patients with OHS is of similar magnitude to that observed after 3 months of cardiac resynchronisation therapy²³ or after 9 months of therapy with a direct renin inhibitor, an angiotensin-receptor blocker or their combination in patients with hypertension,²⁴ or after 12 months of spironolactone in patients with heart failure and preserved ejection fraction.²⁵ Moreover, the degree of improvement in the LV mass index with NIV therapy was similar to what has been achieved with β -blockers.²⁶ It is important to point out that the improvement in LV hypertrophy with NIV was not accompanied by an improvement in daytime blood pressure. Although we did not measure blood pressure during sleep, it is plausible that by being more effective in treating nocturnal hypoventilation, NIV led to better blood pressure control during sleep compared with CPAP and the control group. In contrast to CPAP, improvement in lung volumes with NIV can lead to lower intrathoracic pressure swings during sleep which can further reduce LV afterload. Notably, LV hypertrophy confers an excess risk for cerebrovascular events independently of blood pressure.^{27,28} Therefore, a reduction in LV hypertrophy without a significant change in blood pressure can be considered a clinically relevant outcome. In our cohort, the change in the 6-MWD correlated with the improvement of LV mass index which may be an expression of its clinical significance. However, it remains unclear whether improvements in exercise capacity leads to improvement in LV mass index or vice versa.

NIV therapy also led to a reduction in systolic pulmonary artery pressure. Patients with OHS experience pronounced intermittent hypoxaemia and swings in intrathoracic pressures due to frequent upper airway obstruction. These phenomena may promote a more robust degree of pulmonary vasoconstriction and vascular endothelial remodelling which could ultimately lead to the development of pulmonary hypertension.²⁹ Although several relatively small studies have reported a reduction in pulmonary artery pressure^{30,31} in eucapnic patients with OSA treated with 12 weeks of CPAP, there is a paucity of data on the effects of NIV or CPAP in patients with OHS. Two small clinical series reported a reduction in pulmonary artery pressure after 3 months or 6 months of NIV therapy only in patients who had echocardiographic evidence of right ventricular overload at baseline.^{13,32} In our patients, only NIV reduced the systolic pulmonary artery pressure. We have previously reported that NIV resulted in greater improvements in lung volume, daytime hypercapnia and acid-base balance than CPAP¹ (see online only supplementary material). Hypercapnia and acidosis can lead to pulmonary vasoconstriction and an increase in endothelial tone.^{33,34} Although there were no significant polysomnographic differences at 2 months in the degree of nocturnal hypoxaemia between NIV or CPAP groups, it is possible that patients treated with NIV achieved a better control of nocturnal hypoventilation (in addition to daytime improvement) that may have in turn led to a more significant reduction in pulmonary artery pressures. Although we did not perform transcutaneous CO₂ monitoring during sleep, systolic pulmonary artery pressure improvement was correlated with improvements in daytime PaCO₂ and FEV₁. Moreover, improvement in lung volumes during sleep with NIV can potentially increase the calibre of the airways thereby reducing lower and upper airways resistance which may in turn lead to further improvement of alveolar ventilation.³⁵

Although there could be several explanations on how NIV might reduce pulmonary artery pressures, it still remains unclear whether the magnitude of the reduction in the systolic pulmonary

artery pressure observed with 2 months of NIV therapy (ie, 3.4 mm Hg) is clinically relevant. Only patients treated with NIV experienced a significant improvement in 6-MWD which may be explained by either reduction in systolic pulmonary artery pressure or by improvement in respiratory function (ie, FEV₁).¹ Since 6-MWD improvement was not correlated with the improvement in systolic pulmonary artery pressure, the latter mechanism seems more probable as the causal factor. In a small observational study, it was noted that patients with OHS with right ventricular overload at baseline experienced significant improvements in systolic pulmonary artery pressure and 6-MWD.¹³ Similarly, in our study, the degree of improvement in systolic pulmonary artery pressure and 6-MWD were more robust in the NIV subgroup with systolic pulmonary artery pressure ≥ 40 mm Hg at baseline. Moreover, NIV led to a significant decline in the prevalence of pulmonary hypertension. In another study of 278 patients with pulmonary hypertension, standard doses of sildenafil reduced mean pulmonary artery pressure by 2.1 mm Hg and led to significant improvement in 6-MWD.³⁶ This degree of improvement in mean systolic pulmonary artery pressure is similar to the degree of improvement in pulmonary artery pressure of 3.4 mm Hg measured by echocardiography in our study³⁷ and lower than the improvement obtained in our patients with pulmonary hypertension at baseline (6.4 mm Hg). Although the overall clinical impact of NIV therapy on systolic pulmonary artery pressure in patients with OHS remains unclear, our data reveal that in patients with pulmonary hypertension at baseline, NIV can lead to significant improvement in systolic pulmonary artery pressure and 6-MWD.

In contrast to the limited data in OHS, the impact of CPAP on echocardiographic measures in patients with eucapnic OSA has been assessed in three randomised controlled trials, two observational studies and a case controlled study.^{30,38–42} Three of these studies assessed the impact of CPAP on measures of LV hypertrophy in patients with OSA and did not find a significant improvement.^{38,39,43} It is important to consider that patients with eucapnic OSA differ significantly from patients with OHS. Indeed, patients with OHS have chronic hypercapnic respiratory failure, experiencing more profound nocturnal hypoxaemia, and have a higher severity of OSA and obesity than patients with eucapnic OSA. Moreover, the prevalence of cardiovascular comorbidities and cardiovascular mortality are significantly higher than patients with eucapnic OSA.^{9–11} Therefore, LV hypertrophy may be more prevalent in patients with OHS and as such, these patients may be more susceptible to derive benefit from short-term NIV therapy. As we have previously reported, NIV is superior to CPAP in improving FEV₁ and 6-MWD¹ (see online supplementary material). We hypothesise that the sustained improvement in acid-base balance, reduction in intrathoracic pressure swings, and improvement in lung function may explain the more robust improvement in LV hypertrophy obtained with short-term NIV than with CPAP therapy.

Our study has several limitations. Although we had described a priori that echocardiography was going to be obtained in all patients enrolled in the Pickwick Study, the original sample size calculation was based on estimated changes in PaCO₂, not echocardiographic measures. As such, our sample size may not have been sufficient and therefore increasing the risk of bias. However, we tried to minimise bias by performing adjusted analysis. Another limitation is the short duration of treatment (ie, 2 months). We believe it would have been unethical to extend the period of follow-up beyond 2 months for the control group (ie, lifestyle modification). Accordingly, it is possible that longer duration of therapy would have led to

more significant improvement in echocardiographic measures. Because the ongoing second phase of the Pickwick Study includes follow-up echocardiographic evaluations, in a future analysis we will be able to compare the short-term and long-term echocardiographic changes between NIV and CPAP. Different echocardiographic equipment and technicians may have increased interobserver variability, although it should have affected all three groups similarly. The absence of nocturnal blood pressure and transcutaneous CO₂ monitoring limits our ability to demonstrate that NIV may have been superior at improving ventilation and blood pressure control during sleep. 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 non-invasive tool used routinely in clinical practice. Performing right heart catheterisation in such a large cohort of patients in a clinical trial would not have been pragmatic. Our statistical analysis included multiple group comparisons (ie, NIV, CPAP and control). This may increase the probability of finding statistical significance at random. However, we only performed paired comparisons adjusted by confounders (ANCOVA) if the overall comparison by ANOVA was statistically significant.

In summary, the prevalence of cardiac structural and functional abnormalities as assessed by transthoracic echocardiography is high in patients with OHS. Medium-term NIV therapy seems more effective than CPAP and lifestyle modification in improving measures of LV hypertrophy and systolic pulmonary artery pressure. Moreover, NIV leads to a greater degree of improvement in 6-MWD. Our study suggests that echocardiograms can provide valuable clinical information in the management of patients with OHS being treated with PAP therapy. Long-term comparative studies, however, are necessary to demonstrate whether the beneficial effects of NIV are sustained.

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