ONLINE DATA SUPPLEMENT

Echocardiographic changes with Noninvasive Ventilation and CPAP in Obesity Hypoventilation Syndrome

Authors:

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ADDITIONAL METHODS

Project promotion, centers and internal organization

The project was initially promoted by the National Pulmonologist Society (SEPAR) through the Spanish Sleep Network and Spanish Noninvasive Ventilation Network. Both directing committees asked Dr. Juan F Masa to develop the project, to obtain grants, and to find centres with the following characteristics: 1) a complete sleep laboratory; 2) a home ventilation program; 3) at least three years of experience in the aforementioned areas; and 4)

participation in at least one previous multicenter study promoted by the Spanish Sleep network or Spanish noninvasive ventilation network.

Successive versions of the protocol were discussed between the researchers in three consecutive official meetings of SEPAR and in continuous correspondence between researchers by email for 18 months. In 2008, the final version of the protocol and grant were available. The coordinator centre in Cáceres developed the following necessary tools to conduct a multicenter study: 1) a book collection; 2) electronic databases hosted on a website with a specific domain; 3) a notebook containing the project procedures (explained step-by-step) and the necessary questionnaires to standardize the work among centres; and 4) an external audit every three months to compare the operating variables between groups (dropouts due to medical causes and mortality) on which the continuity of the study depends. In 2009, the patient inclusion process was initiated, and one meeting was conducted with the researchers after the inclusion of the first five patients to make minor changes in the protocol if necessary.

The following actions were established a priori: 1) the preparation of monthly newsletters from the principal investigator to other researchers to report on the comparative inclusion results between centres, encourage participant inclusion, and promptly communicate eventualities; 2) the establishment of an investigator meeting within the two annual official SEPAR meetings; and 3) policy publications with a forecast of the number of publications and authorship based on the number of patients included.

“Pickwick” project and present analysis

The present paper reports the results of the “Pickwick” study, which was designed to understand the mid- and long-term efficacy of CPAP and NIV in obesity hypoventilation syndrome (OHS) and includes two parallel studies (see Figure s1). Patients with OHS and severe obstructive sleep apnoea (OSA) were randomised to continuous positive airway pressure (CPAP), noninvasive ventilation (NIV), or control group for two months of follow-up (first phase). Subsequently, for ethical reasons, patients included in the control group were re-randomised into the CPAP and NIV groups to complete a follow-up of 36 months (second phase). Patients with OHS but without severe OSA (i.e. not clear candidates for CPAP treatment) were directly randomised to the NIV or control groups and followed-up for 36 months. The primary variable for the first phase was $PaCO_2$, and the primary variable for the second phase after three years of follow up was days of hospitalization, with two independent sample size calculations performed. The second phase of the study has not been completed yet.

In the present analysis we used data obtained from 221 patients with OHS and severe OSA, enrolled in the first phase of the randomised controlled trial.

CPAP/NIV treatment tolerance tests and explanation of treatments

Before randomisation, we performed CPAP[1] and NIV tolerance tests. With the patient seated, we adjusted a ventilator in CPAP mode with a pressure of 7 cm H_2O for 15 minutes. Subsequently, the ventilator was switched to bi-level mode during spontaneous breathing, with the CPAP and inspiratory positive airway pressure (IPAP) set at 16 cm H_2O for another 15 minutes. Patients who were unable to adapt, according to the investigator, were excluded.

Once randomised, we spent the necessary time with the patient to prioritize adaptation to treatment and explain the following to the patients: 1) the characteristics of their disease; treating their disease with NIV, CPAP, or lifestyle modifications (depending on the randomisation treatment); and the importance of appropriate follow-up; 2) how lifestyle modifications, NIV, or CPAP devices work and the features of the mask and fastening systems,; and 3) the potential short- and long-term benefits of the treatments and the associated consequences in daily life.

The lifestyle modification consisted of a 1,000-calorie diet and maintenance of adequate sleep hygiene and habits (avoiding supine sleep position; maintaining regular sleep habits and exercise; not consuming sedatives, stimulants, or alcohol; no tobacco smoking; and avoidance of heavy meals within four hours before bedtime). Oxygen therapy was added if baseline daytime or nocturnal hypoxemia was detected.[2]

CPAP titration

This was the second of three PSGs performed by experiment technicians. The initial CPAP was 4 cm H_2O. When obstructive events appeared, the pressure was increased 1 cm H_2O every 5 minutes until obstructive apnoeas resolved. Subsequently, the CPAP was increased every 10 minutes to achieve the elimination of hypopnoeas, thoracoabdominal paradoxical movement, flow limitation, and snoring. Once the respiratory events had disappeared, CPAP was checked during the REM period and in the supine position, and the pressure was increased if respiratory events recurred. After a period without

events and with normal sleep architecture, CPAP was slowly reduced by 1 cm H_2O until the same events reappeared. Subsequently, CPAP was augmented until obstructive events were resolved and normal sleep architecture reappeared. At this point, the pressure was maintained or slightly increased, if necessary, until the end of the study.

Oxygen therapy was added if the daytime or nocturnal hypoxemia was detected after CPAP titration.[2]

A priori, nasal masks were proposed, but in cases of significant oral leakage, oronasal masks could be used. A humidifier was always added with an oronasal mask and only if necessary with a nasal mask.

NIV adjustment

While the patient was awake, the expiratory positive airway pressure (EPAP) was set between 4 and 8 cm H_2O, and the inspiratory positive airway pressure (IPAP) was set between 18 and 22 cm H_2O (EPAP included). The pressures were adjusted to obtain normal oxygen saturation, if possible, as measured by pulse oximetry and patient tolerance. The respiratory rate was adjusted to 12-15 breaths/minute (close to the spontaneous respiratory rate, if possible), and the target volume was set at between 5 and 6 ml/kg of actual weight, allowing for an increase in the maximum pressure over the previously fixed IPAP, if necessary. A check of mechanical ventilation phases (trigger, pressurization, and ending) was also performed to avoid asynchronies and to refine the setting. After 30 minutes of continuous use, with patient adaptation and an adequate patient-ventilator interaction, an ABG was performed. The $PaCO_2$ result was used to

adjust the ventilator parameters. The final adjustment was performed by means of conventional polysomnography (PSG), with the EPAP increased if obstructive apnoeas appeared and the IPAP increased if hypopnoeas, flow limitation, snoring, or non-apnoeic hypoventilation were present, until oxygen saturation normalization or the optimal pressure was reached. No changes were made in the assured volume during this nocturnal titration. Oxygen therapy was added if the daytime or nocturnal hypoxemia was detected after NIV titration.[2]

The ventilators used across the centres were as follows: Breas Vivo 40 (General Electric, England), BiPAP AVAPS (Philips-Respironics, Netherlands), Trilogy 100 (Philips-Respironics, Netherlands), VS Ultra (ResMed, Australia), Monal T50 (Air Liquide, France), and Puritan Bennett 560 (Puritan Bennett, USA).

Oronasal masks were initially proposed, but for those who tolerated oronasal masks poorly, a nasal mask could be used. A humidifier was always added with a oronasal mask and only if necessary with a nasal mask.

Measurement of arterial blood gases

Arterial blood gases were measured following standard procedures.[3] All tests were performed after at least 10 min of rest, at approximately 12 p.m., with the patient seated comfortably and breathing room air at least during 20 minutes before (except when the test was performed for NIV or oxygen titrations). The sample was analyzed immediately.

Dropout definition

Dropouts were defined as patients who decided to leave the study voluntarily or for one of the following medical reasons: 1) pH <7.33 at the first-month evaluation; 2) hospital admission requiring NIV treatment for more than five days, conventional mechanical ventilation for more than three days, or pH <7.33 while breathing room air at hospital discharge; or 3) death.

Sample size calculation

The present study is a secondary analysis of the “Pickwick” study which was designed to assess the mid- and long-term efficacy of CPAP and NIV in patients with OHS, including two parallel studies and two phases (two months and 36 months) (Figure s1). As we have commented before, the main outcome used for sample size for the first phase (i.e. at 2 months) was $PaCO_2$, whereas hospitalisation days was the main outcome used for sample size calculation for the second phase of the study (i.e. 36 months). Therefore, two independent sample size calculations were carried out. The sample size for the two-month phase of the study was calculated to detect differences in the primary outcome variable (daytime $PaCO_2$), assuming an alpha error of 0.05 and a beta error of 0.2. Mean $PaCO_2$ in patients treated with NIV was 45±5 mmHg. We estimated that an inter-group difference of ≥2.5 mmHg with a standard deviation of 5 would be clinically relevant. In order to compare 2 independent means (triple comparison), 64 patients would be needed per group. Expecting a dropout of 20%, the final number of patients per group would be 80. The inclusion of additional patients was stopped when the number of patients reached the estimated sample size with dropouts included or when the three groups (CPAP, NIV and control) had at least 64 patients at the end of 2 months of follow up

(dropouts excluded). We did not perform an independent sample size calculation for the purposes of detecting echocardiographic changes.

PSG measurements and event definitions

We used the American Academy of Sleep Medicine's[4] rule regarding configuration, filters and sample signal rates. The neurological variables were measured using electroencephalogram, electrooculogram, and electromyogram (on the chin and both legs). Flow tracing was provided using a nasal cannula and thermistor for PSG in the absence of mechanical treatments and with flows from CPAP or ventilator devices for PSG performed using CPAP or NIV, respectively. Thoracoabdominal motion was measured by piezoelectric or inductance bands. Oxygen saturation was measured with a pulse oximeter (average signalling time among centres varied from 2-4 seconds). An electrocardiogram and body position measurements were also collected. The PSG studies were analyzed manually at each participating centre according to the 2007 recommendations of the AASM (4) and the respiratory scoring according to the Spanish Sleep Network rule.[5]

Apnoea was defined as the absence of airflow (≥90% reduction) for ≥10 seconds, and hypopnoea was defined as a discernible airflow or band reduction (≥30% and <90%) for at least 10 seconds with a ≥3% drop in oxygen saturation or final arousal.[5]

A valid PSG recording required at least three hours of sleep time. In cases of an invalid recording, the test was repeated one additional time.

Echocardiograph equipment

The echocardiographs used across the centres were as follows: Philips IE33, Philips HD11, Philips HD15, (Philips Healthcare, MA, USA) and KPI Vivid 7 (General Electric ME, USA).

ADDITIONAL RESULTS

Table s1 presents the changes in functional respiratory, blood pressure, ESS, weight and polysomnographic parameters comparing NIV, CPAP and controls.[6] The improvement in $PaCO_2$ and bicarbonate were greater in the NIV treatment, with a significant difference relative to the control treatment but not relative to the CPAP treatment. Additionally, PaO_2 improved with NIV and CPAP treatment, without significant differences between the treatments. FEV_1, FVC, and the 6-MWD improved significantly only in the NIV treatment in intra-group comparisons, whereas the inter-group differences were significant for only FEV_1 and the 6-MWD between NIV and CPAP treatments, as well as for FEV_1 between NIV and control treatments. Systolic blood pressure improved in both CPAP and control groups with statistical inter-group differences compared to NIV treatment. ESS and polysomnographic parameters improved similarly with NIV and CPAP treatments with statistical significant differences with control group.

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FIGURE LEGENDS

Figure s1: Flowchart of the Pickwick study. Abbreviations: OHS= obesity hypoventilation syndrome; OSA= obstructive sleep apnoea; NIV= noninvasive ventilation; and CPAP= continuous positive airway pressure.

Figure s2. Panel A: Changes (mean and standard error) with NIV treatment for systolic pulmonary artery pressure (mmHg) and 6-MWD (meters) according to the presence of pulmonary hypertension at baseline (defined as systolic pulmonary artery pressure ≥40 mmHg). Panel B: Changes with NIV treatment for LV mass index (g/m^2) and 6-MWD (meters) according to the presence of LV hypertrophy at baseline (defined as LV mass index ≥115 g/m^2 male, ≥95 g/m^2 female). Abbreviations: NIV = noninvasive ventilation; PH = pulmonary hypertension; 6-MWD = 6-minute walk distance; and LV = left ventricular.

Table s1: Changes in functional respiratory measures, blood pressure, ESS, weight and polysomnographic parameters

	Intra-group differences, mean (95% CI)			P value of inter-group differences	
	NIV N=71	CPAP N=80	Control N=70	Unadjusted	Adjusted
$PaCO_2$, mmHg	**-5.5 (-7;-3.7)‡**	**-3.7 (-5.2;-2.2)‡**	**-3.2 (-4.6;-1.7)‡**	0.029¶	0.034¶
Bicarbonate, mmol/l	**-2.1 (-2.8;-1.4)‡**	**-1.9 (-2.7;-1.1)‡**	0.7 (-0.03;1.4)	0.010¶	0.005¶
PaO_2, mmHg	**4.8 (2.5;7.1)‡**	**5.5 (2.9;8.1)‡**	1.9 (-0.04;3.8)	NS	--
FEV_1,%	**4.8 (1.8;7.8)†**	-1.8 (-5.1;1.5)	-1.5 (-5.7;2.7)	0.015¶ 0.009¥	0.041¶ 0.003¥
FVC, %	**4.1 (0.4;7.8)***	-1.4 (-5.5;2.8)	-0.6 (-4.8;3.6)	NS	--
6-MWD, meters	**32 (19;46)‡**	6.0 (-7.7;20)	16 (0.3;32)	0.013¥	0.01¥
Weight, kg	**-2.4 (-3.9;-0.87)†**	-1.1 (-2.3;0.12)	**-1.6 (-2.8;-0.43)†**	NS	--
Systolic BP, mmHg	1.1 (-2.6;4.8)	**-5.3 (-9;-1.59)†**	**-5.2 (-9;-1.3)†**	0.017¶ 0.024¥	0.007¶ NS¥
Diastolic BP, mmHg	0.67 (-2.4;3.8)	1.4 (-1.1;3.9)	-0.23 (-3.2;2.7)	NS	--
ESS	**-4.8 (-6:-3.6)‡**	**-4.3 (-5.3;-3.3)‡**	-1.0 (-2;0.03)	0.000¶ §	0.000¶ §
Sleep efficiency	2.3 (-1.9;6.5)	2.2 (-1.9;6.3)	-0.04 (-3.3;3.2)	NS	--
Arousal index	**-38 (-45:-31)‡**	**-42 (-50;-34)‡**	-5.3 (-11;0.32)	0.000¶ §	0.000¶ §
AHI	**-57 (-64;-50)‡**	**-60 (-67;-53)‡**	-6.8 (-14;0.23)	0.000¶ §	0.000¶ §
ODI	**-46 (-53;-39)‡**	**-58 (-65;-51)‡**	-4.7 (-11;1.4)	0.000¶ §	0.000¶ §
SpO_2, %	**5.5 (4.3;6.7)‡**	**6.1 (4.8;7.3)‡**	1.2 (-0.04;2.4)	0.000¶ §	0.000¶ §
%TST <90% oxygen saturation	**-36 (-42;-28)‡**	**-39 (-46;-32)‡**	-6.9 (-13;0.58)	0.000¶ §	0.000¶ §

ESS = Epworth sleepiness scale; OHS= obesity hypoventilation syndrome; CI= confidential interval; FEV1= forced expiratory volume in the first second; FVC= forced vital capacity; 6-MWD = six-minute walk distance; AHI = apnoea-hypopnoea index; ODI = 3% oxygen desaturation index; SpO2 = oxygen saturation by pulse oximetry; and %TST <90% oxygen saturation = sleep time with oxygen saturation below 90%.

P values of intra-group differences (two months - baseline): *=<0.05; †=<0.01; and ‡=<0.001

P values of inter-group differences unadjusted or adjusted by basic adjustment (baseline values of the variable analyzed and age, gender, BMI, and AHI): ¶=NIV and control and §=CPAP and control.

Table s2: Correlation of change in LV mass index and sPAP and variables included in sTable 1.

		LV mass index	sPAP	SBP	DBP	FEV_1	FVC	PaO_2	Bicarbonate	ESS	6-MWD	Arousal index	Sleep efficiency	AHI	SpO2	%TST <90% oxygen saturation	ODI
SBP	R	-.020	-.088														
	P value	.731	.135														
DBP	R	.075	-.070	.433**													
	P value	.192	.236	.000													
FEV_1	R	.045	-.130*	.091	-.036												
	P value	.438	.026	.113	.533												
FVC	R	.073	.069	.058	-.025	.636**											
	P value	.208	.242	.314	.666	.000											
PaO_2	R	.005	-.060	.060	-.102	.131*	.150**										
	P value	.925	.305	.302	.077	.022	.009										
Bicarbonate	R	.076	.045	-.017	.051	-.062	.006	-.096									
	P value	.188	.441	.765	.374	.284	.917	.096									
ESS	R	-.018	.085	-.079	-.022	-.108	-.025	-.152**	.141*								
	P value	.751	.146	.173	.708	.062	.662	.008	.014								
6-MWD	R	-.126*	-.041	.125*	.097	.064	.077	.093	-.011	-.094							
	P value	.029	.482	.030	.094	.270	.183	.105	.848	.103							
Arousal index	R	-.031	-.007	.019	-.049	-.068	-.050	-.030	.142*	.253**	-.103						
	P value	.591	.904	.744	.400	.238	.382	.608	.013	.000	.075						
Sleep efficiency	R	-.070	.006	.072	.084	-.045	-.069	.070	-.026	.036	-.059	.031					
	P value	.227	.914	.214	.144	.433	.231	.226	.653	.536	.303	.588					
AHI	R	-.042	-.026	.026	-.001	-.084	-.023	-.073	.156**	.312**	-.145*	.676**	.022				
	P value	.462	.659	.653	.984	.146	.687	.206	.007	.000	.012	.000	.704				
SpO_2	R	.010	-.072	-.002	.029	.027	-.015	.161**	-.097	-.273**	.186**	-.296**	-.030	-.363**			
	P value	.868	.222	.974	.618	.642	.799	.005	.091	.000	.001	.000	.603	.000			
%TST<90% oxygen saturation	R	.052	.052	.126*	.043	-.015	-.004	-.167**	.157**	.174**	-.016	.333**	-.008	.337**	-.513**		
	P value	.370	.380	.028	.460	.789	.940	.004	.006	.002	.784	.000	.894	.000	.000		
ODI	R	-.034	-.045	.072	-.013	-.040	-.057	-.109	.151**	.300**	-.134*	.646**	.046	.763**	-.432**	.492**	
	P value	.559	.445	.210	.823	.489	.320	.059	.009	.000	.020	.000	.427	.000	.000	.000	
$PaCO_2$	R	-.001	.138*	-.025	.057	-.185**	-.170**	-.335**	.389**	.190**	-.109	.081	-.043	.079	-.213**	.129*	.111
	P value	.991	.019	.661	.321	.001	.003	.000	.000	.001	.057	.160	.459	.169	.000	.025	.053

* = $p<0.05$; and ** = $p<0.01$
Abbreviations: LV = left ventricular; R = correlation coefficient; sPAP = systolic pulmonary artery pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; ESS = Epworth sleepiness scale; FEV1= forced expiratory volume in the first second; FVC= forced vital capacity; CO_3H^- = bicarbonate; 6-MWD = six-minute walk distance; AHI = apnoea-hypopnoea index; ODI = 3% oxygen desaturation index; SpO2 = oxygen saturation by pulse oximetry; and %TST <90% oxygen saturation = sleep time with oxygen saturation below 90%.

Figure s1

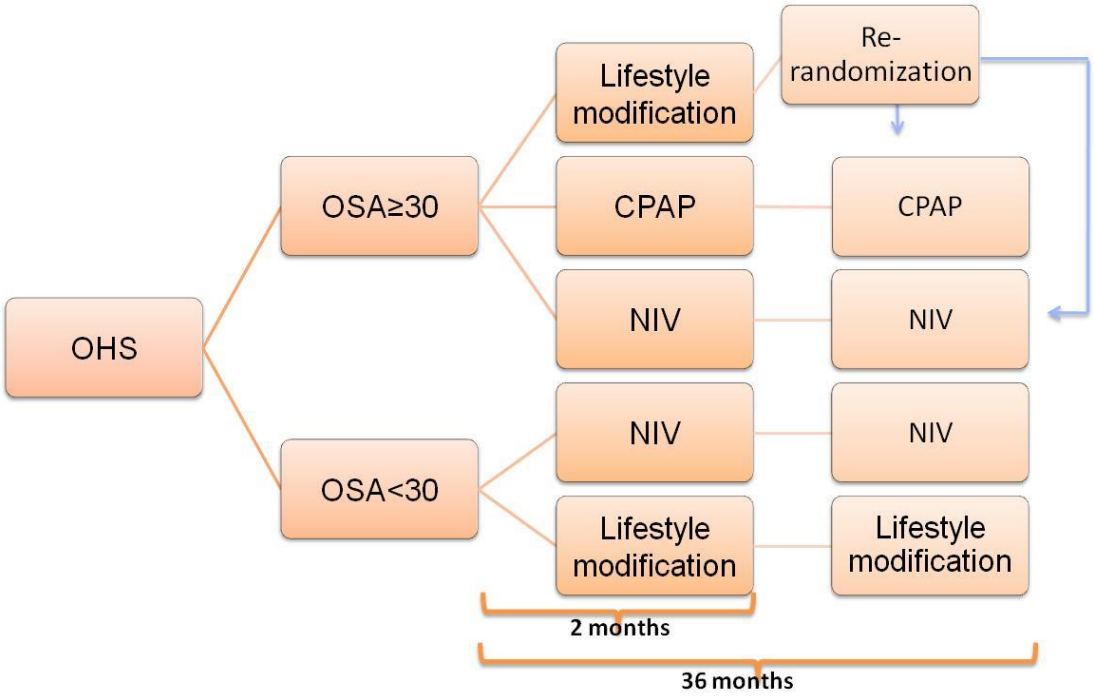
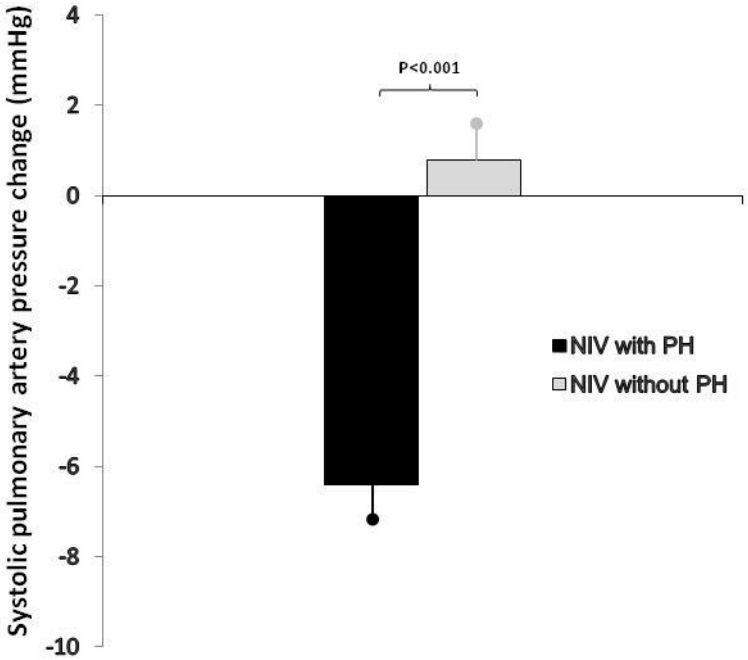
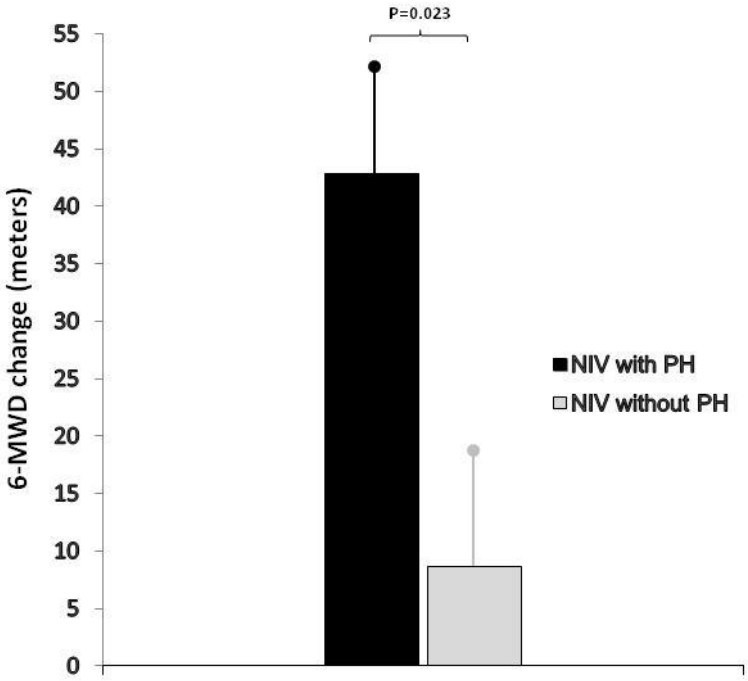

OHS
OSA≥30
OSA<30
Lifestyle modification
CPAP
NIV
NIV
Lifestyle modification
Re-randomization
CPAP
NIV
NIV
Lifestyle modification
2 months
36 months

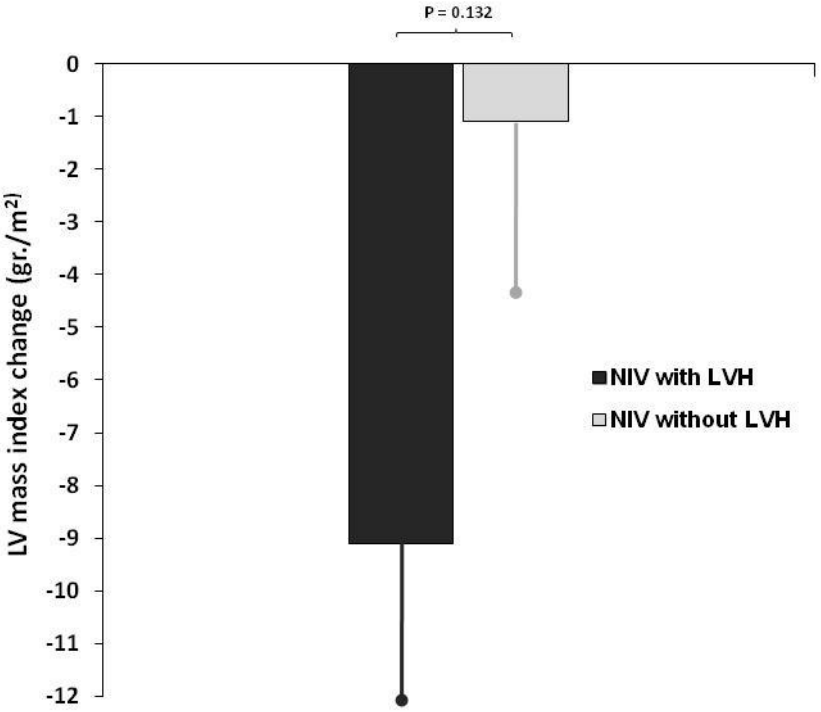
Figure s2

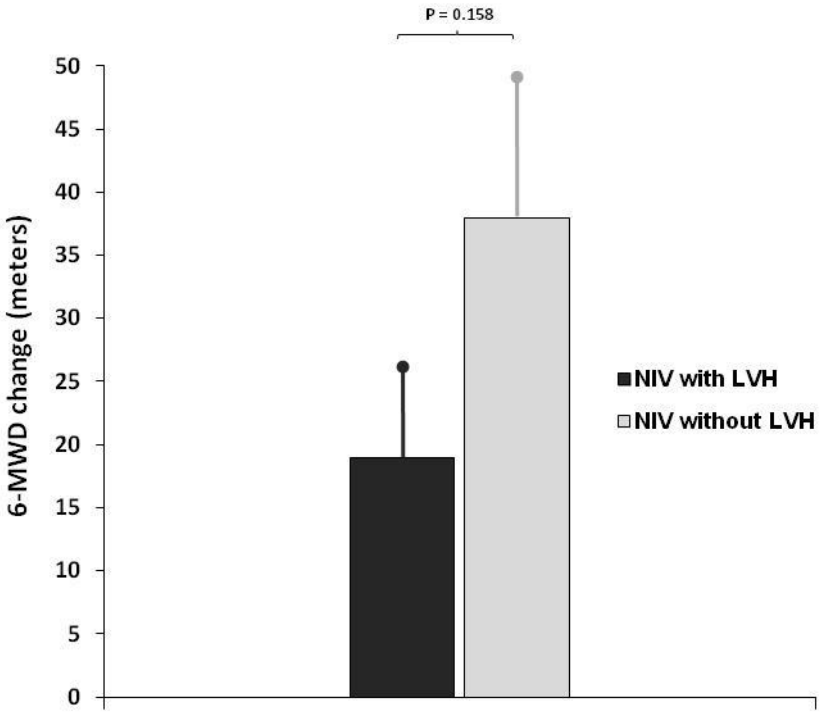
Panel A





Panel B


P = 0.132
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-11
-12
LV mass index change (gr./m²)
NIV with LVH
NIV without LVH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35
30
25
20
15
10
5
0
6-MWD change (meters)
NIV with LVH
NIV without LVH