Original Article

Neural respiratory drive and cardiac function in patients with obesity hypoventilation syndrome following initiation of non-invasive ventilation

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Background: Chronic hypercapnic respiratory failure (HRF) in obesity hypoventilation syndrome (OHS) is commonly treated using non-invasive ventilation (NIV). We hypothesised that treatment of OHS would improve neural respiratory drive index (NRDI) and cardiac function.

Methods: Fourteen patients (8 females) with OHS, who were admitted for initiation of domiciliary NIV, were prospectively studied. Patients had (mean ± SD): age (53±10 years), body mass index (BMI) (50.1± 10.8 kg/m^2), and pCO_2 (7.3±0.9 kPa). NRDI was assessed by surface electromyogram of the parasternal intercostals. Cardiac function was assessed by transthoracic echocardiography (TTE). All measurements were performed at baseline, 6 weeks, and 3 months.

Results: NRDI improved on day one following NIV set-up comparing to baseline (484.2±214.8 *vs.* 316.5±106.5 AU) and this improvement was maintained at 6 weeks (369.1±173.2 AU) and at 3 months (351.2±167.1 AU) (P=0.004). No significant differences were identified in terms of cardiac function between baseline and 3 months [tricuspid annular plane systolic excursion (TAPSE) (24.6±5.8 *vs.* 23.0±4.0 mm, P=0.317); systolic pulmonary artery (PA) pressures (36.7±15.2 *vs.* 44.5±23.9 mmHg, P=0.163].

Conclusions: NIV improves NRDI in patients with OHS, while the cardiac function over a three-month period remains unchanged.

Keywords: Obesity hypoventilation syndrome (OHS); neural respiratory drive (NRD); sleep-disordered breathing; non-invasive ventilation (NIV); respiratory muscle function; pulmonary hypertension (PH)

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Introduction

The prevalence of obesity has increased continuously over recent decades reaching epidemic proportions (1). Obesity increases the load on the respiratory system and the work of breathing (2), leads to high levels of neural respiratory drive (NRD) (3), and is associated with a high prevalence of sleep-disordered breathing (4). An imbalance in the load-to-capacity ratio of the respiratory muscles (2) leads to increased levels of NRD (3); in turn, nocturnal loss of NRD may first lead to hypercapnic respiratory failure (HRF) while asleep and, subsequently, breathlessness in patients with obesity hypoventilation syndrome (OHS) while awake

(5-7).

Obesity-related respiratory failure, the OHS, is an increasingly common problem (8). Current estimates suggest that between 0.3% to 0.4% of the general population may develop OHS (9). Patients with morbid obesity are more likely to develop significant sleep-disordered breathing and OHS (10). However, it remains unclear why some obese patients develop OHS over time (11), while others remain unaffected: approximately a third of morbidly obese patients develop hypercapnia (12).

In addition to the respiratory constraints, pulmonary hypertension (PH) and cardiac impairment, particularly right ventricular (RV) dysfunction, are associated with adverse health outcomes in OHS (13-16). The prevalence of PH in obese patients is higher than in the general population, 5% of all individuals with a body mass index (BMI) greater than 30 kg/m^2 have some degree of PH, while 48% of patients with severe PH are obese (17,18). Moreover, there is a strong correlation between BMI and RV dysfunction, with congestive heart failure being two-fold more common in obese patients (19).

Non-invasive ventilation (NIV) is commonly used to treat HRF in OHS and its impact on mechanical indices of respiratory function and blood gas homeostasis has been previously described (20-24). However, the effect of NIV on NRD and RV function remains largely unexplained (22-24). The aim of this study was to assess the impact of NIV on respiratory and cardiac function in patients with HRF caused by OHS. We hypothesised that NIV improves not only respiratory but also cardiac function, and that this functional improvement would contribute to better oxygenation, quality of life and exercise capacity.

Methods

This was a prospective observational study assessing patients with OHS prior to and immediately following NIV setup, followed up at 6 weeks and 3 months; it was approved by London City & East NHS Research Ethics Committee (reference: 15/LO/1,390). OHS was defined as obesity (BMI >30 kg/m^2) with associated daytime hypercapnia (pCO_2 >6 kPa) and sleep disordered breathing. Patients were recruited at Guy's and St Thomas' NHS Foundation Trust, London (UK) from November 2015 to November 2016. Patients were enrolled within 24 hours of admission to the hospital; follow up was arranged at six weeks with an outpatient review and at three months with a planned inpatient review. Informed and written consent was obtained from all patients. The study was registered on ClinicalTrials.gov (CARE-NIV, NCT02699112).

Primary and secondary outcomes

Primary outcome parameters were NRD and tricuspid annular plane systolic excursion (TAPSE) score. These were used to assess the impact of NIV on the cardiorespiratory system, using markers of NRD, as measured by the electromyography of the parasternal intercostals (EMGpara). These were measured prior to, during and after NIV initiation and at 6 weeks and 3 months. In addition, transthoracic echocardiography (TTE) to assess cardiac function was performed at baseline and 3 months. Secondary outcomes were oxygenation (SpO_2), arterial blood gas analysis including pO_2, pCO_2 and pH, quality of life, and exercise capacity.

Inclusion and exclusion criteria

Inclusion criteria were a confirmed diagnosis of OHS with HRF and the need to commence on NIV (pCO_2 >6 kPa), age ≥18 and <80 years, BMI >30 kg/m^2, confirmed sleep-disordered breathing, and clinical stability without acute deterioration for ≥4 weeks.

Exclusion criteria were patients already established on NIV, patients with an overlap syndrome (OHS and COPD), inability to tolerate NIV, a low compliance with NIV during the hospital stay (usage <4 hours/day), any contraindication to NIV, acute respiratory deterioration, other acute pathology or critical illness, and psychological or social factors that would impair compliance with the protocol (*Figure 1*).

Measurement of NRD

The EMGpara was recorded whilst the patient was awake, at rest and in semi-recumbent position in bed, as previously described (25). EMG electrodes were applied 3cm from the midline in the 2nd intercostal space; a reference electrode was placed on the right clavicle. The skin was prepared using NuPrep abrasive skin preparation gel (D.O.Weaver, Aurora, CO/USA) and alcohol solution. The signal was amplified and processed using a high differential amplifier with band pass filters set at 10 and 2,000 Hz (1902, Cambridge Electronic Design, Cambridge, UK). Additional analogue 50 Hz notch filter and AC coupling were used. Amplified signals were passed to an analogue to

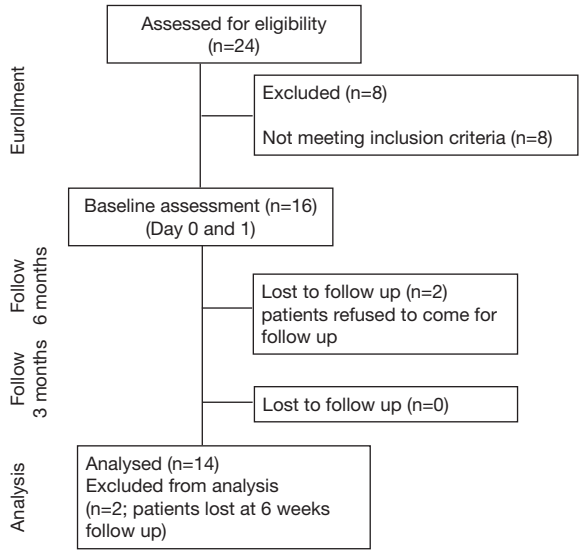

Figure 1 Consort diagram of the study.

digital convertor (Powerlab, ADInstruments, Chalgrove, UK) and passed to a personal computer. Further digital filtering occurred at 20Hz after data acquisition (LabChart v7.1, ADInstruments, Chalgrove, UK). At baseline, EMGpara was recorded during maximal inspiratory and expiratory manoeuvres: sniff, maximal inspiratory pressure (PImax), maximal expiratory pressure (PEmax), and inspiratory capacity. The average EMGpara of two minutes tidal breathing was calculated (mean EMGpara) with a time constant of 100 ms. EMGpara%max was calculated as the mean of EMGpara divided by the maximum EMGpara ×100%; neural respiratory drive index (NRDI) was obtained from EMGpara%max × respiratory rate.

TTE

All TTEs were performed by the same trained technician of the cardiology department of Guy's and St Thomas' NHS Foundation Trust while patients were awake, at rest and supine in bed. The assessment followed the American Society of Echocardiography guidelines (26) using an IE-33 device and an ×5–1 probe (Phillips, Amsterdam/Netherlands). The following cardiac chamber dimensions and pressures were recorded: RV systolic pressure (RVSP), RV diameters [RV basal (RVD1), mid-cavity (RVD2) and longitudinal dimension (RVD3) and RV outflow tract (RVOT)], right atrium major and minor dimension, right atrial pressure (RAP) and inferior vena cava (IVC) diameter. Pulmonary artery (PA) diameter was measured between the valve and the bifurcation point, while the PA pressures [mean, PAP_M and systolic, pulmonary artery pressure (PAP_S)] were derived by measuring the PA acceleration time and tricuspid regurgitation. RV systolic function was assessed by recording the TAPSE score. Left ventricular (LV) systolic and diastolic functions were defined by the ejection fraction (Simpson's rule) and E/E' ratio (between early mitral inflow velocity and mitral annular early diastolic velocity), respectively.

Study protocol

Baseline measurements were taken on the day prior to (day 0) and following NIV set up (day 1), at follow up assessment at six weeks (outpatient; W6) and at three months (inpatient; M3). Demographics and anthropometric parameters were recorded including age, gender, height, weight, BMI, hip, waist and neck circumference, office blood pressure (average of three measurements), oxygen saturation, temperature, respiratory rate and heart rate. The patients filled in the Medical Research Council (MRC) dyspnoea scale (27), the COPD assessment test (CAT) (28), the St George's Respiratory Questionnaire (SGRQ) (29) and the Severe Respiratory Insufficiency Questionnaire (SRI) (30). Electrocardiogram (ECG) and chest X-ray were performed routinely and were reviewed to exclude ischaemic heart disease, arrhythmias, cardiomegaly, signs of acute heart failure and respiratory co-morbidities like fibrosis or emphysema. All subjects underwent standard spirometry (31). Blood tests included the full blood count, the renal profile, thyroid stimulating hormone (TSH), N-terminal pro-brain natriuretic peptide (NT-proBNP), glucose and a radial artery blood gas (ABG) analysis. At baseline, a nocturnal transcutaneous oximetry and capnography (TCM TOSCA, Radiometer Medical ApS, Bronshoj/Denmark) and a walking test (4-metre gait speed) were performed (32). EMGpara and TTE were measured prior to NIV setup.

NIV setup followed established guidelines of the Lane Fox Unit for NIV in OHS, as described elsewhere (33). The aim was to control snoring, avoid chest wall paradox with oxygen desaturations, to maintain oxygen saturation (SpO_2) >88% and transcutaneous CO_2 <7.0 kPa, while using nocturnal NIV. Oxygen supplementation was applied, if indicated, to maintain SpO_2 >88%. NIV modes used were spontaneous/timed (S/T) and volume-assured pressure assistance (AVAPS-AE). A full face mask was used as standard interface. Following the first night of NIV usage

Table 1 Demographics, spirometry, respiratory muscle strength, and exercise capacity at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
Height (m)	1.64 (1.60–1.66)	–	1.64 (1.60–1.66)	1.000
BMI (kg/m^2)	50.1±10.8	50.8±10.0	50.0±10.2	0.382
FEV_1 (% predicted)	43±13	42±12	43±19	0.738
FVC (% predicted)	40±13	42±15	41±16	0.892
FEV_1/FVC (%)	85±8	82±12	82±13	0.745
SNIP (cmH_2O)	−44.9±18.6	−59.9±14.3	−45.1±31.4	0.239
PI, max (cmH_2O)	−38.6±20.2	−47.7±13.2	−48.9±15.7	0.089
PE, max (cmH_2O)	92.5±55	81.5±50.3	83.8±49.8	0.773
4-metre gait speed (sec)	5.02±2.10	–	4.24±1.85	0.258

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months. BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; SNIP, maximal sniff nasal inspiratory pressure; PI, max, maximum inspiratory mouth pressure; PE, max, maximum expiratory mouth pressure; SD, standard deviation; IQR, interquartile range.

(within 4 hours) the ABG was repeated, and EMGpara (EMGpara%max) and NRDI were measured and compared to baseline. At six weeks' outpatient follow-up, NIV settings and usage were recorded, the patient was clinically re-assessed and NRDI measurements performed. Adherence to NIV (hours/day) and percentage of nights used were retrieved from NIV built-in software at 6 weeks and 3 months follow-up. Anthropometrics, questionnaires, ABG, spirometry and NRDI measurements were repeated. At three months inpatient follow-up, all baseline measurements and an overnight assessment were repeated, including NRDI measurements and TTE.

Sample size calculation

The sample size was calculated with an alpha of 5% and a statistical power of 90%. A standard deviation was available from previous studies using the TAPSE score (standard deviation of 3.5 and a minimum clinical significant difference of 6 mm) (26). With these parameters, a total number of 14 patients were required for this observational pre-/post-comparison study design.

Statistics

Normal distribution of the data was checked with the Shapiro-Wilk test. Data were expressed as mean (± standard deviation) for normally distributed variables, while median (interquartile range with 25th–75th percentile) were used for non-normally distributed data. Comparisons were made using paired *t*-test, Wilcoxon signed rank test, one way and two way repeated measures ANOVA, and McNemar's test. Holm-Sidak and Dunn's post hoc correction methods were used where appropriate. A P value <0.05 was considered significant. Statistical analysis was performed using SigmaPlot V13.0 statistical software (Systat Software Inc., CA, USA).

Results

Sixteen patients were recruited at baseline with two drop-outs (*Figure 1*). The anthropometric, demographic, and respiratory function data (spirometry, respiratory muscle strength, and exercise capacity) of the 14 patients (8 females, age 53.3±9.9 years) who completed the study did not change during the observation period (*Tables 1* and *S1*).

Arterial blood gas analysis

The arterial blood gas analysis confirmed chronic compensated HRF at baseline with an improvement in the pCO_2 and bicarbonates at 3 months (*Table 2*).

Venous blood tests

The patients were not anaemic, had no significant infection

Table 2 Arterial blood gas analysis at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
SpO_2 (%)	92.9±4.6	93.8±4.1	94.0±2.0	0.560
pO_2 (kPa)	8.1±0.8	8.8±0.9	8.7±1.1	0.064
pCO_2 (kPa)	7.3±0.9*	6.8±0.9	6.7±0.8*	0.045
pH	7.39±0.02	7.38±0.04	7.38±0.04	0.351
HCO_3 (mmol/L)	31.7±2.9*	29.6±2.8	29.2±2.7*	0.036

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months; *, significantly different. SpO_2, oxygen saturation; pO_2, partial pressure of oxygen; pCO_2, partial pressure of carbon dioxide; HCO_3, bicarbonates; SD, standard deviation; IQR, interquartile range.

Table 3 Nocturnal transcutaneous capnography data at baseline and during follow up

Parameters	Day 0	Day 1	3 months	P value
Mean SpO_2 (%)	87±8*	91±4	94±4*	0.024
4%ODI ($hour^{-1}$)	69.1±51.8*,#	38.6±28.9*	21.2±19.7#	0.002
Mean tCO_2 (kPa)	7.4 (7.1–7.9)	7.2 (6.8–7.9)	6.7 (5.9–7.6)	0.174
Max tCO_2 (kPa)	8.7 (8.0–9.6)*	9.1 (7.4–9.6)	7.3 (7.1–8.4)*	0.023

Values are presented as mean ± SD or median (IQR) unless otherwise stated. Day 0, day pre non-invasive titration; day 1, day post non-invasive titration; 3 months: follow up in 3 months; *,#, significantly different. SpO_2, oxygen saturation; 4%ODI, 4% oxygen desaturation index; tCO_2, transcutaneous carbon dioxide levels; SD, standard deviation; IQR, interquartile range.

or renal problems; one patient had an abnormal elevated serum creatinine level. The NTpro BNP levels were increased in 6 patients. Although the TSH changed slightly, it remained within the normal range during the study period (*Table S2*).

NIV and nocturnal transcutaneous capnography

At baseline, 12 patients received NIV with an S/T mode, while two patients were set up on AVAPS-AE; the pressure settings were not significantly altered over the three months follow up period. Three patients required supplemental oxygen (1 L/min by day and 2 L/min by night) at initial discharge, but were weaned off oxygen over the follow up period. At six weeks and three months follow up, only 6 patients used NIV longer than 4 hours/day (compliant patients). There were no differences in adherence at 6 weeks and 3 months. Two patients did not use NIV at all at three months, and one patient utilised NIV less than 1 hour daily, while 4 patients used the NIV 3–4 hours daily. One patient was non-compliant at six weeks and became more compliant during further follow up.

Night-time ventilation improved respiratory control over time with higher average oxygenation, whilst oxygen desaturations were diminished. Transcutaneous CO_2 monitoring indicated that the maximal tCO_2 was lower at three months than the mean tCO_2 at baseline (*Table 3*). Efficacy of the ventilation was also confirmed by the improved daytime ABG results (*Table 2*) and the weaning of supplemental oxygen in all patients.

Dyspnoea and quality of life

The MRC dyspnoea and SGRQ scores did not change over time, but the SRI indicated an improvement in "attendant symptoms and sleep" at 6 weeks and 3 months (*Table S3*).

Parasternal intercostal electromyography

NRDI improved significantly over time (*Table 4*). NIV successfully offloaded the work of breathing, when comparing the electromyographic activity of the inspiratory muscles on NIV *vs.* off NIV. EMG raw (D1 P=0.002, W6 P=0.016, M3 P=0.004), EMG %max (D1 P=0.001, W6

Table 4 Respiratory muscle activity on and off NIV at baseline and during the follow up period

Parameters	Day 0	Day 1	6 weeks	3 months	P value
EMGpara (μV) off NIV	5.5±1.3	5.0±1.1	5.5±1.6	5.1±1.8	0.699
EMGpara (μV) on NIV	–	2.7±0.7	3.8±1.1	3.4±0.9	0.324
EMGpara (%max) off NIV	21.7±8.5	16.2±4.6	18.7±7.9	17.5±7.5	0.080
EMGpara (%max) on NIV	–	8.94±4.1	12.9±5.7	12.0±5.9	0.481
NRDI (a.u.) off NIV	484.2±214.8$^{*,\#,\%}$	316.5±106.2*	369.1±173.2$^{\#}$	351.2±167.1$^{\%}$	0.004
NRDI (a.u.) on NIV	–	166.8±99.4	219.6±105.3	221.2± 116.4	0.626

Values are presented as mean ± SD or median (IQR) unless otherwise stated. Day 0, Day pre non-invasive titration; Day 1, Day post non-invasive titration; 3 months: follow up in 3 months; $^{*,\#,\%}$, significantly different. EMGpara, parasternal intercoastal electromyography; NRDI, neural respiratory drive index; NIV, non-invasive ventilation; SD, standard deviation; IQR, interquartile range.

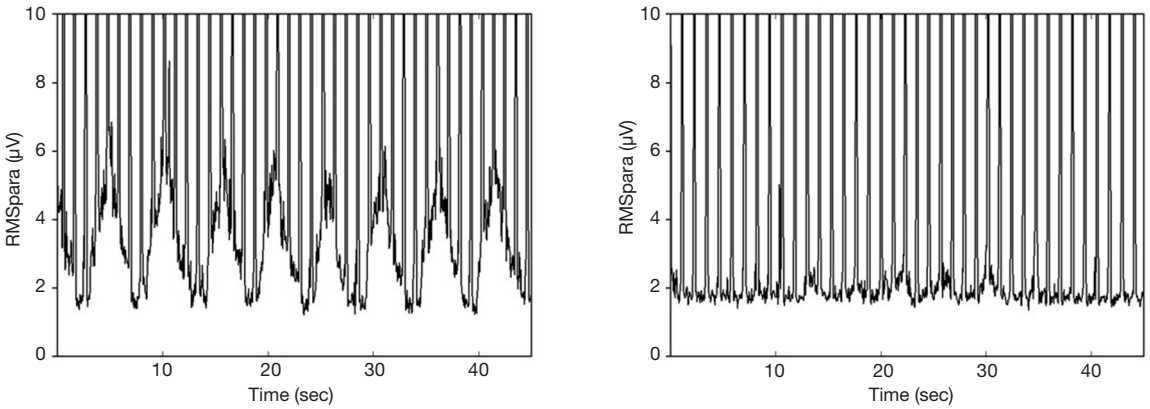

Figure 2 Root mean square (RMS) of the parasternal electromyography (EMG) during self-ventilation (Left) and when on NIV (Right). The QRS complex artefacts of the ECG (truncated) are clearly visible superimposed on the activity of the EMG trace. sec, seconds; ECG, electrocardiogram.

P=0.011, M3 P=0.002), and EMG NRDI (D1 P=0.014, W6 P=0.021, M3 P=0.014) significantly improved at all follow up assessments (*Figure 2*).

TTE

The systolic pulmonary artery pressure (PAP_S) could only be assessed in 7 patients, 3 of which had a PAP_S >40 mmHg. Five patients had dilated RV dimensions at baseline and at 3 months, while five had E/E' Ratio impairment (correlated with LV diastolic dysfunction) at baseline and two at 3 months follow up; all three patients that required oxygen at baseline had LV diastolic dysfunction. LV systolic function was normal in all patients, whereas LV diastolic function was impaired in 3 patients at baseline and in 2 patients at follow up. One patient had RV impairment (*Table 5*).

Discussion

NIV in patients with OHS improves the NRD, sleep-disordered breathing and arterial blood gases over a three-month period by offloading the work of breathing. Furthermore, it positively impacts symptoms and sleep quality. However, cardiac function, spirometry, respiratory muscle strength, and exercise capacity do not change significantly.

NIV in OHS reduces the NRD. The NRD was reduced while patients were on NIV comparing to self-ventilating. Furthermore, our data suggests that the initiation of nocturnal use of NIV reduces the NRD while self-ventilating, and this effect remains unchanged during a 3 months period. A possible explanation for this is that NIV offloads the respiratory muscles and as a result reduces the work of breathing. The effect of NIV on respiratory neural

Table 5 Transthoracic echocardiography results at baseline and follow up

Parameters	Baseline	3 months	P value
RVSP (mmHg)	32.0 (24.0–48.0)	36.0 (26.5–65.8)	0.313
RVD1 (mm)	41.0 (35.5–49.8)	41.0 (38.0–44.5)	0.839
RVD2 (mm)	36.6±11.4	37.6±8.8	0.806
RVD3 (mm)	74.9±11.8	74.1±12.5	0.958
RVOT (mm)	32.0 (24.5–35.0)	35.5 (27.0–41.8)	0.413
RAP (mmHg)	6.8±4.4	5.9±3.9	0.379
RA major diameter (mm)	42.0±8.7	37.0±9.4	0.298
RA minor diameter (mm)	40.1±8.6	38.5±9.0	0.796
IVC diameter (mm)	20.3±4.2	19.4±6.4	0.913
PA diameter (mm)	25.1±3.6	23.4±5.5	0.342
PAP_s (mmHg)	36.7±15.2	44.5±23.9	0.163
PVAT (ms)	88.5±18.2	73.7±44.5	0.372
E/E' ratio	6.0±4.2	5.4±2.2	0.819
Tricuspidal regurgitation (cm/m^2)	2.65±0.62	2.97±0.73	0.110
TAPSE score (mm)	24.6±5.8	23.0±4.0	0.317
LVEF (%)	59.0±7.2	58.8±7.4	0.880

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 3 months, follow up in 3 months. RVSP, right ventricular systolic pressures; RVD, right ventricular diameter; RVOT, right ventricular outflow diameter; RAP, right atrium systolic pressures; RA, right atrial; IVC, inferior vena cava; PA, pulmonary artery; PAPs, systolic pulmonary pressure; PVAT, pulmonary velocity acceleration time; E/E', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; TAPSE, tricuspid annular plane systolic excursion; LVEF, left ventricular ejection fraction; SD, standard deviation; IQR, interquartile range.

drive has been previously demonstrated in neuromuscular disease and COPD (34). To the best of our knowledge, this is the first study showing the positive effect of NIV on NRD in OHS, acutely and in the long term.

In this context, cardiac function remained unchanged. Our data show that any potential effect of NIV on the cardiovascular may be less profound than on the respiratory system. In contrast with these findings, Castro-Añón *et al*. screened OHS patients established on positive airway pressure therapy for PH and followed them for 6 months, using TTE (35). They demonstrated a significant decrease in pulmonary arterial pressure at 6 months. Moreover, Kauppert *et al*. demonstrated in 21 OHS patients established on NIV using right heart catheterization and echocardiography that pulmonary pressures decreased with better NIV compliance (36). Held *et al*., retrospectively identified 18 patients with hypoventilation and PH who were treated with PAP therapy (37). They assessed PA pressure and cardiac function using right heart catheterization and echocardiography, and found significant improvements in mean and systolic PA pressures, pulmonary vascular resistance, right ventricular systolic function and improvements in walking distance at 3 months follow up. Possible explanations for the discrepancy with the aforementioned studies are the use of right heart catheterization, different compliance and follow up periods.

The data of this study support the hypothesis that the positive treatment effect of NIV on the respiratory system does not significantly impact on the pathophysiology of the cardiovascular system in the short term. This is limited by the relatively short follow up, limited sample size, lack of invasive PA pressure measurement and observation of patients who had relatively preserved RV function. Larger cohort studies of patients with OHS will be necessary to define improved clinical outcomes on NIV, particularly in patients who have significant right heart strain due to

PH. Moreover, as there are sparse data regarding long-term NIV treatment (38-39) in OHS, extended observation periods are needed. Furthermore, invasive measurements of pulmonary pressures and cardiac function might better elucidate the role of right ventricular function and PH in the pathophysiology of OHS in order to identify relevant future treatment targets and outcomes. This could include specific targeting of patients who have an insufficient response to NIV therapy beyond the initial treatment period, as right heart failure significantly impacts on long-term outcomes and can, potentially, be modified using drug specific treatment for PH.

Conclusions

NIV controls HRF and improves NRD in OHS in the domiciliary setting. Any potential impact on the cardiovascular system might be less responsive to NIV than the respiratory system.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: It was approved by London City & East NHS Research Ethics Committee (reference: 15/LO/1,390). Informed and written consent was obtained from all patients.

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Supplementary

Table S1 Anthropometrics, demographics, and cardiorespiratory measurements at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
Weight (kg)	134.1±34.3	136.1±33.9	134.2±34.5	0.388
Neck circumference (cm)	44.5±5.0	44.7±5.2	44.8±4.8	0.851
Waist circumference (cm)	130.6±14.9	130.9±17.6	133.4±16.5	0.346
Hip circumference (cm)	146.8±17.1	141.1±16.1	145.5±16.5	0.055
Waist/hip ratio	0.82±0.06	0.81±0.05	0.81±0.06	0.740
SpO_2 (%)	92.9±4.6	93.8±4.1	94.0±2.0	0.560
Heart rate (min^{-1})	80.0±11.3	74.7±16.2	74.8±13.3	0.309
Respiratory rate (min^{-1})	19.9±2.7	19.9±4.1	20±4.5	0.996
Systolic BP (mmHg)	128.4±17.7	129.7±19.6	131.6±22.7	0.804
Diastolic BP (mmHg)	77.7±14.2	77.5±14.6	77.1±12.1	0.987

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months. BMI, body mass index; SpO_2, oxygen saturation; BP, blood pressure; SD, standard deviation; IQR, interquartile range.

Table S2 Blood test results at baseline and follow up

Parameters	Baseline	3 months	P value
Hb (g/dL)	13.6±1.9	13.3±1.5	0.368
Hct (%)	45.9±9.0	44.0±6.8	0.357
White blood cells ($x10^3/mm^3$)	7.9±2.0	8.7±2.8	0.147
Platelets ($x10^3/mm^3$)	223.3±70.0	191.9±89.6	0.327
Urea (mg/dL)	6.0±1.9	5.7±1.9	0.780
Creatinine (µmol/L)	80.3±20.7	78.3±19.0	0.337
Clearance creatinine (mL/min)	79.5±22.1	79.4±17.7	0.875
TSH (mUI/L)	2.16±1.14	2.11±1.07	0.033
NT-proBNP (pg/mL)	70.5 (35.0–178.0)	107.0 (23.0–352.0)	0.067
Glucose (mmol/L)	6.98±2.14	6.53±2.22	0.871

Values are presented as mean ± SD or Median (IQR) unless otherwise stated. 3 months, follow up at 3 months. Hb, haemoglobin; Hct, haematocrit; TSH, thyroid stimulating hormone; NT-proBNP, n-terminal pro-brain natriuretic peptide; SD, standard deviation; IQR, interquartile range.

Table S3 Dyspnoea and quality of life scores at baseline and follow up

Parameters	Baseline	6 weeks	3 months	P value
MRC (points)	3.8±1.3	3.4±1.15	3.5±1.0	0.345
CAT (points)	23.5±7.5	20.8±10.0	20.5±10.1	0.287
SGRQ summary (points)	63.8±19.7	49.9±27.1	54.0±22.6	0.093
Symptoms (points)	61.3±31.1	54.3±32.8	51.7±27.5	0.443
Activity (points)	89.0 (69.4–92.7)	80.3 (50.4–92.2)	92.5 (54.7–92.5)	0.091
Impact (points)	57.6 (27.5–69.2)	40.0 (24.9–60.2)	49.3 (18.2–66.0)	0.173
SRI, summary (points)	39.1(26.5–65.4)	54.0 (32.8–74.7)	43.5 (31.5–70.5)	0.092
Respiratory complaints (points)	44.6±24.2	60.9±26.6	50.2±24.1	0.060
Physical functioning (points)	36.3±24.3	45.5±22.9	40.7±30.5	0.115
Symptoms and sleep (points)	35.3±15.5$^{*,\#}$	53.8±24.3*	50.0±16.5$^{\#}$	0.011
Social relation (points)	61.3±23.3	65.2±18.2	67.0±18.0	0.410
Anxiety (points)	36.1±31.3	46.1±36.0	33.9±30.9	0.488
Psychological well-being (points)	45.8 (32.6–68.7)	47.2 (35.4–78.5)	52.8 (34.7–72.2)	0.926
Social functioning (points)	46.9 (27.3–79.7)	73.9 (31.2–88.3)	59.4 (28.1–82.8)	0.487

Values are presented as mean ± SD or median (IQR) unless otherwise stated. 6 weeks, follow up at 6 weeks; 3 months, follow up in 3 months; $^{*,\#}$, significantly different. MRC, medical research council dyspnoea scale; CAT, Chronic Obstructive Pulmonary Disease assessment test; SGRQ, Saint George's respiratory questionnaire; SRI, severe respiratory index questionnaire SD, standard deviation; IQR, interquartile range.