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Functional Impact of Pulmonary Hypertension due to Hypoventilation and Changes under NIPPV

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Daytime pulmonary hypertension due to alveolar hypoventilation is asscociated with functional impairment and improved by NIPPV.

Abstract

We aimed to characterize the association of pulmonary hypertension due to hypoventilation and exercise capacity, and the haemodynamic and functional changes under non-invasive ventilation.

A retrospective analysis was done to assess haemodynamics and functional capacity in 18 patients with daytime pulmonary hypertension due to hypoventilation at baseline and after three months of non-invasive ventilation.

Patients presented with a mean pulmonary artery pressure of 49 ± 13 mmHg, preserved cardiac index (3.2 ± 0.66 l/min/m^2), six-minute walking distance of 303 ± 134 m, and severely elevated NT-proBNP levels. Mean pulmonary artery pressure correlated negatively with maximum work rate (R = −0.72, p = 0.03) and six-minute walking distance (R = −0.62, p = 0.01). Following non-invasive ventilation we found a significant reduction of mean pulmonary artery pressure (−18 mmHg, p= < 0.001), NT-proBNP levels (−2110 pg/ml, p = 0.001), improvement in the six-minute walking distance (+66 m, p = 0.008), and maximum work rate (+18 W, p = 0.028). Changes in work rate correlated inversely to pulmonary artery pressure. (R = −0.75, p = 0.031).

In this specific cohort with hypoventilation and severe PH, pulmonary hypertension was associated with reduced exercise capacity. Following non-invasive ventilation, haemodynamics and exercise capacity improved significantly.

Keywords: Pulmonary artery pressure, pulmonary circulation, pulmonary hypertension, obesity hypoventilation syndrome, non-invasive ventilation, non-invasive mechanical ventilation.

Introduction

Severe obesity hypoventilation syndrome (OHS) is gaining interest because of its increasing incidence and associated high morbidity and mortality [1]. The rising number of patients with severe pulmonary hypertension (PH) due to alveolar hypoventilation is of particular concern. In obstructive sleep apnoea (OSA) and overlap syndrome, PH is rare and pulmonary artery pressure (PAP) is only mildly elevated. In contrast, in alveolar hypoventilation PH is more frequently observed and of higher severity [2-6]. The pathogenesis of PH in patients with alveolar hypoventilation is still unclear. Hypoxia may lead to an increase in PAP, but significant interspecies and in humans inter-individual differences of acute pulmonary vasoconstriction were reported [3, 7-9]. Although carbon dioxide (CO_2) and acidosis influence pulmonary vasoconstriction, not all patients with hypoventilation and hypercapnia develop PH [10, 11]. A high prevalence of pulmonary artery and pulmonary venous hypertension was reported in obese patients in an autopsy study [12]. The positive correlation of body weight and pulmonary artery pressure in OSA underscores the possible influence of obesity on pulmonary haemodynamics [3]. However, PH does not occur in all obese patients [6]. The extent of functional impact of PH in patients with hypoventilation is still unknown.

Current guidelines recommend to treat the underlying disease for PH occurring due to lung diseases and ventilatory disorders [13, 14]. Oxygen administration alone stabilized, but did not reduce PAP in patients with chronic obstructive pulmonary disease (COPD) [15], and failed to improve haemodynamics in patients with chest wall diseases and OHS [16]. Following surgically induced weight loss, a long-term decline in PAP has been shown [6, 17]. Despite improving blood gases in patients with OSA and hypercapnia [18], application of continuous positive airway pressure (CPAP) had no effect on pulmonary haemodynamics in

patients with OSA [19]. Non-invasive positive–pressure ventilation (NIPPV) in patients with OHS improved blood gases [20-23], vital capacity, expiratory reserve volume [21, 23], daytime sleepiness, and dyspnoea [24, 25]. Moreover, long-term NIPPV has been found to increase serum leptin levels [26]. Patients with OSA and hypercapnia exhibited an increased chemo-responsiveness to CO_2 and hypoxaemia under CPAP [23, 26, 27]. NIPPV was shown to have a positive effect on haemodynamics of patients with alveolar hypoventilation due to thoracic restriction [28]. However, the effect of NIPPV on PH and exercise capacity of obese patients with alveolar hypoventilation, has not been studied.

Objective

The objective of this research was to study a cohort of patients with daytime PH and alveolar hypoventilation concerning haemodynamics as well as to define the impact of PH on functional capacity. Furthermore, we aimed to analyze the effect of NIPPV on haemodynamics and functional capacity.

Methods

Study subjects were recruited from all consecutive 160 patients who presented to the Medical Mission Hospital between October 2009 to July 2011 for further evaluation and treatment of PH. 18 patients met the criteria of daytime PH and alveolar hypoventilation and were retrospectively analyzed (Fig 1). Patients with confirmed PH (mean PAP (mPAP) at rest >/= 25 mm Hg or mPAP at rest < 25 mmHg and mPAP at exercise >/=50 mm Hg or, if right heart catheterization could not be performed, an echocardiographic SPAP >/=50 mm Hg at rest and daytime CO_2 of at least 45 mmHg or a mean nighttime CO_2 of at least 55 mmHg were included. Exclusion criteria were chronic thromboembolic pulmonary hypertension (CTEPH) or pulmonary arterial hypertension (PAH) associated diseases as cardiac shunt,

collagen vascular disease, porto-pulmonary hypertension, HIV-associated PAH and drug and toxin induced PAH. Written informed consent was obtained from all patients prior to analysis. The study was approved by the local Ethics Committee.

Diagnosis was established according to current guidelines [13]. Echocardiography (Vivid7®, GE Medical Systems, Solingen, Germany) was performed to measure systolic right ventricular pressure, right and left ventricular function, as well as to rule out a cardiac shunt and significant valvular pathology. Electrocardiography (ECG 550020728®, GE Medical Systems, Germany) was also performed. Moreover, bodyplethysmography (Masterscreen Body/Diff® CareFusion, Germany) was performed according to the European Respiratory Society Statement [29]. Inspiratory mouth pressures were measured as described [30]. Computed tomography (Activion 16®, Toshiba Medical Systems, Neuss, Germany) was conducted to rule out structural lung disease. A ventilation-perfusion scan (Technegas-Generator®, Tetley Medical Limited, Australia; E Cam Variable®, Siemens Medical Solutions Inc., Hoffman Estates, Illinois, USA) was performed to rule out pulmonary embolism. Blood gases were measured at rest and under exercise (ABL 800 Basic®, Radiometer, Cadolzburg, Germany). Functional capacity was characterized by a six-minute walking test according to the American Thoracic Society Statement (ATS) [31]. In capable patients, a bicycle cardiopulmonary exercise test (Masterscreen CPX®, CareFusion, Hoechberg, Germany; E-bike basic PC plus, GE Medical Systems, Solingen, Germany) was performed according to the ATS and the American College of Chest Physicians (ACCP) Statement [32]. Daytime right heart catheterization was performed according to the guidelines using a Swan Ganz-catheter (Smith Medical, Grasbrunn, Germany) [15]. Measurements were conducted with the monitor system (IntelliVue MP70 (M8007A)®, Philips Medizinsysteme, Böblingen, Germany). A nighttime cardio-respiratory polygraphy, including measurement of nocturnal oxygen

saturation, and CO_2 tension (Somnocheck®, Weinmann, Hamburg, Germany; TOSCA®, Willich, Germany) was performed according to the ACCP-Guidelines [33]. Serum levels of NT-proBNP were measured by ECLIA (Elecys 2010, Roche Diagnostik, Germany).

All 18 patients with confirmed PH and alveolar hypoventilation were treated by non-invasive bi-level positive-pressure ventilation according to the guideline of the German Respiratory Society [34] (using Harmony II®, Respironics, Herrsching, Germany or Stellar 150®, RES MED, Martinsried, Germany). All patients were assessed by a routine follow-up three months after initiation of the ventilation therapy. The same diagnostic tests used at baseline were done during the follow-up.

Only the patients with data available at both baseline and three month follow-up period were considered for analyzing mean changes in each parameter. Statistical analyses were performed using Statistica® (Version 10, StatSoft, Inc., Tulsa, OK, USA). The mean and standard deviation were calculated. Correlations of the parameters were evaluated by Spearman test. Statistical significance was expressed as *p*-values with the Wilcoxon test and assumed if *p*-value was <0.05.

Results

Baseline characteristics

Patients were selected as shown in Figure 1. Table 1 and online supplementary tables 2-3 show the characteristics of the 18 patients (11 females, 7 males). Mean age was 62 ± 10 years; mean body-mass-index (BMI) was 36.1 ± 9.8 kg/m^2, and mean body weight was 104 ± 30 kg. Twelve patients fulfilled the criteria of an OHS. Three of twelve patients had concomitant COPD. In five patients COPD was the sole cause for hypoventilation.

Patients had a reduced vital capacity (VC) (51 ± 19 % pred.), forced expiratory volume at one second (FEV_1) (43 ± 18 % pred.), elevated residual volume (RV) (167 ± 77 % pred.) and a mean total lung capacity (TLC) of 94 ± 33 % pred. The cohort showed daytime hypercapnia and hypoxaemia, which was aggravated at nighttime.

Apnoea-hypopnoea-index (AHI) was elevated in two patients (30/h and 60/h). The mean AHI of the other patients was 3/h +/- 2. The maximum inspiratory mouth pressure was severely reduced to 3.3 ± 1.9 kPa, and the respiratory load was 0.5 ± 0.2 kPa.

Echocardiography showed signs of right ventricular dysfunction, but normal left ventricular systolic function. E/E' was 10 ± 4. Left atrial (LA) LA volume was slightly elevated. We calculated the RA/LA volume-ratio and found a value of 1.8± 0.6 (Online supplementary table 2).

Right heart catheterization revealed severely elevated mPAP (49 ± 13 mmHg). In 14 patients pulmonary artery wedge pressure (PAWP) was lower than 15 mm Hg, in three patients it was higher than 15 mm Hg. However, all patients showed a diastolic pulmonary pressure

gradient higher than 9 mm Hg (23 ± 10 mmHg) and a transpulmonary vascular gradient (TPG) higher than 12 mm Hg (38 mmHg ± 12 mm Hg). Cardiac index (CI) was normal. Heart rate at rest was 75 ± 10 (1/min) and systemic blood pressure was 128/75 ± 18/10 mm Hg.

The mPAP correlated positively with BMI and maximum nighttime CO_2. The pulmonary vascular resistance (PVR) correlated negatively with the maximum inspiratory mouth pressure (Fig2). There was a positive correlation of mPAP with P(A-a)O_2 (R 0.67, p =0.049*)* and VE/VCO_2 (R = 0.84, p < 0.01) and a negative correlation of mPAP with respiratory exchange rate (RER) at maximum exercise (R = -0.80, p = 0.01) as well as a negative correlation of PVR with PET CO_2 at anaerobic treshhold (AT)(R = -0.89, p<0.01). There was no significant correlation of PAP with nighttime oxygen saturation, daytime oxygen partial pressure at rest or exercise, left ventricular function or static and dynamic pulmonary volumes (data not shown).

Peak oxygen uptake and maximum work rate at exercise were reduced. Mean six-minute walking distance was 303 ± 134 m. At baseline, we found normal values for heart rate reserve (HRR) (33 ± 19 (1/min), breathing reserve (BR) (31 ± 26 %) and a respiratory exchange rate (RER) of 0.97± 0.12. Partial pressure of end-tidal (PET) $C0_2$ was normal at rest and increased during exercise. P(A-a) O_2 was elevated (online supplementary table 3).

Maximum work rate was inversely correlated to mPAP, PVR (Fig 3) and P(A-a)O_2 (-0.72, *p = 0.03)* and VE/VCO_2 (-0.87, p < 0.01). Six-minute walking distance was negatively correlated to mPAP (Fig 3) and positively correlated to PET CO_2 at AT (0.83, *p = 0.04*).

NT-proBNP serum levels were elevated, but not correlated to exercise capacity.

Effect of non-invasive positive-pressure ventilation

NIPPV was performed as follows: IPAP 21 ± 3 mbar, EPAP 5.5 ± 1 mbar, Ti 1.4 ± 0.2 sec, frequency 20 ± 3.5, oxygen flow 2.9 ± 1.9 (l/min). Mean duration of NIPPV was 5.4 ± 2.6 h. Table 1 shows the treatment effect of NIPPV at three-months follow-up. Systolic, diastolic and mean PAP (−18 mm Hg, $p < 0.001$) and PVR (−199 mm Hg, $p < 0.001$) was decreased compared to pre-treatment values (Figure 4); CI and PAWP were not significantly changed. There was an improvement in exercise capacity, as indicated by a significant increase in maximum work rate (+18 W) and six-minute walking distance (+66 m) (Figure 5).

There was no change in systemic blood pressure, heart rate, left ventricular ejection fraction and E/E' following NIPPV. The volume of the RA decreased from 97 ± 57 ml to 65 ± 34 ml *(p* = 0.002), whereas it increased in the LA from 57 ± 33 to 77 ± 45b ml ($p = 0.002$); the ratio of RA/LA volume decreased. There was no change in LV performance, measured by echocardiography, but RV function improved after 3 months of NIPPV. Consistent with the improved cardiac function, NT-proBNP serum levels decreased significantly (Table 1 and figure 5). The haemodynamic improvement correlated positively with the increase in maximum work rate (Fig 6). Following NIPPV, FEV_1 and VC increased, RV and ITGV decreased (not shown). O_2 saturation and CO_2 improved at night and daytime. There was no correlation between improved exercise capacity and changes in lung function (data not shown).

Discussion

To our knowledge this is the first study to demonstrate a severe negative association of PH and exercise capacity in patients with alveolar hypoventilation and preserved CI. The findings

strongly support positive treatment effects of NIPPV on haemodynamics and functional capacity in these patients.

All patients showed hypoventilation with nighttime and daytime hypercapnia and hypoxaemia. Twelve patients were obese and fulfilled the criteria of OHS [33].

The mean mPAP of our cohort was much higher than previously reported [1, 5, 28]. These patients could represent a specific phenotype of severe PH associated with hypoventilation that is different from the majority of patients with hypoventilation. In obese patients, histological findings indicating PH seemed to be more frequent than the prevalence of PH reported in clinical studies [12]. Right heart catheterization has not been done routinely in other studies dealing with PH and alveolar hypoventilation. Recently, Marik et al. [1] provided a detailed analysis of patients with OHS, but did not measure haemodynamics invasively. Since echocardiography is difficult to perform in obese patients, the non-invasive approach is prone to underestimate both prevalence and severity of PH in these patients. Moreover, the higher number of patients with severe PH in our study might be partly due to selection bias, as we studied patients who were referred with suspected PH for evaluation and treatment.

In an autopsy study, Haque et al. found histological features of pulmonary arterial and pulmonary venous hypertension in 72% of obese patients compared with only 26% and 6% of non-obese controls [12]. In our study, all but one patient underwent right heart catheterization. Although mitral flow pattern might reflect a type 1 diastolic dysfunction, LA area was normal and LA volume was only slightly elevated. Most of our patients had evidence for severe pre-capillary PH. Only three patients had PAWP above 15 mm Hg, however PA mean -to-capillary wedge-pressure and PA diastolic-to-capillary wedge-pressure gradients were severely elevated, reflecting a relevant pre-capillary component of PH [35]

Systemic blood pressure at rest was normal and, despite severely elevated mPAP, patients responded with an increase in systolic blood pressure during exercise.

In patients with pulmonary arterial hypertension (PAH) and vasculopathy, CI decreases with progressive disease [37]. In our cohort with severe PH and alveolar hypoventilation, CI was normal or slightly elevated, which we interpret as a compensation for hypoventilation, ventilatory failure and hypercapnic hypoxia.

Hypoventilation can occur in the context of a variety of disorders [5, 6, 28], but it is still unclear how hypoventilation and PH develop. In our study the majority of patients did not have a sleep-related breathing disorder. Only two patients (AHI 30/h and 60/h) presented with severe sleep apnea syndrome, indicating that OHS is not inevitably associated with sleep apnea.

Five patients had COPD alone, three more had both COPD and OHS, resulting in an overall reduction of FEV1 and VC in our cohort. Reduced lung volumes may have been affected by reduced strength of breathing. Compared to published data for healthy cohorts, the patients in our study had reduced maximum inspiratory mouth pressure as a sign of disturbed respiratory muscle strength and elevated respiratory load [30]. We assume that hypercapnia and hypoxaemia were a consequence of hypoventilation.

We found an inverse correlation of PVR and maximum inspiratory mouth pressure. Reduced strength of breathing might be a cofactor for hypoventilation which was associated with PH in our patients. Conversely, it is conceivable that in patients with severe PH, respiratory muscle function is altered leading to reduced inspiratory mouth pressure as described by Meyer et al [38] .

The positive correlation of mPAP with BMI, nighttime CO_2, but not with oxygen partial pressure, lung volumes or left ventricular function suggest that PH was driven by BMI and hypercapnic vasoconstriction.

Due to the preserved CI, it was unclear whether PH has a functional impact on patients with alveolar hypoventilation. Our study subjects had a marked impairment of functional capacity as shown by reduced six-minute walking distance, maximum work rate, and maximum oxygen uptake. Since heart rate and breathing reserve were normal, our patients were not affected by cardiac or ventilatory limitation sensu strictu. However, in patients with hypoventilation, breathing reserve has to be interpreted with caution. P(A-a)02 was elevated reflecting a limitation in gas exchange. We noticed high VE/VCO_2-Slope was associated with lower VCO_2 and RER, probably reflecting inefficient ventilation which may have contributed to earlier termination of exercise and reflect poor respiratory function. We found a negative correlation between mPAP and work rate/ walking distance (Figure 4) indicating the importantance of pulmonary haemodynamics for normal exercise capacity . However, low RER and increasing PET CO2 under exercise reveals that this specific cohort is different from patients with PAH, i.e. our observations concerning the physiology on exercise are compatible with respiratory rather than haemodynamic limitation.

Although correlation does not proof causality, the fact that NIPPV was associated with a significant decrease in mPAP which then correlated with an increase in maximum work rate, suggests that PH can have a substantial functional impact on patients with severe PH due to alveolar hypoventilation despite having normal CI.

The cardiopulmonary exercise testing was done in nine patients. This was not due to a selection bias, but it merely reflects that many of these severely ill patients are unable to perform CPET due to morbid obesity or severity of disease.

Although our study population had normal CI and normal systolic left ventricular function, the patients showed echocardiographic signs of right ventricular dysfunction and elevated serum NT-proBNP levels. NT-proBNP levels did not correlate with six-minute walking distance, maximum work rate and CI, but the levels still indicate a poor prognosis according to published literature. Patients with obesity hypoventilation have increased mortality as shown by several reports [1, 24, 39], and NT-proBNP levels seem to have a prognostic impact on PAH [40, 41]. This argues for a possible role of NT-proBNP serum levels as biomarker for patients with alveolar hypoventilation and needs to be explored in a prospective trial.

To our knowledge, this is the first report about the effect of NIPPV on haemodynamics and exercise capacity in cohort of obese patients. The high mortality rates of patients with OHS and PH underscore the need for early and effective treatment [1]. For PH secondary to structural lung disease and ventilatory disorders, current treatment guidelines recommend to focus on managing the underlying disease [13, 14]. Despite these recommendations, it is still unclear whether this will improve PH or not. In our cohort, after three months NIPPV therapy, PAP and PVR decreased significantly ($p < 0{,}001$), without affecting CI and PAWP.

Interestingly, following NIPPV the RA volume decreased while LA volume increased. Not surprisingly, this resulted in a decrease of the RA/LA volume ratio. These findings suggest that NIPPV decreased RA pressure as a consequence of improving PAP and PVR. The reduction of the RA volume then allows improved filling of LA.

Moreover, we found an improvement of six-minute walking distance and maximum work rate. Interestingly, decreased mPAP correlated with increased maximum work rate under

exercise. There was no correlation to daytime and nighttime blood gases, underscoring the relevance of pulmonary haemodynamics for exercise capacity in this patient group. Patients with poor compliance to NIPPV (using it < 50% of nights and < 4 hr/night, n=5), did not show an improvement of PAP and functional capacity, further supporting an overall benefit of NIPPV in these patients.

Our study is limited by a relatively small number of subjects and the single-center observational design. However, the robustness of the data, including the fact that PH was determined by RHC, allows to postulate that NIPPV can improve haemodynamics and functional capacity in patients with PH due to alveolar hypoventilation. Of note, the increase in six-minute walking distance in our study was higher than treatment effects reported in studies with vasoactive drugs for PAH [42-45].

Conclusion

The present study shows an association of elevated PAP and reduced exercise capacity of patients with alveolar hypoventilation and severe daytime PH despite preserved cardiac index. In these patients the use of NIPPV was associated with improved daytime haemodynamics and functional capacity. A larger prospective study should be initiated to confirm these data.

The data were presented at the ERS Annual Meeting 2012 as an oral presentation.

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References:

1.Marik PE, Desai H. Characteristics of patients with the malignant obesity hypoventilation syndrome admitted to an ICU. J Intensive Care Med 2012 may 6. (Epub ahead of print) doi:10.1177/0885066612444261.

2.Bradley TD, Rutherford R, Grossmann RF, Lue F, Zamel N, Moldofsky H,Phillipson EA. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive Sleep Apnea Syndrome. Am Rev Respir Dis 1985; 131: 835-839.

3.Hawrylkiewicz I, Sliwinski P, Gorecka D, Plywaczewski R, Zielinski J. Pulmonary haemodynamics in patients with OSAS or an overlap syndrome. Monaldi Arch Chest Dis 2004; 61: 148-152.

4.Fletcher EC, Schaaf JM, Miller J, Fletcher JG. Long-term cardiopulmonary sequelae in patients with sleep apnea and chronic lung disease. Am Rev Respir Dis 1987; 135: 525-533.

5. Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger J, Weitzenblum E. The Obesity Hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. Chest 2001; 120: 369-376.

6. Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic Dysfunction in Obesity Hypoventilation Syndrome and the effect of treatment with surgically induced weight loss. Ann Surg 1988; 207: 604-613.

7. Zielinski J. Effects of intermittent hypoxia on pulmonary haemodynamics: animal models versus studies in humans. Eur Respir J 2005; 25: 173-180.

8. Fletcher EC, Luckett RA, Miller T, Fletcher JG. Exercise hemodynamics and gas exchange in patients with chronic obstruction pulmonary disease, sleep desaturation, and a daytime Pa02 above 60 mmHg. Am Rev Respir Dis 1989; 140: 1237-1245.

9. Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Ehrhart M, Levi-Valenski P,Zielinski J, Delaunois L, Cornudella R, Moutinho dos Santos J. Sleep related 02 desaturation and daytime pulmonary hemodynamics in COPD patients with mild hypoxaemia. Eur Respir J 1997; 10: 1730-1735

10.Lloyd TC Jr. Influence of blood pH on hypoxic pulmonary vasoconstriction. J Appl Phsiol 1966; 21: 358-364.

11. Mc Guire M, Bradford A. Chronic intermittent hypercapnic hypoxia increases pulmonary arterial pressure and heamtocrit in rats. Eur Respir J 2001; 18: 279-285.

12. Haque AK; Gadre S; Taylor J; Haque SA; Freeman D, Duarte A. Pulmonary and cardiovascular complications of obesity – an autopsy study of 76 obese subjects. Arch Pathol Lab Med 2008; 132: 1397-1404.

13. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA. Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G; ESC Commitee for Practice Guidelines (CPG). Guidelines for

the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009, 30:2493-2537.

14. Hoeper MM, Andreas S, Bastian A, Claussen M, Ghofrani HA, Gorenflo M, Grohé C, Günther A, Halank M, Hammerl P, Held M, Krüger S, Lange TJ, Reichenberger F, Sablotzki A, Staehler G, Stark W, Wirtz H, Witt C, Behr J. Pulmonary hypertension due to chronic lung disease: updated Recommendations of the Cologne Consensus Conference 2011. Int J Cardiol 2011;154 Suppl 1: S 45-53.

15. Zielinski J, Tobiasz M, Hawrylkiewicz I, Sliwinski P, Palasiewicz G. Effects of long-term oxygen therapy on pulmonary hemodynamics in COPD patients: a 6-year prospective study. Chest 1998; 113: 65-70.

16. Masa JF, Celli BR, Riesco JA, Sanchez de Cos J,Disdier C, Sojo A. Noninvasive positive pressure ventilation and not oxygen may prevent overt ventilatory failure in patients with chest wall diseases. Chest 1997; 112: 207-213.

17. Sugerman HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. Am J Clin Nutr 1992; 55(2Suppl): 597s-601s.

18. Mokhlesi B, Tulaimat A, Evans AT, Wang Y, Itani A, Hassaballa HA, Herdegen JJ, Stepanski EJ. Impact of adherence with positive airway pressure therapy on hypercapnia in obstructive sleep apnea. J Clin Sleep Med 2006; 2: 57-62.

19. Sforza E, Krieger J, Weitzenblum E, Apprill M, Lampert E, Ratamaharo J. Long-term effects of treatment with nasal continous positive airway pressure on daytime lung function and pulmonary hemodynamics in patients with obstructive sleep apnoea. Am Rev Respir Dis 1990; 141: 866-870

20. Masa J F, Celli BR, Riesco JA, Hernandez M, Sanchez de Cos J, Disdier C. The Obesity Hypoventilation Syndrome can be treated with noninvasive mechanical ventilation. Chest 2001; 119: 1102-1107.

21. Heinemann F, Budweiser S, Dobroschke J, Pfeifer M. Non-invasive positive pressure ventilation improves lung volumes in the obesity hypoventilation syndrome. Respir Med 2007; 101: 1229-1235.

22. Piper AJ, Sullivan CE. Effects of short-term NIPPV in the treatment of patients with severe obstructive sleep apnea and hypercapnia. Chest 1994; 105: 434-440.

23. De Lucas-Ramos P, De Miguel-Diez J, Santacruz-Siminiani A, Gonzalez- Moro JM, Buendia-Garcia MJ, Izquierdo-Alonso JL. Benefits at 1 year of nocturnal intermittent posistive pressure ventilation in patients with obesity-hypoventilation syndrome. Respir Med. 2004:98, 961-967.

24.Pérez de Lllano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vazquez Caruncho M, Caballero Muinelos O, Alvarez Carro C. Short-term and long-term effects of nasal intermittent positive pressure ventilationin patients with Obesity Hypoventilation Syndrome. Chest 2005; 128: 587-594.

25. Chouri-Pontarollo N, Borel JC, Tamisier R, Wuyam B, Levy P,Pepin JL. Impaired objective daytime vigilance in obesity-hypoventilation syndrome: impact of non-invasive ventilation. Chest 2007; 131: 148-155

26. Redolfi S, Corda L, La Piana G, Spandrio S, Prometti P, Tantucci C. Long-term non-invasive ventilation increases chemosensitivity and leptin in obesity-hypoventilation syndrome. Respiration Med. 2007; 101: 1191-1195.

27. Han F, Chen E, Wei H,He Q, Ding D,Strohl K P. Treatment effects on carbon dioxide retention in patients with obstructive sleep apnea-hypopnea syndrome. Chest 2001; 119: 1814-1819.

28. Schönhofer B, Barchfeld T, Wenzel M, Köhler D. Effect of intermittent ventilation on pulmonary hypertension in chronic respiratory failure. Pneumologie 1999; 53 Suppl 2:S113-S115.

29. Quanjer PH, Tammeling GJ, Gotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Functional Tests, European Community for Steel and Coal. Official Staement of the European Respiratory Society. Eur Respir J Suppl. 1993; 16: 5-40.

30. Koch B, Schäper C, Ittermann T, Bollmann T, Völzke H, Felix B, Ewert R, Gläser S. Reference values for respiratory pressures in a general adult population – results of the Study of Health in Pomerania (SHIP). Clin Physiol Funct Imaging 2010; 30:460-465.

31. ATS Statement: Guidelines for the six-minute walking test. Am J Respir Crit Care Med 2002; 166:111-117.

32. ATS/ACCP-Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003; 167: 211-277.

33. American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of the American Academy of Sleep Medicine Task Force. Sleep 1999; 22: 667-689.

34. Windisch W, Brambring J, Budweiser S, Dellweg D, Geiseler J, Gerhard F, Köhnlein T, Mellies U, Schönhofer B, Schucher B, Siemon K, Walterspacher S, Winterholler M, Sitter H. Non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. S2-Guidelines published by the German Medical Association of Pneumology and Ventilatory Support. Pneumologie 2010; 64:207-40

35. Naeije R, Vachiery J L, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013;41:217-223.

36. Lang R M, Bierig M, Devereux R B, Flachskampf F A, Foster E, Pellikka P A,Picard M H, Roman M J, Seward J, Shanewise J, Solomon S, Spencer K T, John Sutton M S, Stewart W. Recommendations for chamber quantification. Eur J Echocardiography 2006; 7:79-108

37. D'Alonso GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991; 115: 343-349.

38. Meyer F J, Lossnitzer D, Kristen A V, Schoene A M, Kübler W, Katus H A, Borst M M. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. Eur Respir J 2005; 25:125-130.

39. Nowbar S, Burkhart KM, Gonzales R, Fedorowicz A,Gozansky WS, Gaudio JC, Taylor MR, Zwillich CW. Obesity associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. Am J Med. 2004; 116:1-7

40. Fijalskowska A, Kurzyna M, Torbicki A, Szewczyk G, Florczyk M, Pruszczyk P,Szturmowicz M. Serum N-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. Chest 2006; 129; 1313-1321

41. Nickel N, Golpon H, Greer M, Knudsen L, Olsson K, Westerkamp V, Welte T, Hoeper MM. The prognostic impact of follow-up assesments in patients with idiopathic pulmonary arterial hypertension. Eur Respi J 2012; 39; 589-596.

42. Galiè N, Ghofrani HA, Torbicki A, Barst R J, Rubin L, Badesch D, Fleming T, Parpia T, Burgess G,Branzi A, Grimminger F, Kurzyna M, Simmoneau G for the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005; 353: 2148-2157.

43. Galiè N, Rubin LJ, Hoeper MM, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with Bosentan (EARLY study): a double-blind, randomized controlled trial. Lancet 2008; 371; 2093-2100.

44. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, Mc Goon MD, Mc Laughlin VV, Roecker EB, Gerber MJ, Dufton C, Wiens BL, Rubin LJ. Ambrisentan in Pulmonary Arterial Hypertension, Randomized Double-Blind, Placebo controlled Multicenter efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized

double-blind, placebo controlled multicenter efficacy (ARIES)study 1 and 2. Circulation 2008; 117: 3010-3019.

45. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simmoneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst R J; Pulmonary Arterial Hypertension and Response To Tadalafil (PHIRST) Study Group. Circulation 2009; 119: 2894-2903.

Figure legends:

Figure 1:

Patient selection for retrospective analysis of 18 patients with pulmonary hypertension and alveolar hypoventilation.

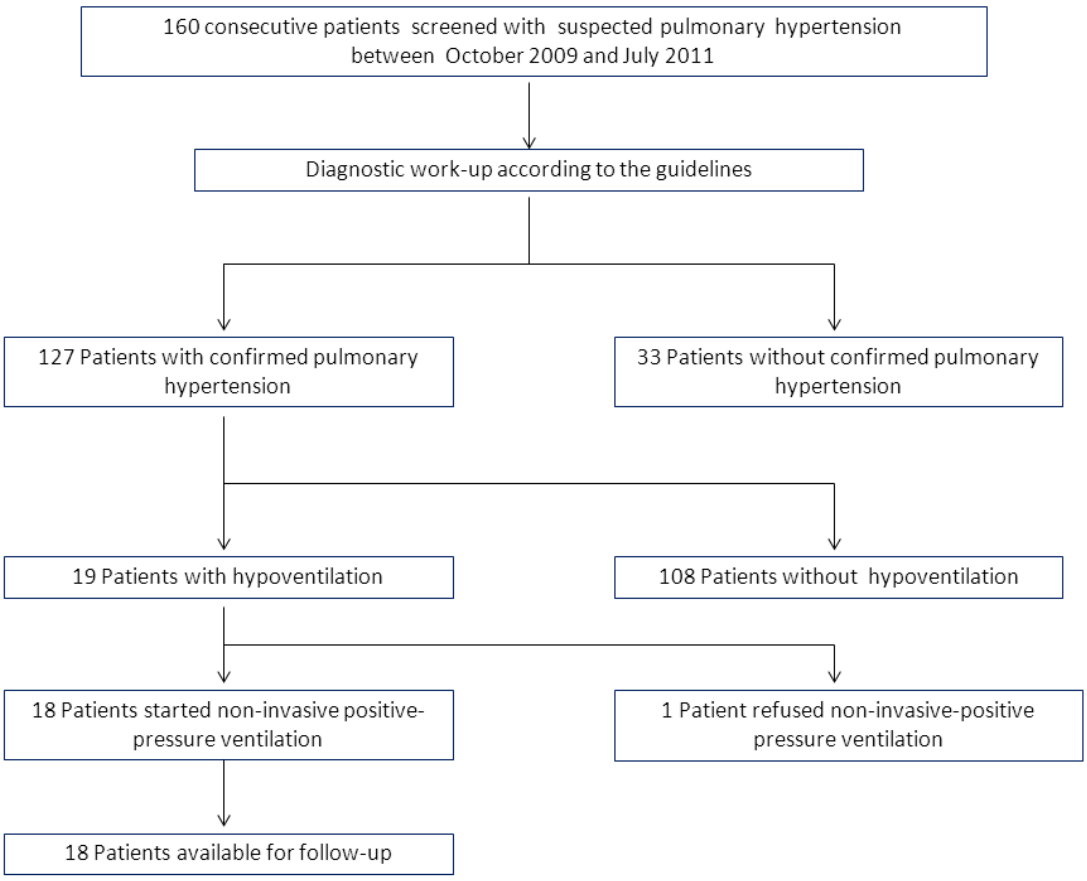

Figure 2: Correlation of (a) mPAP and BMI; (b) mPAP and maximum nighttime $C0_2$; (c) pulmonary vascular resistance and maximum inspiratory mouth pressure. N: number of patients; R = Spearman correlation; CI = 95 %: confidence interval; *p*: *p*-value.

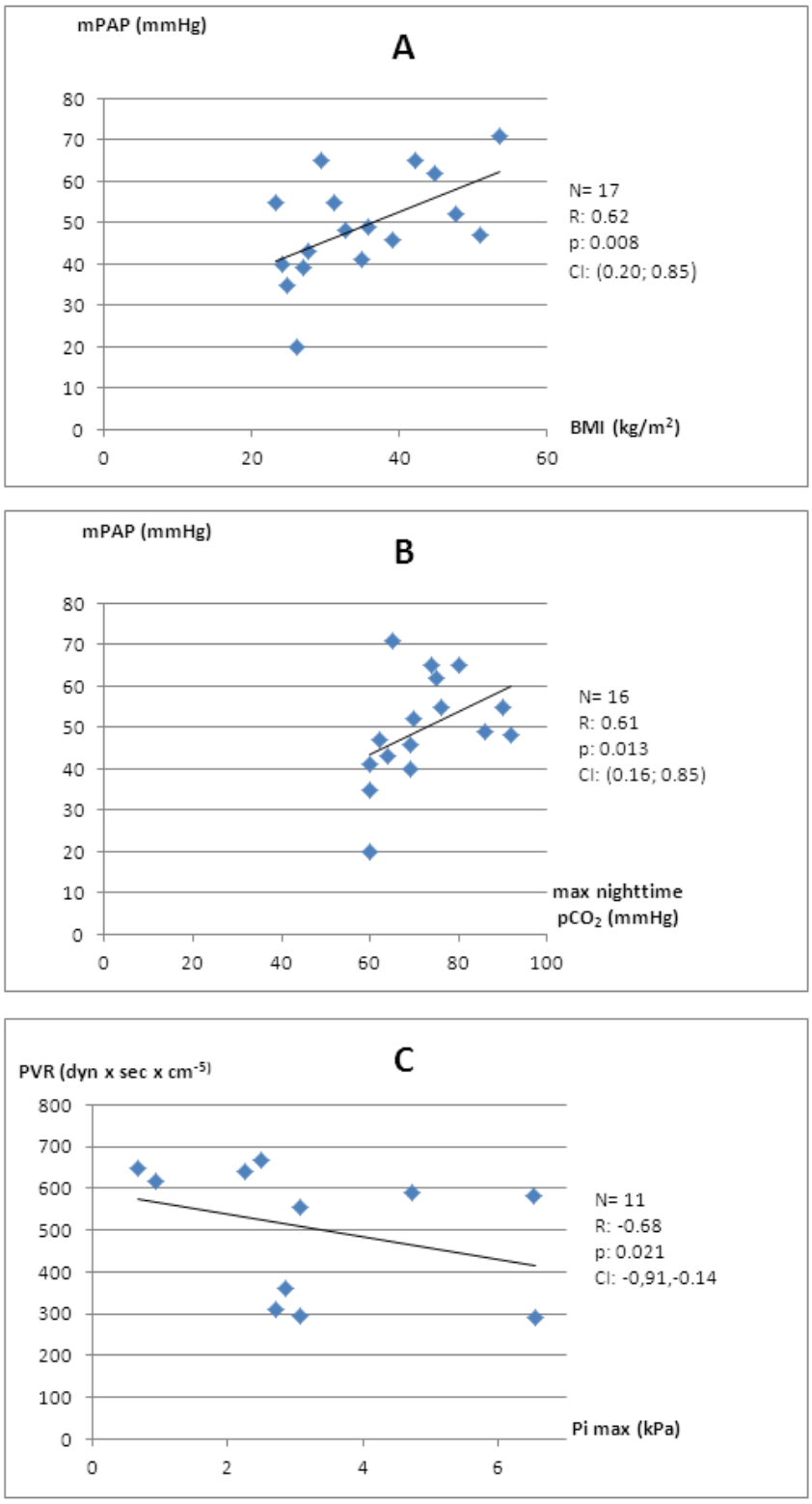

Fig 2 a: Correlation of mPAP = mean pulmonary artery pressure (mm Hg) and BMI = body mass index (kg/m^2).

Fig 2 b: Correlation of mPAP = mean pulmonary artery pressure (mm Hg) and maximum nighttime pCO_2 (mm Hg).

Fig 2 c: Correlation of PVR = pulmonary vascular resistance (dyn*sec*cm^{-5}), and PI max = maximum inspiratory mouth pressure (kPa).

Figure 3: Correlations of (a) work rate and mPAP; (b) work rate and pulmonary vascular resistance; (c) six-minute walking distance and mPAP. N: number of patients; R = Spearman correlation; CI = 95 % confidence interval; *p*= *p*-value.

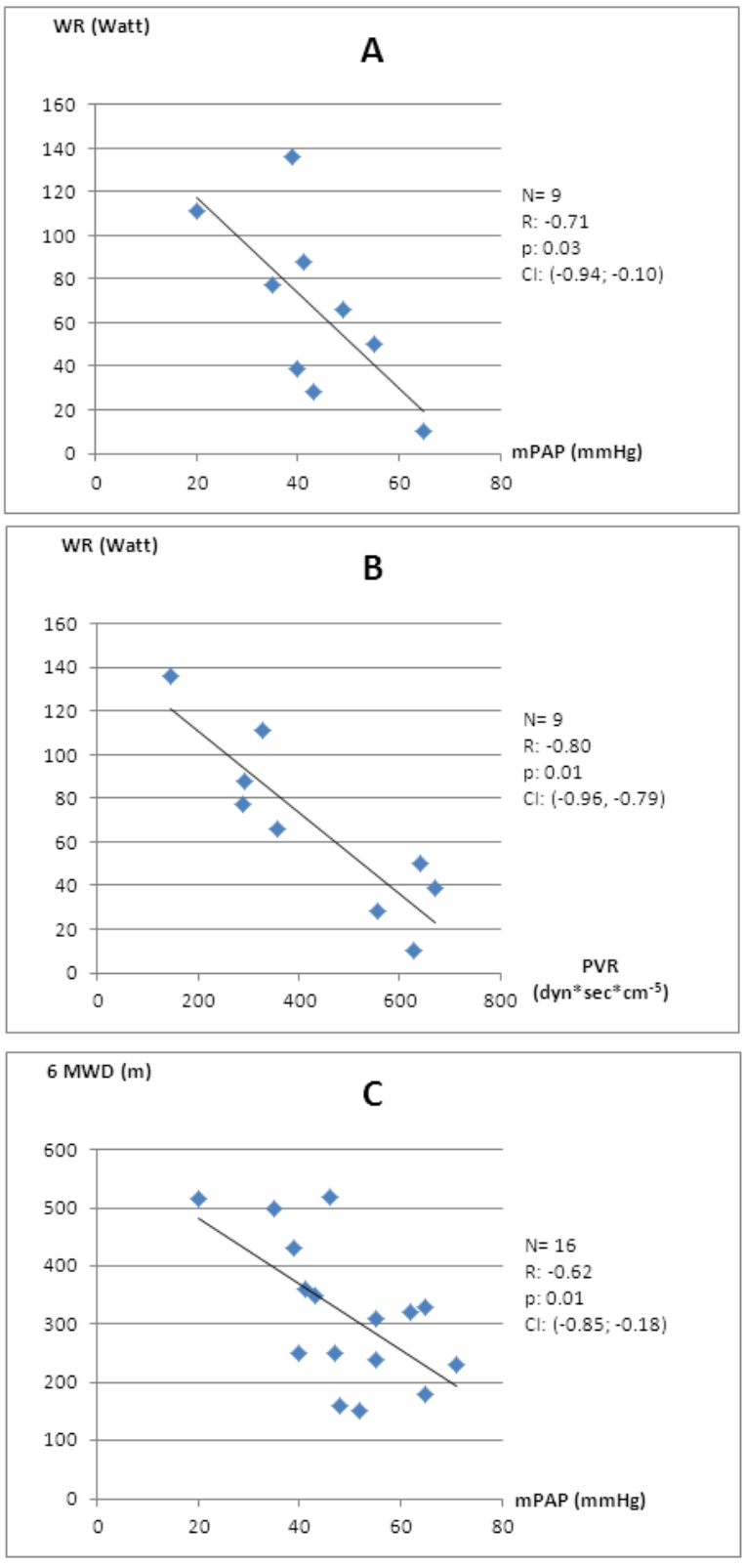

Fig 3 a: Correlation of work rate (Watt) and mPAP = mean pulmonary artery pressure (mmHg).

Fig 3 b: Correlation of work rate (Watt) and PVR = pulmonary vascular resistance (dyn*sec*cm^{-5})

Fig 3 c:Correlation of six-minute walking distance (m) and mPAP = mean pulmonary artery pressure (mmHg).

Figure 4: Changes of hemodynamic parameters after three months of non-invasive positive-pressure ventilation. N: number of patients; *p*: *p*-value.

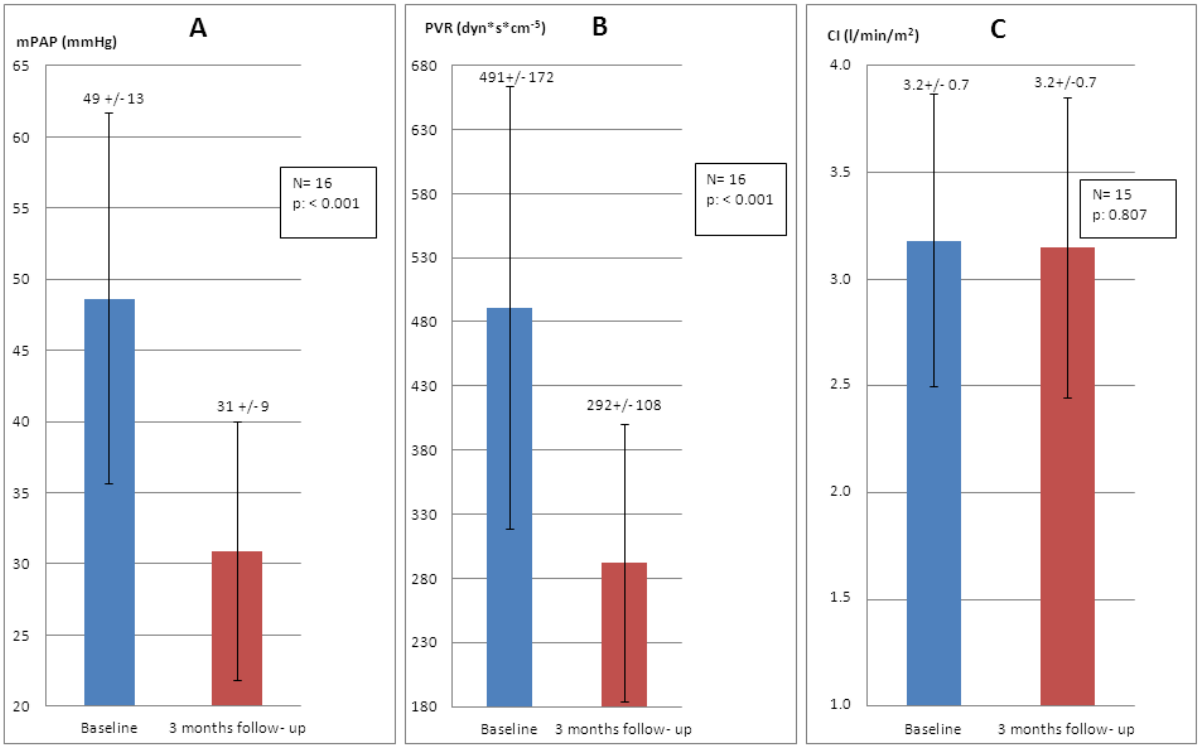

Figure 4 a: mPAP = mean pulmonary artery pressure (mmHg).

Figure 4 b: PVR = pulmonary vascular resistance (dyn* sec*cm^{-5}).

Fig 4 c: CI = Cardiac index (l/min/m^2).

Figure 5: Changes of exercise capacity and NT-proBNP levels after three months of non-invasive positive-pressure ventilation. N: number of patients; *p*: *p*-value.

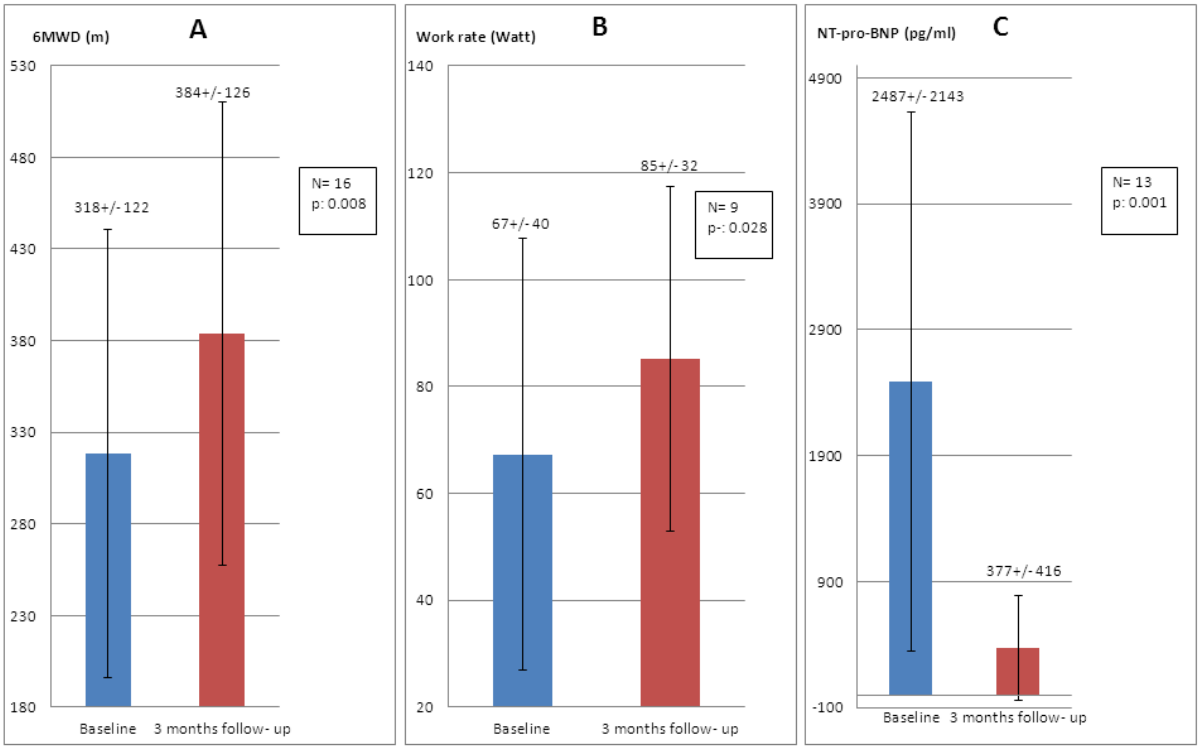

Fig 5 a: 6 MW = six-minute walking distance (m).

Fig 5 b: Work rate (Watt)

Fig 5 c: NT-proBNP serum concentration (pg/ml).

Figure 6: Correlation of change of mPAP (x-axis) and change of maximum work rate (y-axis) after three months of non-invasive positive-pressure ventilation. N: number of patients; *p*: *p*-value.

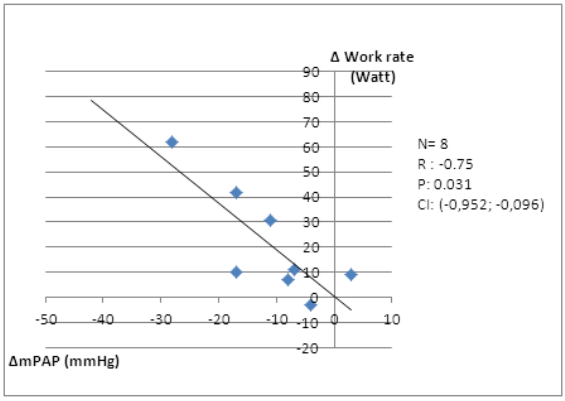

Table 1: Values at baseline and at follow-up after three months of non-invasive positive-pressure ventilation

		Baseline		**Follow-Up**	
Method/parameter	N		N	mean ± SD	p
BMI	18	36.1 ± 9.8	18	35.1 ± 9	0.14
Mean body weight (kg)	18	104. ± 30	18	102 ± 27	0.14
Right heart catheterization					
sPAP (mm Hg)	17	71 ±18	16	44 ± 13	0.001
mPAP (mm Hg)	17	49 ± 13	16	31 ± 9	<0.001
dPAP (mmHg)	17	35 ± 10	16	23 ± 7	0.001
PAWP (mm Hg)	17	11 ± 4	16	9 ± 5	0.167
dPVG (mm Hg)	17	23 ± 10	16	14 ± 4	<0.001
PVR (dyn x sec x cm^{-5})	17	499 ± 171	16	292 ±108	<0.001
CI	17	3.2 ± 0.7	15	3.2 ±0.7	0.807
RAP	17	14±8	15	8 ± 3	<0.01
Six-minute walking test					
6-minute walking distance	17	303 ± 133	16	384 ± 127	<0.01
Echocardiography					
EF (%)	18	67 ± 11	18	67 ± 9	0.931
E/E‘	17	10 ± 4	17	8.5± 2	0.124
LA-volume (ml)	18	57 ± 33	18	77 ± 45	0.002
RA area (cm^2)	18	25.0 ± 7.9	18	19.5 ± 5.9	0.002
TAPSE (mm)	18	18 ± 5	18	25 ± 4	<0.001
Daytime blood gases					
pO_2 at rest (mmHg)	17	56.4 ± 14.4	16	71.2 ± 11.3	0.01
pCO_2 at rest (mmHg)	17	52.2 ± 5.8	16	44.5 ± 4	<0.001

SO_2 at rest (%)	17	87 ± 7	16	94 ± 3	<0.01
Nighttime oxymetry and capnometry					
Mean nighttime CO_2 (mmHg)	17	61.8 ± 7.7	14	46.4 ± 9	0.001
Maximum nighttime CO_2 (mmHg)	17	72.7 ± 10.6	13	54.7 ± 7.4	0.002
Mean nighttime SO_2 (%)	18	82 ± 10	16	94 ± 3	0.001
Cardiopulmonary exercise test					
Maximum work rate (Watt)	9	67 ± 40	9	85 ± 32	0.028
VO2 peak (% pred)	9	65 ± 25	9	71± 23	0.24
Laboratory					
nt-proBNP (pg/ml)	14	2403 ± 2082	13	377 ± 416	0.001

Values are presented as mean ± SD. Only the patients with data available at both baseline and three month follow-up period were considered for analyzing mean changes in each parameter.