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Impairment of respiratory muscle function in pulmonary hypertension

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Short title

Impaired respiratory muscle function in PH

Keywords

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Abstract

It has been suggested that impaired respiratory muscle function occurs in patients with pulmonary hypertension (PH). However, comprehensive investigation of respiratory muscle function – including the application of non-volitional tests – needed to verify impairment of respiratory muscle strength in PH-patients has yet not been performed.

Respiratory muscle function was assessed in 31 PH-patients (20 female, mean pulmonary artery pressure 51 ± 20 mmHg, median WHO-class 3.0 ± 0.5 , pulmonary arterial hypertension $n=25$, chronic-thromboembolic PH $n=6$) and in 31 control subjects (20 female) well-matched for gender, age and body-mass index. A six-minute walking test was performed to rate exercise capacity.

Volitionally assessed maximal inspiratory (7.5 ± 2.1 vs 6.2 ± 2.8 kPa; $p=0.04$) and expiratory (13.3 ± 4.2 vs 9.9 ± 3.4 kPa; $p<0.001$) mouth pressures, sniff nasal (8.3 ± 1.9 vs 6.6 ± 2.2 kPa; $p=0.002$) and transdiaphragmatic (11.3 ± 2.5 vs 8.7 ± 2.5 kPa; $p<0.001$) pressures, non-volitionally assessed twitch mouth (1.46 ± 0.43 vs 0.97 ± 0.41 kPa; $p<0.001$) and transdiaphragmatic (2.08 ± 0.55 vs 1.47 ± 0.72 kPa; $p=0.001$) pressures during bilateral anterior magnetic phrenic nerve stimulation were markedly lower in PH-patients compared to control subjects. Maximal inspiratory mouth ($r=0.58$; $p<0.001$) and sniff transdiaphragmatic ($r=0.43$; $p=0.02$) pressures were correlated to six-minute walking distance in PH-patients.

The present study provides strong evidence that inspiratory muscle strength is reduced in PH-patients compared to well-matched control subjects. Furthermore, six-minute walking distance is significantly linked to parameters assessing inspiratory muscle strength.



Introduction

Daily activities of patients suffering from pulmonary hypertension (PH) are limited by dyspnea on exertion and fatigue. These symptoms have been mainly attributed to a mismatch in systemic oxygen delivery and oxygen demand due to the overloaded right ventricle [1]. However, impairment of respiratory muscle function might partly contribute to these symptoms as has been previously suggested in patients with chronic left heart failure [2,3,4,5]. Moreover, reduced inspiratory muscle strength is known to be an independent predictor of prognosis in patients with chronic left heart failure [6]. In contrast, the role of impaired inspiratory muscle strength in PH-patients remains unclear.

The only pre-existing study on respiratory muscle strength which indicated possible respiratory muscle dysfunction in patients with PH has used volitional tests on respiratory muscle strength only [7]. However, volitional tests are highly dependent on the patient's co-operation and motivation and are thus fraught with variability [8,9]. Therefore, additional measurements for assessment of inspiratory muscle function have been demanded recently to be investigated in patients with PH [1].

It has been clearly outlined that the definitive diagnosis of inspiratory muscle weakness requires non-volitional tests, such as measurement of twitch pressures during magnetic phrenic nerve stimulation [8]. For this reason, the present study was aimed at prospectively evaluating respiratory muscle function in PH-patients.



Materials and Methods

The study was performed in agreement with the ethical standards laid down in the Declaration of Helsinki. The study protocol was approved by the institutional review board for human studies at the Albert-Ludwigs University Freiburg, Germany. All participants gave their written informed consent.

Patients and control subjects

Thirty-one patients (20 women) who were treated in experienced PH-centers and who suffered from PH (selected forms of pulmonary arterial hypertension, n=25; chronic-thromboembolic PH, n=6) according to the 2003 Venice classification [10] were enrolled in this prospective study. PH was diagnosed in an experienced PH-center (including right heart catheterization and echocardiography in all patients). All patients were clinically stable with no evidence of syncope within two months prior to the study. Appropriate medical therapy was provided in all patients. Criteria for inclusion of patients were WHO functional classes II–IV [11]. Exclusion criteria covered primary lung diseases, rib cage abnormalities, neuromuscular disorders, oral steroids (>10 mg Prednisolone-equivalent/day) and malnutrition.

In addition, 31 healthy subjects (20 women and 11 men), well-matched for gender, age and body-mass index served as controls. All patients and controls were naive to magnetic stimulation and the experimental setting.

Lung function parameters, exercise testing and serological markers

Lung function parameters were measured using body-plethysmography (Masterlab-Compact[®], Jaeger, Hochberg, Germany) in accordance with recent guidelines [12]. Intrathoracic gas volume



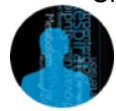
(ITGV) assessed during body-plethysmography was used as the best available measure of functional residual capacity. A six-minute walking test with assessment of the six-minute walking distance (6MWD), dyspnea using the modified Borg Dyspnea Scale (BDS) and blood gas analysis (BGA) was performed [13]. In addition, a venous blood sample was drawn from sitting patients to provide data on NT-proBNP and uric acid.

Pressure and airflow recordings

The pneumotachograph ZAN-100-Flowhandy-II[®] and the pressure transducer ZAN-400[®] (ZAN[®], Oberthulba, Germany) were used for airflow and pressure recordings. Ventilatory drive ($P_{0.1}$) and effective inspiratory impedance ($P_{0.1}/V_T/t_i$), used as a marker of the load imposed on the inspiratory muscles, were assessed according to recent recommendations [9,14]. Maximal inspiratory ($P_{I\max}$, measured from residual volume) and expiratory ($P_{E\max}$, assessed from total lung capacity) mouth pressure, and respiratory capacity ($P_{0.1}/P_{I\max}$) were measured in line with previous recommendations [9,15,16,17]. Sniff pressures were obtained at functional residual capacity as outlined previously [18]. Twitch mouth (TwP_{mo}) and transdiaphragmatic (TwP_{di}) pressures including inspiratory flow (F_{trig}) and pressure (P_{trig}) during inspiratory pressure triggering were assessed by bilateral anterior magnetic phrenic nerve stimulation (BAMPS) (Magstim[®] 200², Magstim[®] Inc., Wales, United Kingdom) [19,20]. Further details on the methods for making these measurements have been published previously [20,21].

Predetermination of study endpoints

The primary endpoint of the current study was defined as the difference in inspiratory muscle strength between PH-patients and control subjects assessed by TwP_{mo} due to its superior non-



volitional and at the same time non-invasive characteristics. Secondary endpoints were differences in the non-volitional but invasive TwPdi and volitionally assessed respiratory muscle function between PH-patients and controls, and associations between parameters assessing respiratory muscle function and 6MWD in PH-patients.

Statistical analysis

Sigma-Stat[®] Software (Version 3.1, Systat Software, Inc., Point Richmond, California, USA) was used for statistical analysis. All data are presented as mean \pm standard deviation (SD). The null-hypothesis (H_0) was determined as there is no difference in mean TwPmo between PH-patients and controls. For H_0 rejection 29 subjects are needed in each group following sample size determination (unpaired t-test, power 0.9, two-sided type I error 0.05) with an estimated SD of 0.4 kPa for mean TwPmo and a difference of at least 0.35 kPa between the two groups. Comparison between two groups was performed using the unpaired t-test/Mann-Whitney rank-sum test for normally/non-normally distributed data. Due to the fact that TwPmo was designated as primary endpoint no data adjustment for multiple comparisons has been performed. Correlation analysis was performed using Pearson product-moment correlation. Linear regression analysis was performed where appropriate [22]. A p-value <0.05 was considered statistically significant.



Results

Anthropometric and lung function characteristics for all participants are presented in Table 1. Hemodynamic and serological parameters for PH-patients are given in Table 2. There is no difference in gender composition, age and BMI when comparing patients with PH and controls. Lung function parameters revealed mildly reduced values for forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) and a trend towards reduced maximal expiratory flow at 50 percent of FVC (MEF₅₀) in PH-patients compared to controls (Table 1).

Exercise testing, ventilatory characteristics and volitional tests on respiratory muscle function

Results of the six-minute walking test with 6MWD, BDS-scores and BGA-data are given in Table 1. All PH-patients stated that their exercise capacity was limited by dyspnea and not by skeletal muscle exhaustion or weakness of the legs. The 6MWD was significantly shorter ($p < 0.001$) and BDS was higher ($p < 0.001$) in PH-patients compared to controls (Table 1). In addition, oxygen and carbon dioxide partial pressures were lower in PH-patients compared to controls both at rest and following exercise ($p < 0.001$ in all instances). Data for ventilatory characteristics and volitional tests on respiratory muscle function are presented in Table 3. Breathing frequency (18 ± 5 vs 17 ± 5 /min; $p = 0.30$), tidal volume (0.8 ± 0.3 vs 0.7 ± 0.2 l; $p = 0.23$), ventilatory drive and respiratory capacity (Table 3) showed trends towards higher values in PH-patients compared to controls. However, this did not reach statistical significance. Importantly, the load imposed on the inspiratory muscles is equal between PH-patients and controls (Table 3). In contrast, all volitional tests on respiratory muscle strength revealed significantly reduced values for PH-patients compared to controls (Figure 1).



Non-volitional tests on inspiratory muscle strength

Results for non-volitional assessment of inspiratory muscle strength, represented by twitch pressures and corresponding data are given in Table 3. TwPmo was sufficiently recorded in all of the 31 patients and in 29 controls. The remaining two control subjects declined magnetic stimulation. Catheter placement for measurement of transdiaphragmatic pressures was declined by five controls and by five PH-patients. Group comparison revealed highly significant reduction of TwPmo ($p < 0.001$) and TwPdi ($p = 0.001$) in PH-patients compared to controls (Table 3). Values for TwPmo and TwPdi in PH-patients and controls are illustrated in Figure 2. Adequacy of twitch pressures assessment was assured in both PH-patients and controls, as can be deduced by the lack of difference in P_{trig} and F_{trig} values between the two groups (Table 3).

Relationship between respiratory muscle function and exercise capacity in patients with pulmonary hypertension

P_{Imax} ($r = 0.58$; $p < 0.001$) and S_{nPdi} ($r = 0.43$; $p = 0.02$), but not twitch pressures ($p > 0.05$ in both instances), were significantly correlated to 6MWD in PH-patients. The relationship between P_{Imax} and 6MWD following linear regression analysis is illustrated in Figure 3. In contrast, hemodynamic characteristics assessed during right heart catheterization - mean pulmonary artery pressure, pulmonary vascular resistance, central venous pressure, and cardiac index - were not correlated to 6MWD ($p > 0.05$ in all instances). Following stepwise multiple linear regression analysis, 6MWD can only be predicted from P_{Imax} ($p < 0.01$) but neither from TwPmo nor mean pulmonary artery pressure ($p > 0.8$ in both instances), considering P_{Imax} , TwPmo and mean pulmonary artery pressure.



Comparisons of tests on respiratory muscle strength between patients with PAH and CTEPH

For all instances, P_Imax (6.4±2.9 vs 5.3±2.2 kPa), P_Emax (10.3±3.6 vs 8.1±1.9 kPa), SnP_{na} (6.8±2.3 vs 5.5±1.5 kPa), SnP_{di} (8.8±2.7 vs 7.9±2.0 kPa), TwP_{mo} (1.00±0.43 vs 0.84±0.29 kPa) and TwP_{di} (1.52±0.74 vs 1.17±0.54 kPa) patients with CTEPH (n=6) show lower values of respiratory muscle strength compared to patients with PAH (n=25). Due to the low and unequal sample sizes these data are purely descriptive without any further statistical analyses performed.



Discussion

The present study establishes evidence of substantially impaired respiratory muscle function in a representative collective of patients with PH by using both volitional and non-volitional tests on respiratory muscle function. The main finding of the present study is that respiratory muscle strength is markedly reduced in patients suffering from PH when compared to controls. These differences are more distinct considering non-volitional tests on inspiratory muscle strength as reflected by TwPmo and TwPdi in comparison to volitional tests.

There is solely one pre-existing study on respiratory muscle dysfunction in patients with PH, applying volitional tests on respiratory muscle function only [7]. However, the definitive diagnosis of respiratory muscle weakness in PH-patients can only be established by the use of non-volitional tests on inspiratory muscle function [1], since volitional tests are highly variable due to their dependency on the participant making a truly maximal effort [8,9].

The finding of impaired respiratory muscle function is suggested to have major clinical impact on patients suffering from PH. The application of combined respiratory and exercise training to PH-patients resulted in an improvement each in quality of life, WHO functional class, peak oxygen consumption and achieved workload [23]. The findings of the present study might serve as a pathophysiological background for these reported improvements. This is supported by the observation that respiratory muscle training in patients with chronic left heart failure resulted in improvement of both inspiratory muscle strength and important clinical parameters such as dyspnea on exertion and quality of life [24,25]. Therefore, future studies are needed to investigate possible improvements of respiratory muscle strength in PH-patients undergoing respiratory muscle training.



Several studies have suggested that respiratory muscle strength is reduced in patients with chronic left heart failure [3,4,6,26,27], but, again, solely volitional tests on respiratory muscle function have been applied, thus reducing the reliability of these findings [8,9]. However, when using non-volitional tests with assessment of twitch pressures, the reduction in inspiratory muscle strength in patients with chronic left heart failure was reported to be less evident and hence not to be of clinical importance since inspiratory muscle strength remains well preserved [4,28]. This is in clear contrast to findings of the present study in PH-patients in whom substantially reduced inspiratory muscle strength has been clearly established by a 34% difference of non-volitionally assessed TwPmo compared to controls. Interestingly, patients with CTEPH presented with even more impaired respiratory muscle strength compared to patients with PAH. However, due to the low and unequal sample sizes between the two groups, data are purely descriptive without any further statistical analyses performed. The reasons for the observed differences remain unclear and future studies are needed to address this issue.

The underlying pathophysiological mechanisms responsible for the impairment of respiratory muscle strength in PH-patients have not yet been conclusively investigated. Based on observations mainly derived from chronic left heart failure, several mechanisms accounting for a reduction in respiratory muscle strength have been suggested. Structural skeletal muscle abnormalities and abnormal expression of myosin isoforms highly suggestive of fiber type transformation predominantly pronounced in the diaphragm of patients with chronic left heart failure have been reported [29]. Furthermore, fiber type changes associated with a myopathic pattern [30], cross-sectional muscle fiber reduction [31] and fast-to-slow transformations for myosin and regulatory proteins [32,33] in the diaphragm have been reported. In addition, besides an intracellular calcium regulation disorder in the diaphragms of patients with chronic left heart



failure [34] the occurrence of a depressed oxidative capacity of the working muscles [35], linked to underperfusion of respiratory muscles and deoxygenation [36], has been described in chronic left heart failure. However, in contrast to patients with chronic left heart failure in previous studies, PH-patients in the current study presented without relevant functional restrictions of the left heart, as can be seen by normal values for left ventricular ejection fraction and pulmonary artery wedge pressure. In addition, by taking into account the more reliable non-volitional tests on inspiratory muscle strength, the PH-patients of the present study are suggested to have more severely impaired inspiratory muscle strength compared to chronic left heart failure patients of previous studies. Therefore, even if there are several similarities between PH and chronic left heart failure pathophysiological findings in these patients cannot easily be transferred to PH-patients and further investigations are needed to confirm these suggestions. Importantly, none of the PH-patients in the present study suffered from malnutrition or wasting since these factors are known to be potential confounders with regard to reduced respiratory muscle strength in chronic left heart failure [37]. Finally, PH-patients in the current study presented with hypocapnia both at rest and following exercise, indicating higher demands on the inspiratory muscles. This overstraining might in part account for reduced inspiratory muscle strength in PH-patients. Interestingly, hypocapnia has recently been recognized as an independent marker of mortality in PH-patients [38].

The present study indicates that maximal inspiratory mouth pressure and sniff transdiaphragmatic pressure are significantly linked to exercise capacity in PH-patients. Interestingly, reduced inspiratory muscle strength, as assessed by maximal inspiratory mouth pressure, is known to be an important determinant of maximal oxygen consumption and exercise tolerance [26] and, moreover, an independent predictor of prognosis [6] in patients with chronic



left heart failure. Whether this compares to PH-patients remains unclear and requires additional investigations.

Minute ventilation is known to be increased in patients with PH both at rest and during exercise [39]. Accordingly, in both the present and a previous study [7], ventilatory drive revealed trends towards higher values while respiratory capacity tended to be reduced in PH-patients compared to controls. Importantly, no difference could be observed in the effective inspiratory impedance between PH-patients and controls, indicating that the load imposed on the inspiratory muscles is not increased in PH-patients [14]. Therefore, impairment of respiratory muscle function in PH-patients cannot be explained by known changes in breathing pattern. Since changes in lung volume are known to have substantial impact on respiratory muscle strength care was taken to apply all tests on respiratory muscle function at comparable lung volumes both in PH-patients and control subjects. This was assured by the computer device as outlined above. Importantly, pre-existing differences in ITGV as the best available measure of functional residual capacity between PH-patients and control subjects have been ruled out as confounding factor. Both PH-patients and normal subjects presented with ITGV values within the predicted norm. However, there was a non-significant difference of approximately 0.3 l in ITGV between PH-patients and control subjects. Since it is known that TwPdi decreases by 0.34 kPa/l changes in ITGV [40] this difference might account for a reduction in TwPdi of 0.1 kPa for PH-patients compared to control subjects. However, this leaves the major component of 0.5 kPa of difference unexplained and, therefore, the observed marked differences in respiratory muscle function between PH-patients and control subjects cannot be attributed to differences in lung volume. Since lung volume correction has been established for TwPdi only and effects are suggested to be at best small no further parameter of inspiratory muscle strength was corrected for lung volume.



The present study has certain limitations which need to be addressed. Firstly, the assessment of muscle function focused on respiratory muscles only. A generalized systemic muscle weakness process in PH-patients is likely to accompany the demonstrated respiratory muscle weakness in PH-patients as has been demonstrated in patients with chronic left heart failure [29]. However, since peripheral muscle function was not investigated in the present study this remains speculative and clearly needs further investigations. Secondly, patients with PH showed mild airway obstruction compared to controls. However, it is well known that mild peripheral airway obstruction is common in patients suffering from PH, and values presented in the current study are comparable to those published previously [41]. Therefore, inclusion of PH-patients with mild airway obstruction could not be avoided. Nevertheless, impairment of lung function in PH-patients was at best slight and is, therefore, suggested to be irrelevant with regard to the observed marked differences in respiratory muscle strength between PH-patients and controls.

In conclusion, this study provides strong evidence that inspiratory muscle strength is reduced in PH-patients compared to well-matched controls. Furthermore, six-minute walking distance in PH-patients is significantly linked to parameters of inspiratory muscle strength.



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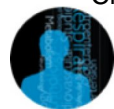


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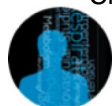


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Tables

Table 1. Anthropometric characteristics, lung function and exercise parameters in patients with pulmonary hypertension (n=31) and control subjects (n=31).

		Control subjects	PH-patients	p-value
Gender (f/m)	[n]	20/11	20/11	
Age	[a]	55.0 ± 12.2	56.5 ± 14.3	0.66
BMI	[kg/m ²]	26.6 ± 4.9	26.0 ± 5.5	0.67
ITGV	[l]	2.9 ± 0.6	3.2 ± 1.0 [†]	0.21
ITGV	[% pred]	88 ± 17	99 ± 26 [†]	0.08
FEV₁	[% pred]	98 ± 13	84 ± 19	0.001
FVC	[% pred]	110 ± 13	97 ± 18	0.001
FEV₁/FVC	[%]	78 ± 6	74 ± 9	0.054
MEF₅₀	[% pred]	70 ± 25	60 ± 28	0.16
6MWD	[m]	619 ± 79	407 ± 118*	<0.001
BDS		0.2 ± 0.5	6.4 ± 2.4*	<0.001
PaO₂ rest	[mmHg]	77 ± 5	68 ± 9 [†]	<0.001
PaCO₂ rest	[mmHg]	39 ± 3	35 ± 3 [†]	<0.001
PaO₂ exercise	[mmHg]	87 ± 8	64 ± 16 [†]	<0.001
PaCO₂ exercise	[mmHg]	38 ± 3	34 ± 4 [†]	<0.001

Values are expressed as mean (± SD). BDS = Borg dyspnea scale; BMI = body-mass index; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; ITGV = intrathoracic gas volume; MEF₅₀ = maximal expiratory flow at 50 percent of FVC; % pred = percent predicted; PaCO₂ rest/exercise = carbon dioxide partial pressure at rest / following exercise; PaO₂ rest/exercise = oxygen partial pressure at rest / following exercise; 6MWD = distance walked in 6 minutes. *n=30; †n=18.

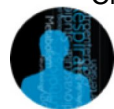


Table 2. Hemodynamic and serological parameters in patients with pulmonary hypertension ($n=31$).

		PH-patients
WHO II/III/IV	[n]	2/23/6
MPAP	[mmHg]	51 ± 20
PVR	[dyn*s*cm ⁻⁵]	759 ± 425
PAWP	[mmHg]	9 ± 5
CVP	[mmHg]	6 ± 3
CI	[l/min/m ²]	2.6 ± 0.5
EF	[%]	56 ± 8
NT-proBNP	[pg/ml]	1117 ± 1656
Uric acid	[mg/dl]	6.8 ± 2.6

Values are expressed as mean (\pm SD). PAWP = pulmonary artery wedge pressure; CI = cardiac index; CVP = central venous pressure; EF = left ventricular ejection fraction (assessed by echocardiography); NT-proBNP = N-terminal pro brain-derived natriuretic peptide; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; WHO II/III/IV = World Health Organization functional classes.

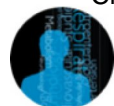


Table 3. Ventilatory characteristics, tests on respiratory muscle strength and corresponding data in patients with pulmonary hypertension (n=31) and control subjects (n=31).

		Control subjects	PH-patients	p-value
P_{0.1}	[kPa]	0.23 ± 0.10	0.28 ± 0.15	0.12
P_{0.1}/V_T/t_i	[kPa/l/s]	0.5 ± 0.2	0.5 ± 0.2	0.68
P_{0.1}/P_Imax	[%]	3 ± 2	6 ± 7	0.13
P_Imax	[kPa]	7.5 ± 2.1	6.2 ± 2.8	0.04
P_Emax	[kPa]	13.3 ± 4.2	9.9 ± 3.4	<0.001
SnPna	[kPa]	8.3 ± 1.9	6.6 ± 2.2	0.002
SnPdi	[kPa]	11.3 ± 2.5*	8.7 ± 2.5*	<0.001
TwPmo	[kPa]	1.46 ± 0.43 [†]	0.97 ± 0.41	<0.001
TwPdi	[kPa]	2.08 ± 0.55*	1.47 ± 0.72*	0.001
P_{trig}	[kPa]	0.5 ± 0.1 [†]	0.5 ± 0.1	0.74
F_{trig}	[ml/s]	32 ± 14 [†]	32 ± 12	0.88

Values are expressed as mean (± SD). F_{trig} = inspiratory flow at triggering twitch pressures; P_{0.1} = mouth occlusion pressure after 0.1 seconds of inspiration; P_{0.1}/P_Imax = respiratory capacity (higher values indicate reduced capacity); P_{0.1}/V_T/t_i = effective inspiratory impedance; P_Emax = maximal expiratory mouth pressure; P_Imax = maximal inspiratory mouth pressure; P_{trig} = inspiratory pressure at triggering twitch pressures; SnPdi = Sniff transdiaphragmatic pressure; SnPna = Sniff nasal pressure; TwPdi = twitch transdiaphragmatic pressure; TwPmo = twitch mouth pressure. *n=26; [†]n=29.



Figures

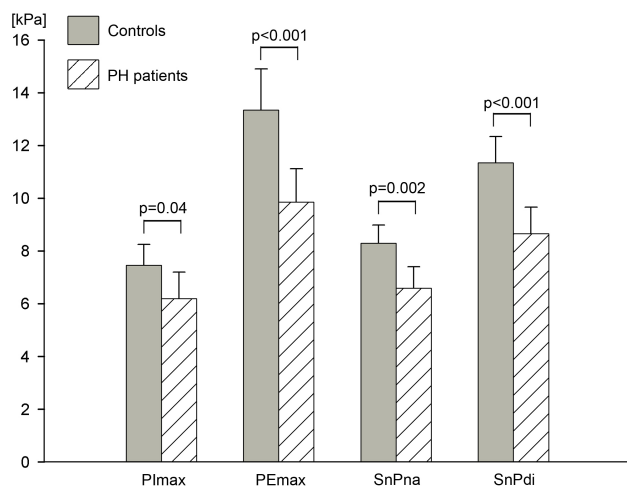


Figure 1. Comparison of volitional assessed maximal inspiratory (PImax) and expiratory (PEmax) mouth pressures and sniff nasal (SnPna) and transdiaphragmatic (SnPdi) pressures in patients with pulmonary hypertension and control subjects. Solid bars represent mean values for control subjects. Hatched bars represent mean values for patients with pulmonary hypertension. T-bars represent 95 % confidence interval of the mean.

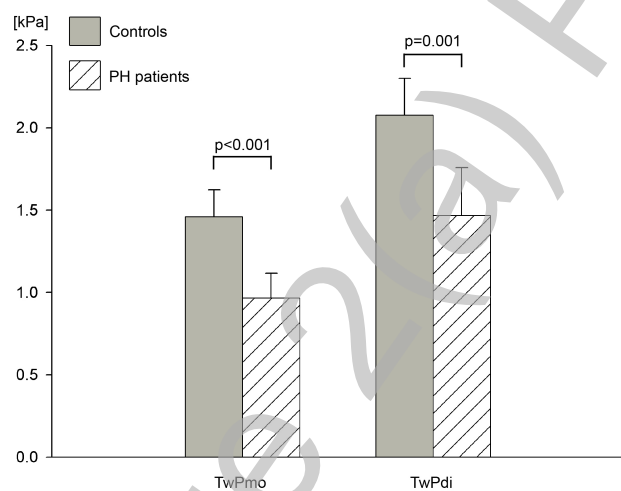


Figure 2. Values for non-volitional assessed twitch mouth (TwPmo) and transdiaphragmatic (TwPdi) pressures in patients with pulmonary hypertension as compared to control subjects. Solid bars represent mean values for control subjects. Mean values for patients with pulmonary hypertension are represented by the hatched bars. T-bars represent 95 % confidence interval of the mean.

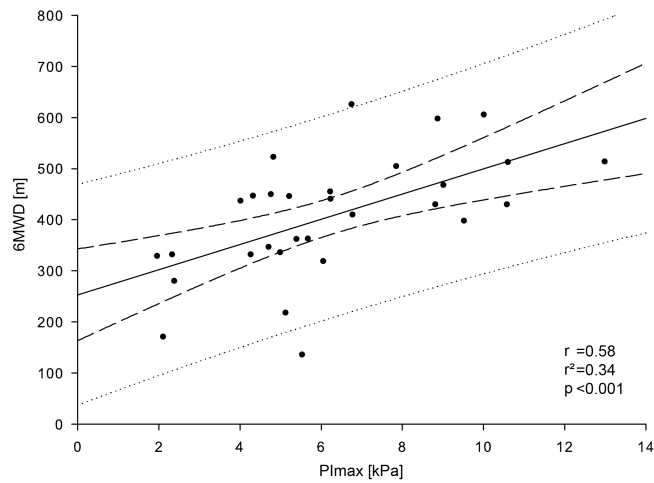


Figure 3. Relationship between maximal inspiratory mouth pressure (PImax) and six-minute walking distance (6MWD) in patients with pulmonary hypertension following linear regression analysis. The regression line between PImax and 6MWD is represented by the solid line. Dashed line reflects 95 percent confidence interval for the regression. Dotted line represents 95 percent confidence interval for the population.