Impairment of respiratory muscle function in pulmonary hypertension

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A B S T R A C T

It has been suggested that impaired respiratory muscle function occurs in patients with PH (pulmonary hypertension); however, comprehensive investigations of respiratory muscle function, including the application of non-volitional tests, needed to verify impairment of respiratory muscle strength in patients with PH have not yet been performed. In the present study, respiratory muscle function was assessed in 31 patients with PH (20 females and 11 males; mean pulmonary artery pressure, 51 ± 20 mmHg; median World Health Organization class 3.0 ± 0.5; 25 patients with pulmonary arterial hypertension and six patients with chronic thromboembolic PH) and in 31 control subjects (20 females and 11 males) well-matched for gender, age and BMI (body mass index).

A 6-min walking test was performed to determine exercise capacity. Volitionally assessed maximal inspiratory (7.5 ± 2.1 compared with 6.2 ± 2.8 kPa; P = 0.04) and expiratory (13.3 ± 4.2 compared with 9.9 ± 3.4 kPa; P = 0.001) mouth pressures, sniff nasal (8.3 ± 1.9 compared with 6.6 ± 2.2 kPa; P = 0.002) and transdiaphragmatic (11.3 ± 2.5 compared with 8.7 ± 2.5 kPa; P = 0.001) pressures, non-volitionally assessed twitch mouth (1.46 ± 0.43 compared with 0.97 ± 0.41 kPa; P < 0.001) and transdiaphragmatic (2.08 ± 0.55 compared with 1.47 ± 0.72 kPa; P = 0.001) pressures during bilateral anterior magnetic phrenic nerve stimulation were markedly lower in patients with PH compared with control subjects. Maximal inspiratory mouth (r = 0.58, P < 0.001) and sniff transdiaphragmatic (r = 0.43, P = 0.02) pressures were correlated with the 6-min walking distance in patients with PH. In conclusion, the present study provides strong evidence that respiratory muscle strength is reduced in patients with PH compared with well-matched control subjects. Furthermore, the 6-min walking distance is significantly linked to parameters assessing inspiratory muscle strength.

Key words: exercise, lung function, pulmonary heart disease, pulmonary hypertension, respiratory muscle strength, twitch pressure.

Abbreviations: BDS, Borg dyspnoea scale; BGA, blood gas analysis; BMI, body mass index; CI, cardiac index; CVP, central venous pressure; FEV1, forced expiratory volume in 1 s; Fmax, maximal inspiratory flow at triggering twitch pressure; FVC, forced vital capacity; ITGV, intrathoracic gas volume; MEF50, maximal expiratory flow at 50 % of FVC; MPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; P2i/VTi, effective inspiratory impedance; PaCO2, partial pressure of CO2; PAH, pulmonary arterial hypertension; PaO2, partial pressure of O2; Pmmax, maximal expiratory mouth pressure; PH, pulmonary hypertension; CTEPH, chronic thromboembolic PH; Pmmax, maximal inspiratory mouth pressure; Pmtrig, inspiratory pressure at triggering twitch pressure; PVR, pulmonary vascular resistance; 6MW, 6-min walking distance; SnPdi, sniff transdiaphragmatic pressure; SnPn, sniff nasal pressure; TwPdi, transdiaphragmatic pressure; TwPn, twitch mouth pressure; WHO, World Health Organization.

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INTRODUCTION

Daily activities of patients suffering from PH (pulmonary hypertension) are limited by dyspnoea 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 suggested previously in patients with chronic heart failure [2–5]. Moreover, reduced inspiratory muscle strength is known to be an independent predictor of prognosis in patients with chronic heart failure [6]. In contrast, the role of impaired inspiratory muscle strength in patients with PH remains unclear.

The only previous study on respiratory muscle strength which indicated possible respiratory muscle dysfunction in patients with PH used only volitional tests on respiratory muscle strength [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 the assessment of inspiratory muscle function have been demanded 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 aim of the present study was to prospectively evaluate respiratory muscle function in patients with PH.

MATERIALS AND METHODS

Ethics

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, Freiburg, Germany. All participants gave their written informed consent.

Patients and control subjects

A total of 31 patients (20 women and 11 men) who were treated in experienced PH centres and suffered from PH [25 with selected forms of PAH (pulmonary arterial hypertension) and six with CTEPH (chronic thromboembolic PH)], according to the 2003 Venice classification [10], were enrolled into this prospective study. PH was diagnosed in an experienced PH centre (including right heart catheterization and echocardiography in all patients). All patients were clinically stable with no evidence of syncope 2 months prior to the study. Appropriate medical therapy was provided in all patients. Criteria for inclusion of patients were WHO (World Health Organization) functional classes II–IV [11]. Exclusion criteria included primary lung diseases, rib cage abnormalities, neuromuscular disorders, oral steroids (> 10 mg of prednisolone-equivalent/day) and malnutrition.

In addition, 31 healthy subjects (20 women and 11 men), well-matched for gender, age and BMI (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) in accordance with recent guidelines [12]. ITGV (intrathoracic gas volume) assessed during body plethysmography was used as the best available measure of functional residual capacity. A 6-min walking test with assessment of the 6MWD (6-min walking distance), dyspnoea using the modified BDS (Borg dyspnoea scale) and BGA (blood gas analysis) was performed as described previously [13]. In addition, a venous blood sample was drawn from sitting patients to provide data for NT-proBNP (N-terminal fragment of pro-brain natriuretic peptide) and uric acid.

Pressure and airflow recordings

The pneumotachograph ZAN-100-Flowhandy-II® and the pressure transducer ZAN-400® were used for airflow and pressure recordings. Ventilatory drive ($P_{0.15}$; mouth occlusion pressure after 0.1 s of inspiration) and $P_{0.15}/V_{T}/t_{i}$ (effective inspiratory drive, used as a marker of the load imposed on the inspiratory muscles, were assessed according to recent recommendations [9,14]. $P_{\text{max}}$ (maximal inspiratory mouth pressure; measured from the residual volume), $P_{\text{in}}$ (expiratory mouth pressure; assessed from the total lung capacity) and $P_{0.1}/P_{\text{max}}$ (respiratory capacity) were measured in line with previous recommendations [9,15–17]. Sniff pressures [$SnpNa$ (sniff nasal pressure) and $SnpDi$ (sniff transdiaphragmatic pressure)] were obtained at functional residual capacity as described previously [18]. $TwPmo$ (twitch mouth pressure) and $TwPdi$ (transdiaphragmatic pressure), including $F_{\text{es}}$ (inspiratory flow at triggering twitch pressure) and $P_{\text{v}}$ (inspiratory pressure at triggering twitch pressure), were assessed by BAMPS (bilateral anterior magnetic phrenic nerve stimulation; Magstim® 200®) [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 present study was defined as the difference in inspiratory muscle strength between patients with PH and control subjects assessed by $TwPmo$, 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 patients with PH and controls, and associations between parameters assessing respiratory muscle function and 6MWD in patients with PH.

**Statistical analysis**

Sigma-Stat® Software (Systat Software) was used for statistical analysis. Results are means ± S.D. The null-hypothesis was determined as there is no difference in mean TwPmo between patients with PH and controls. For rejection of the null-hypothesis, 29 subjects were needed in each group following sample size determination (unpaired Student’s t-test; power, 0.9; two-sided type I error, 0.05) with an estimated S.D. of 0.4 kPa for mean TwPmo and a difference of at least 0.35 kPa between the two groups. Comparison between the two groups was performed using an unpaired Student’s t-test/Mann–Whitney rank-sum test for normally/non-normally distributed data. Owing to the fact that TwPmo was designated as the primary endpoint no data adjustment for multiple comparisons was performed. Correlation analysis was performed using Pearson’s product-moment correlation. Linear regression analysis was performed where appropriate, as described by Bland and Altman [22]. A P value < 0.05 was considered statistically significant.

**RESULTS**

Anthropometric and lung function characteristics for all participants are shown in Table 1, and the haemodynamic and serological parameters for patients with PH are shown in Table 2. There is no difference in gender composition, age and BMI when comparing patients with PH with controls. Lung function parameters revealed slightly reduced values for FEV₁ (forced expiratory volume in 1 s) and FVC (forced vital capacity), and a trend towards a reduction in MEF₅₀ (maximal expiratory flow at 50 % of FVC) in patients with PH compared with controls (Table 1).

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

Results of the 6-min walking test with 6MWD, BDS scores and BGA results are given in Table 1. All patients with PH stated that their exercise capacity was limited by dyspnoea and not by skeletal muscle exhaustion or weakness of the legs. 6MWD was significantly shorter (P < 0.001) and BDS was higher (P < 0.001) in patients with PH compared with controls (Table 1). In addition, PaO₂ (partial pressure of O₂) and PaCO₂ (partial pressure of CO₂) both at rest and following exercise were lower in patients with PH compared with controls (P < 0.001 in all instances; Table 1). Results for the ventilatory characteristics and volitional tests on respiratory muscle function are shown in Table 3 and Figure 1. Breathing frequency (18 ± 5 compared with 17 ± 5 breaths/min; P = 0.30), tidal volume (0.8 ± 0.3 compared with 0.7 ± 0.2 l; P = 0.23), ventilatory drive and respiratory capacity (Table 3) had trends towards higher values in patients with PH compared with controls; however, these did not reach statistical significance. Importantly, the load imposed on the inspiratory muscles is equal between patients with PH and controls (Table 3). In contrast, all volitional tests on respiratory muscle strength

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**Table 1** Anthropometric characteristics, lung function and exercise parameters in patients with PH and control subjects

<table>
<thead>
<tr>
<th>Control subjects</th>
<th>Patients with PH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>20/11</td>
<td>20/11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55.0 ± 12.2</td>
<td>56.5 ± 14.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 4.9</td>
<td>26.0 ± 5.5</td>
</tr>
<tr>
<td>ITGV (litres)</td>
<td>13.0 ± 17</td>
<td>99 ± 26</td>
</tr>
<tr>
<td>ITGV (% pred)</td>
<td>88 ± 17</td>
<td>99 ± 26</td>
</tr>
<tr>
<td>MEF₅₀ (% pred)</td>
<td>70 ± 13</td>
<td>84 ± 19</td>
</tr>
<tr>
<td>MEF₅₀ (% pred)</td>
<td>70 ± 13</td>
<td>84 ± 19</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>619 ± 79</td>
<td>407 ± 118*</td>
</tr>
<tr>
<td>BDS</td>
<td>0.2 ± 0.5</td>
<td>6.4 ± 2.4*</td>
</tr>
<tr>
<td>PaO₂ rest (mmHg)</td>
<td>77 ± 5</td>
<td>68 ± 9†</td>
</tr>
<tr>
<td>PaCO₂ rest (mmHg)</td>
<td>39 ± 3</td>
<td>35 ± 3†</td>
</tr>
<tr>
<td>PaCO₂ exercise (mmHg)</td>
<td>87 ± 8</td>
<td>64 ± 16†</td>
</tr>
<tr>
<td>PaO₂ exercise (mmHg)</td>
<td>38 ± 3</td>
<td>34 ± 4†</td>
</tr>
</tbody>
</table>

**Table 2** Haemodynamic and serological parameters in patients with PH

| Values are expressed as means ± S.D. PAWP, pulmonary artery wedge pressure. |
|------------------|------------------|--------|        |
| Control subjects | Patients with PH |        |
| n                | 31               |        |
| WHO functional class II/III/IV (n) | 2/23/6 |        |
| MPAP (mmHg)      | 51 ± 10          |        |
| PVR (dynes · s · cm⁻¹) | 759 ± 425 |        |
| PAWP (mmHg)      | 9 ± 5            |        |
| CVP (mmHg)       | 6 ± 3            |        |
| CI (litres · min⁻¹ · m⁻²) | 2.6 ± 0.5 |        |
| LVEF (%)         | 56 ± 8           |        |
| NT-proBNP (pg/ml) | 1117 ± 1456 |        |
| Uric acid (mg/dl) | 6.8 ± 2.6       |        |

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Table 3 Ventilatory characteristics and corresponding results for twitch pressures in patients with PH and control subjects

Values are expressed as means ± S.D. *n = 29.

<table>
<thead>
<tr>
<th></th>
<th>Control subjects</th>
<th>Patients with PH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>$P_{0.1}$ (kPa)</td>
<td>0.23 ± 0.10</td>
<td>0.28 ± 0.15</td>
<td>0.12</td>
</tr>
<tr>
<td>$P_{0.1}/F_{1}/V_{1}$ (kPa/litres/s)</td>
<td>0.5 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>0.68</td>
</tr>
<tr>
<td>$P_{trig}$ (kPa)</td>
<td>0.5 ± 0.1*</td>
<td>0.5 ± 0.1</td>
<td>0.74</td>
</tr>
<tr>
<td>$F_{trig}$ (ml/s)</td>
<td>32 ± 14*</td>
<td>32 ± 12</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Figure 1 Comparison of $P_{max}$, $P_{Emax}$, Sn$P_{na}$ and Sn$P_{di}$ in patients with PH and control subjects

Values are means ± 95% confidence interval.

revealed significantly reduced values in patients with PH compared with 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 results are given in Table 3 and Figure 2. Tw$P_{mo}$ 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 patients with PH. Group comparison revealed highly significant reductions in Tw$P_{mo}$ ($P < 0.001$) and Tw$P_{di}$ ($P = 0.001$) in patients with PH compared with controls (Figure 2).

The adequacy of twitch pressure assessment was assured in both patients with PH 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 PH

$P_{max}$ ($r = 0.58, P < 0.001$) and Sn$P_{di}$ ($r = 0.43, P = 0.02$), but not twitch pressures ($P > 0.05$ in both instances), were significantly correlated with 6MWD in patients with PH. The relationship between $P_{max}$ and 6MWD following linear regression analysis is shown in Figure 3. In contrast, haemodynamic characteristics assessed during right heart catheterization, including MPAP (mean pulmonary artery pressure), PVR (pulmonary vascular resistance), CVP (central venous pressure) and CI (cardiac index), were not correlated with 6MWD ($P > 0.05$ in all instances). Following stepwise multiple linear regression analysis, 6MWD can only be predicted from $P_{max}$ ($P < 0.01$), but not from either Tw$P_{mo}$ or
MPAP ($P > 0.8$ in both instances), considering $P_{\text{Imax}}$, $TwP_{\text{mo}}$ and MPAP.

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

For all instances, $P_{\text{Imax}}$ ($6.4 \pm 2.9$ compared with $5.3 \pm 2.2$ kPa), $P_{\text{Emax}}$ ($10.3 \pm 3.6$ compared with $8.1 \pm 1.9$ kPa), $SnP_{\text{na}}$ ($6.8 \pm 2.3$ compared with $5.5 \pm 1.5$ kPa), $SnP_{\text{di}}$ ($8.8 \pm 2.7$ compared with $7.9 \pm 2.0$ kPa), $TwP_{\text{mo}}$ ($1.00 \pm 0.43$ compared with $0.84 \pm 0.29$ kPa) and $TwP_{\text{di}}$ ($1.52 \pm 0.74$ compared with $1.17 \pm 0.54$ kPa) in patients with CTEPH ($n = 6$) had lower values of respiratory muscle strength compared with patients with PAH ($n = 25$). Owing to the low and unequal sample sizes, these results are purely descriptive without any further statistical analyses performed.

**DISCUSSION**

The present study establishes evidence of substantially impaired respiratory muscle function in a representative sample of patients with PH 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 with controls. These differences are more distinct considering non-volitional tests on inspiratory muscle strength, as reflected by $TwP_{\text{mo}}$ and $TwP_{\text{di}}$, compared with volitional tests.

The one previous study on respiratory muscle dysfunction in patients with PH only applied volitional tests to determine respiratory muscle function [7]. However, the definitive diagnosis of respiratory muscle weakness in patients with PH 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 a major clinical impact on patients suffering from PH. The application of combined respiratory and exercise training in patients with PH resulted in an improvement 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 in both inspiratory muscle strength and important clinical parameters, such as dyspnoea on exertion and quality of life [24,25]. Therefore future studies are needed to investigate possible improvements in respiratory muscle strength in patients with PH 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, only 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 as inspiratory muscle strength remains well preserved [4,28]. This is in clear contrast with the results of the present study in patients with PH in whom substantially reduced inspiratory muscle strength has been clearly established by a $34\%$ difference in non-volitionally assessed $TwP_{\text{mo}}$ compared with controls. Interestingly, patients with CTEPH had even more impaired respiratory muscle strength compared with patients with PAH; however, due to the low and unequal sample sizes between the two groups, the results are purely descriptive and are 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 in respiratory muscle strength in patients with PH have not yet been investigated conclusively. On the basis of 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 fibre type transformation predominantly pronounced in the diaphragm of patients with chronic left heart failure, have been reported [29]. Furthermore, fibre type changes associated with a myopathic pattern [30], cross-sectional muscle fibre reduction [31] and fast-to-slow transformations of myosin and regulatory proteins [32,33] in the diaphragm have also 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 under-perfusion of respiratory muscles and deoxygenation [36], has been described in chronic left heart failure. However, in contrast with patients with chronic left heart failure in previous studies, patients with PH in the present study had no relevant functional restrictions of the left heart, as can be seen by normal values for LEVF and PAWP (pulmonary artery wedge pressure). In addition, by taking into account the more reliable non-volitional tests on inspiratory muscle strength, the patients with PH in the present study are suggested to have more severely impaired inspiratory muscle strength compared with chronic left heart failure patients in 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
patients with PH, and further investigations are needed to confirm these suggestions. Importantly, none of the patients with PH in the present study suffered from malnutrition or wasting, as these factors are known to be potential confounders with regard to reduced respiratory muscle strength in chronic left heart failure [37]. Finally, patients with PH in the present study had 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 patients with PH. Interestingly, hypocapnia has recently been recognized as an independent marker of mortality in patients with PH [38].

The present study indicates that $P_{\text{max}}$ and $Sn\cdot P_{\text{di}}$ are significantly linked to exercise capacity in patients with PH. Interestingly, reduced inspiratory muscle strength, as assessed by $P_{\text{max}}$, 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 with patients with PH remains unclear and requires additional investigation.

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, whereas respiratory capacity tended to be reduced in patients with PH compared with controls. Importantly, no difference was observed in the effective inspiratory impedance between patients with PH and controls, indicating that the load imposed on the inspiratory muscles is not increased in patients with PH [14]. Therefore impairment of respiratory muscle function in patients with PH 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 patients with PH and control subjects. This was assured by the computer device outlined above. Importantly, pre-existing differences in ITGV as the best available measure of functional residual capacity between patients with PH and control subjects have been ruled out as a confounding factor. Both patients with PH and control subjects had ITGV values within the predicted normal range; however, there was a non-significant difference of approx. 0.3 litres in ITGV between patients with PH and control subjects. As it is known that $Tw\cdot P_{\text{di}}$ decreases by 0.34 kPa/litre change in ITGV [40], this difference might account for a reduction in $Tw\cdot P_{\text{di}}$ of 0.1 kPa for patients with PH compared with control subjects. However, this leaves 0.5 kPa difference unexplained and, therefore, the observed marked differences in respiratory muscle function between patients with PH and control subjects cannot be attributed to differences in lung volume. As lung volume correction has been established for $Tw\cdot P_{\text{di}}$ only and effects are suggested to be, at best, small, no further parameters of inspiratory muscle strength were corrected for lung volume.

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

In conclusion, the present study provides strong evidence that respiratory muscle strength is reduced in patients with PH compared with well-matched controls. Furthermore, 6MWD in patients with PH is significantly linked to parameters of inspiratory muscle strength.

ACKNOWLEDGMENTS

We thank all of the participants for their effort devoted to this study, Bruno Kopp on behalf of Pulmonale Hypertonie e.V. for their support, Roland Merklein (ZAN® GmbH, Oberthulba, Germany) for software assistance, Dr. Sandra Dieni for proofreading the manuscript prior to submission, and Stephanie Rubenbauer for statistical consultations. Support for this project was provided by a grant from the German Pulmonary Hypertension Group (Pulmonale Hypertonie e.V.), Rheinstetten, Germany.

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