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PULMONARY HYPERTENSION

# Physical activity in incident patients with pulmonary arterial and chronic thromboembolic hypertension

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## Abstract

**Introduction** The cardinal symptom of pulmonary hypertension (PH) is dyspnea on exertion, leading to decreased activity in daily living. The aim of this study was to analyze daily physical activity in incident patients with arterial or chronic thromboembolic PH (PAH/CTEPH) and to investigate its correlation with pulmonary hemodynamics, symptoms, exercise capacity, and other outcomes.

**Methods** Incident patients with PAH/CTEPH had a 1-week activity assessment by the arm-worn accelerometer SenseWear within − 3 months/+ 2 weeks of the diagnostic right heart catheterization (RHC) and baseline assessments including 6-minute walking distance (6MWD). Activity was correlated to RHC data at rest and exercise and to other outcomes.

**Results** Thirty-nine PH-patients (24 PAH, 15 CTEPH, 23 females, 65(54;73) years, mean pulmonary artery pressure (mPAP) 38(30;46) mmHg, cardiac output (CO) 5.2(4.6;6.3) l/min, 6MWD 458(300;593) m) were included. 64% had a sedentary lifestyle ( < 5000 steps/day), 26% were moderately active (5000–9999 steps/day), and 10% were active. In a multivariate stepwise regression analysis including age, gender, 6MWD and hemodynamics at rest and during exercise (heart rate, mPAP, stroke volume), the 6MWD was the only independent predictor of steps/day ($B = 16.8$ (95% CI 11.6–22.0), $p < 0.001$).

**Conclusion** Daily physical activity as steps/day assessed in incident patients with PAH/CTEPH did not well correlate with invasive hemodynamics at rest or during exercise, but very well with the 6MWD. Whether daily activity assessments provide additional information to simple walk distance on risk factor profiles during follow-up in patients with PAH/CTEPH remains to be clarified.

**Keywords** Physical activity · Pulmonary arterial hypertension · Actigraphy · Hemodynamics · Exercise · Pulmonary hypertension

## Introduction

Pulmonary hypertension (PH) is a chronic condition which leads to reduced exercise capacity, quality of life (QoL), and premature death. Precapillary PH has been recently redefined hemodynamically as a mean pulmonary artery pressure (mPAP) ≥ 20 mmHg, along with a pulmonary vascular resistance > 3 WU and a pulmonary artery wedge pressure (PAWP) < 15 mmHg. In the absence of relevant lung disease, the two major forms of precapillary PH are pulmonary arterial and chronic thromboembolic pulmonary hypertension (PAH/CTEPH) [1, 2]. Over the last decades, several medical treatment options have been approved for patients with PAH and recently, some also for CTEPH, a disease which can be considerably ameliorated or even hemodynamically cured with surgical pulmonary endarterectomy or balloon pulmonary angioplasty [3]. Despite these advances, PH remains a chronic disease associated with reduced exercise capacity and impaired quality of life and thus, additional supportive therapies are warranted. Strenuous activity and exercise training were discouraged until 2009 in patients with precapillary PH due to fear of exacerbated stress to the right ventricle and its subsequent failure. However, several recent studies have shown that a supervised training program is beneficial for PH-patients improving 6-minute walking

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distance (6MWD), maximal exercise capacity, and also QoL. The latest guidelines included a level IIa B statement recommendation on supervised exercise training in physically deconditioned PAH-patients under medical therapy [1].

Physical activity was defined by Capsersen et al. as "any bodily movement produced by skeletal muscles that results in energy expenditure". In the same statement, exercise is defined as a subcategory of physical activity, which is planned, structured and has a purpose [4]. A commonly used risk assessment and trial endpoint in PH is the 6MWD, which allows to measure a specific domain of activity, namely exercise capacity. According to the WHO Global Recommendations on Physical Activity for Health there are several domains included in physical activity, such as leisure-time activity, occupational activity, household activity, and commuting activity [5].

Physical activity can be measured in different ways: self-reported with questionnaires (often overestimates the level of physical activity) or by devices such as a pedometer or an accelerometer. Activity monitors have been validated in healthy and chronic diseases [6] including chronic lung diseases [7] to assess physical activity. The most accurate measuring method of physical activity is indirect calorimetry, but this is impracticable (breath-by-breath measures are needed) and expensive [7].

As increased physical activity has been shown to correlate with survival in patients with PAH/CTEPH [8], physical activity assessment might be a promising endpoint of clinical trials and serve as a risk parameter in PH. However, data on physical activity assessment in PH are scarce.

Therefore, the aim of this study was to analyze daily physical activity in incident patients with PAH/CTEPH, and to study its association with the 6MWD, invasive pulmonary hemodynamics, and symptoms.

## Methods

### Design and Patients

In this cross-sectional study incident patients newly diagnosed with PAH or CTEPH have been recruited in the PH-outpatient clinic of the University Hospital of Zurich from October 2014 until October 2018. All patients had invasive hemodynamic assessment by right heart catheterization (RHC) to diagnose precapillary PH and a full assessment to diagnose PAH or CTEPH according to current guidelines [1]. Patients with other forms of PH, especially those with PH due to lung or left heart disease were excluded.

All patients gave written informed consent to participate in the study. The study was approved by the local ethics committee and has been registered on clinicaltrials.gov (NCT02249806).

### Assessments and Outcomes

#### Clinical Assessment, Symptoms and 6-Minute Walking Distance

All patients had full clinical assessment including patients' history and clinical examination. New York Heart Association (NYHA) class was assessed by the treating physician. The 6MWD was performed according to the ATS guidelines [9].

#### Right Heart Catheterization

To assess the hemodynamics a balloon-tipped, triple-lumen, fluid-filled 7.5 Fr Swan Ganz catheter (Baxter/Edwards, Deerfield, IL) was introduced via the jugular vein [10]. Transducers were set at the mid-axillary line and zeroed to atmospheric pressure [11, 12]. The cardiac output (CO) was assessed by thermodilution (Baxter/Edwards) and CO/body surface area yielded the cardiac index (CI). The stroke volume (SV) was calculated as CO/heart rate (HR). The pulmonary vascular resistance (PVR) was calculated as: PVR = (mPAP-PAWP)/CO. Mean baseline measurements after 15 min of rest were noted as resting values [13]. Semi supine/supine cycling exercise was performed according to a symptom-limited, stepwise incremental protocol starting with a workload of 10 watts followed by an increase of 10 watts every 3 min (TheraVital, MedicaGMbH, Ravensburg) at a cycle rate of 60 revolutions/min. Measurements were taken during the last 30 s of each workload.

#### Activity Monitor

The 1-week activity monitoring was performed with SenseWear (Sensewear®, BodyMedia, Inc, Pittsburgh, Pennsylvania) on the non-dominant upper arm. This device was chosen as it delivers reliable data when worn at least 3 days weekly and it has been validated with indirect calorimetry [14, 15].

Patients were instructed to wear the device for 1 week and they were only allowed to take it off for having a shower or taking a bath. The device measures temperature, heat flux, and galvanic skin resistance, and is able to measure acceleration biaxial. Provided by a software from the manufacturer, the data are then linked to gender, age, body weight, and height using algorithms. The following physical activity parameters expressed as average per day are provided: steps, energy expenditure, metabolic equivalents (METs) (1MET is equivalent to 3.5 ml $O_2$/kg/min).

The main outcome was the number of steps per day. A common graduation used for physical activity level, according to achieved steps/day is [16]:

< 5000 steps per day: sedentary lifestyle.

5000–9999 steps per day: moderately active.

≥ 10,000 steps per day: active.

Additional outcomes were energy expenditure (kJ), active energy expenditure (3 METs expressed in kJ), METs and correlations of daily physical activity with the 6MWD, and invasive measured hemodynamics.

### Statistics

Data are shown as median and quartiles. Correlation coefficients between activity parameters and hemodynamics or other clinical assessment were calculated. Pearson correlations coefficients of 0–0.25 were considered as little, 0.25–0.5 as fair, 0.5–0.75 as moderate—good, and > 0.75 as very good—excellent [17]. Multivariate stepwise regression was performed with steps/day as dependent variable and clinically relevant independent variables, such as 6MWD, resting and exercise hemodynamics, as well as age and gender.

Data were analyzed with the statistical program SPSS 25 (SPSS, Chicago, IL, USA). A $p$-value < 0.05 was considered significant.

## Results

The study flow chart is shown in Fig. 1. Baseline characteristics of the 39 included patients are shown in Table 1.

All patients tolerated the SenseWear device without any problems and wore it for 5.9 (5.0;6.4) days (min. 4 days) on average during 23 h 44 min per day (23 h 11 min; 23 h 48 min).

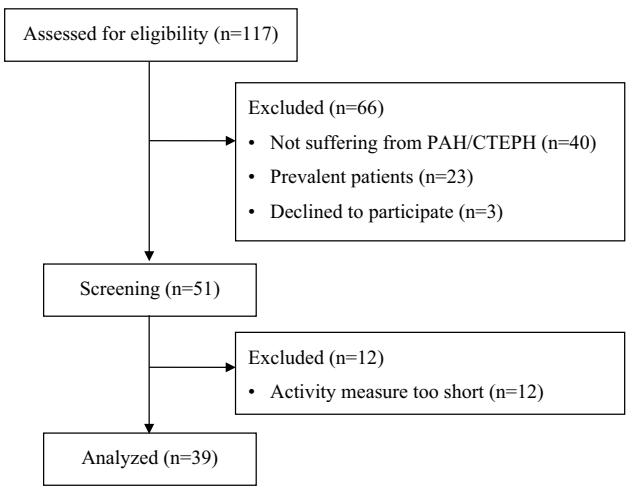


**Fig. 1** Study flow chart

Physical activity parameters are shown in table 2. Two third of PAH/CTEPH patients were inactive ( < 5000 steps/day), one quarter moderately active, and 10% active ( ≥ 10,000 steps/day). Correlations between physical activity and the 6MWD and invasive hemodynamics at rest and at maximal exercise are shown in Tables 3 and 4. The strongest correlations were found between the 6MWD and steps per day.

In addition, oxygen saturation at rest showed a significant positive correlation with steps per day. A statistically significant, but weaker correlation was found between the 6MWD with total and active energy expenditure and oxygen saturation at rest and total energy expenditure, respectively (Table 3). There was no statistically significant correlation between mPAP or PVR at rest and any measure of daily physical activity. Whereas there was no correlation between CO and steps per day, there were significant fair or moderate positive correlations of CO at rest and maximal exercise with measures of energy expenditure. Correlations of steps/day with 6MWD respectively PVR are shown in Fig. 2.

We further checked for seasonal differences of patients' activity, however, we found no correlation of season and steps/day ($r = -0.091$, $p = 0.581$).

In a multivariate stepwise regression analysis including age, gender, 6MWD, and hemodynamics at rest and exercise (HR, mPAP, SV), the 6MWD was the only independent predictor of steps/day ($\beta = 16.8$ (95% CI 11.6–22.0), $p \leq = 0.001$).

In table 5 we divided the patients according to steps/day and listed clinical parameters and resting hemodynamics according to steps/day.

## Discussion

According to our knowledge this is the first study investigating the association of daily physical activity in incident patients with PAH/CTEPH with prognostic parameters such as functional status, 6MWD, and invasive hemodynamics at rest and during exercise. We found an excellent and highly significant correlation of steps/day with the 6MWD, but also with HR and CO maximal exercise during RHC.

The majority of patients with PAH or CTEPH investigated in the present study were fairly inactive. The median steps/day of 3534 (1638;7579) in our cohort is lower compared to a previous published study in prevalent PAH/CTEPH (4976.7 steps/day) [18]. This cohort of patients with PAH/CTEPH was less active compared to patients with heart failure assessed with SenseWear, where 50% of the patients made < 5000 steps/day, 35% performed 5000–9999 steps/day and 15% more than 9999 steps/day [19]. The same

**Table 1** Patients characteristics ($n=39$)

| | |
|---|---|
| Gender (women/men) | 23/16 |
| Age (years) | 65 (54;73) |
| Body mass index (kg/m$^2$) | 26.1 (22.1;29.1) |
| Pulmonary arterial hypertension (PAH) | 24 (61.6) |
| – Idiopathic PAH | 14 (35.9) |
| PAH associated with | |
| – Connective tissue disease | 7 (17.9) |
| – Portal hypertension | 2 (5.1) |
| – Schistosomiasis | 1 (2.6) |
| Chronic thromboembolic pulmonary hypertension | 15 (38.5) |
| NYHA functional class I/II/III/IV | 1/13/21/4 |
| 6-Minute walking distance (6MWD) (min) | 458 (300;593) |
| Oxygen saturation at rest (%) | 96 (94;97) |
| Oxygen saturation at end 6MWD (%) | 92 (84;94) |
| Hemodynamics by right heart catheterization (RHC) at rest | |
| Heart rate (bpm) | 74 (68;82) |
| Mean pulmonary artery pressure (mPAP) (mmHg) | 38 (30;46) |
| Pulmonary artery wedge pressure (mmHg) | 12 (11;14) |
| Pulmonary vascular resistance (WU) | 5.0 (3.6;6.8) |
| Cardiac output (l/min) | 5.2 (4.6;6.3) |
| Cardiac index (l/min/m$^2$) | 2.9 (2.6;3.5) |
| Stroke volume (ml) | 69.7 (57.5;92.9) |
| Hemodynamics by RHC at maximal exercise | |
| Maximal workload achieved during stepwise incremental cycling exercise (watt) | 45 (30;77.5) |
| Heart rate (bpm) | 116 (98;130) |
| Mean pulmonary artery pressure (mmHg) | 60 (52;72) |
| Pulmonary artery wedge pressure (mmHg) | 15 (12;19) |
| Pulmonary vascular resistance (WU) | 6.9 (4.9; 9.7) |
| Cardiac output (l/min) | 6.9 (5.0;8.2) |
| Cardiac index (l/min/m$^2$) | 3.9 (2.9;4.4) |
| Stroke volume (ml) | 62.4 (46.5;77.0) |

Data are given as number (%) or median (interquartile range)

*NYHA* New York Heart Association

**Table 2** Average daily physical activity data

| | |
|---|---|
| Steps | 3534 (1638;7579) |
| $<5000$ steps/day (sedentary) ($n$) | 25 (64.1) |
| 5000–9999 steps/day (moderately active) ($n$) | 10 (25.6) |
| $>10{,}000$ steps/day (active) ($n$) | 4 (10.3) |
| Energy expenditure (kJ) | 8544 (7753;10,188) |
| Active energy expenditure (kJ) | 678 (132;1790) |
| Metabolic equivalent units | 1.2 (1.1;1.4) |
| Daily activity up to 3METs (h) | 22.6 (20.7;23.4) |
| Daily activity 3 to 6METs (h) | 0.7 (0.2;1.7) |

Data are given as $n$ (%) or median (Interquartile range)

Metabolic equivalent units (1MET is 3.5 ml $O_2$/kg/min)

is true for the comparison with sarcoidosis patients who walked on average $7490 \pm 3007$ steps/day [20]. However, these patients were on average younger (50 years) and had a longer 6MWD ($525 \pm 85$ m) compared to the hereby presented PAH/CTEPH-collective.

Steps per day depend on age, as has been stated in a review on activity in healthy older adults ($\geq 50$ years), which were found to perform 2000–9000 steps/day. In the presence of a chronic disease, such as diabetes or COPD, the average daily steps decline to 1200–8800 [21], which is in the range shown in the current cohort of PAH/CTEPH.

Mainguy et al. compared daily physical activity of idiopathic PAH and PAH associated with systemic sclerosis to the 6MWD. Similarly to our study steps/day correlated well with the 6MWD ($r=0.76$ in idiopathic PAH and $r=0.85$ in PAH with systemic sclerosis) [22]. Interestingly, those PH-patients had a comparable physical activity when expressed

**Table 3** Correlations between physical activity parameters, 6-minute walk test, and hemodynamics at rest ($n=39$)

| | Steps/day | Energy expenditure (EE) (kJ) | Active EE/ day (kJ) | Daily activity up to 3 METs (min) | Daily activity 3 to 6 METs (min) |
|---|---|---|---|---|---|
| 6MWD (min) | 0.834** | 0.439** | 0.450** | −0.283 | 0.460** |
| $SpO_2$ at rest (%) | 0.544** | 0.415* | 0.282 | −0.292 | 0.343* |
| $SpO_2$ end 6MWD (%) | 0.038 | 0.015 | 0.082 | − 0.034 | −0.214 |
| Heart rate (bpm) | −0.186 | −0.364* | − .0216 | 0.188 | −0.227 |
| mPAP (mmHg) | −0.115 | −0.248 | −0.088 | 0.081 | −0.130 |
| PAWP (mmHg) | 0.024 | −0.317* | −0.208 | 0.192 | − 0.214 |
| PVR (WU) | −0.203 | −0.309 | −0.199 | 0.164 | −0.216 |
| CO (l/min) | 0.233 | 0.435** | 0.387* | −0.243 | 0.397* |
| SV (ml) | 0.309 | 0.592** | 0.480** | − 0.308 | 0.481** |

*6MWD* 6-minute walking distance, *mPAP* mean pulmonary artery pressure, *PAWP* pulmonary artery wedge pressure, *PVR* pulmonary vascular resistance, *CO* Cardiac output, *CI* cardiac index, *MET* Metabolic equivalent units (1MET is 3.5 ml $O_2$/kg/min)

*$p<0.05$, **$p<0.01$

**Table 4** Correlations between physical activity parameters and hemodynamics at maximal exercise ($n=30$)

| | Steps/day | Energy expenditure (EE) (kJ) | Active EE/ day (kJ) | Daily activity up to 3 METs (min) | Daily activity 3 to 6 METs (min) |
|---|---|---|---|---|---|
| Watts | 0.467** | 0.401* | 0.289 | −0.184 | 0.321 |
| Heart rate (bpm) | 0.570** | 0.248 | 0.251 | −0.210 | 0.273 |
| mPAP (mmHg) | 0.163 | −0.057 | 0.053 | 0.013 | 0.016 |
| PAWP (mmHg) | −0.123 | −0.251 | −0.099 | 0.203 | −0.064 |
| PVR (WU) | −0.257 | −0.391* | −0.263 | 0.293 | −0.313 |
| CO (l/min) | 0.500** | 0.577** | 0.384* | −0.304 | 0.418* |
| SV (ml) | 0.191 | 0.431* | 0.228 | −0.179 | 0.255 |
| mPAP increase | 0.243 | 0.268 | 0.211 | −0.146 | 0.231 |
| CO increase | 0.424* | 0.387* | 0.166 | −0.195 | 0.190 |

*mPAP* mean pulmonary artery pressure, *PAWP* pulmonary artery wedge pressure, *PVR* pulmonary vascular resistance, *CO* Cardiac output, *CI* cardiac index, *MET* Metabolic equivalent units (1MET is 3.5 ml $O_2$/kg/min)

*$p<0.05$, **$p<0.01$

in steps/day compared to our cohort, however 6MWD was shorter. Idiopathic PAH had 401 ± 89 m and PAH associated with systemic sclerosis performed 349 ± 129 m. Half of the patients in our cohort had a 6MWD of > 440 m, the other half had a 6MWD of 165–440 m and only one patient had a very reduced 6MWD of < 165 m, using these cut-off values of the risk assessment tool from the current guidelines, patients of this trial were in the low to intermediate risk group.

Our study focused on correlations between physical activity and hemodynamics in PH, a disease defined by resting hemodynamics assessed during RHC [2]. However, the severity of PH, in terms of how much a patient is limited in his daily life, is not necessarily explained by the hemodynamic severity. There is a global shift in perspective from physiological measure to the level of functioning in many diseases and also PH. The WHO is currently working on the ICD 11 with the goal of combining these two aspects. Assessing daily physical activity by an accelerometer allows measuring what a patient is effectively able to perform in his daily life.

Up to now, no recommendations about the optimal physical activity level in patients with PH exist. A recommended type and level of activity might not solely depend on hemodynamics—especially not on the mere extent of pulmonary artery pressure. Indicative therefore is the weak correlation of activity with hemodynamics found in our PAH/CTEPH cohort. Age, disease severity and risk status, and comorbidities may be relevant and the recommendation for PH-patients may differ from healthy and other cardio-respiratory disease. PH-patients are often severely limited in their exercise capacity; however it remains unclear if a recommendation such as for other cardiac patients with

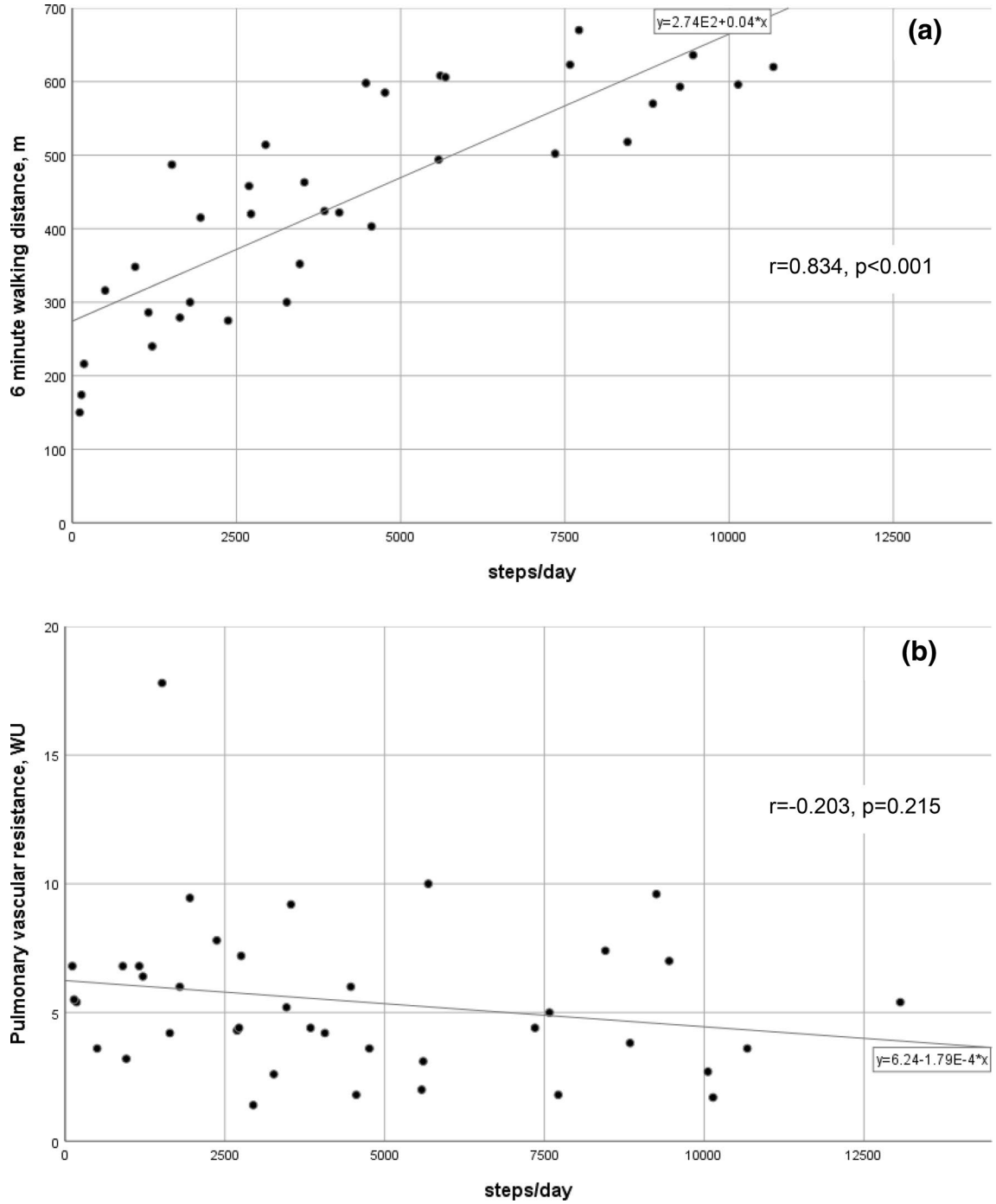


**Fig. 2** Correlation of steps/day versus 6-minute walking distance, four missing values because patients did not perform the 6-minute walking distance (**a**) and pulmonary vascular resistance (**b**)

30 min/day of moderate to vigorous activity [23] would also be suitable for PH-patients.

Two studies used the Human Activity Profile (HAP) [24], a self-administered questionnaire which was validated mostly by comparing the values with the peak oxygen consumption, which is a measure of maximal exercise performance and not physical activity [25]. PAH-patients significantly increased their maximum Activity Score and the Adjusted Activity Score (HAP scores) after 10 weeks of aerobic exercise training.

Another study assessed fatigue and physical activity in stable PAH/CTEPH patients by questionnaires, an activity monitor (ActiGraph wGT3X-BT) and an activity diary showed that 85% of these patients were sedentary. In that

**Table 5** Comparison of patients' characteristics and resting hemodynamics according daily physical activity

| | < 5000 steps/day (sedentary lifestyle) | ≥ 5000 steps/day (moderately active) |
|---|---|---|
| *n* | 25 | 14 |
| Gender (female/male) | 15/10 | 8/6 |
| Age (years) | 69 (57;73) | 56 (37;71) |
| Body mass index (kg/m$^2$) | 26.5 (22.6;29.3) | 24.7 (21.0;28.4) |
| NYHA functional class I/II/III/IV | 0/6/16/3 | 1/7/5/1 |
| 6-Minute walk distance, meter | 352 (279;458) | 601 (531;622)* |
| Oxygen saturation at rest (%) | 95 (94;96) | 98 (96;98)* |
| Oxygen saturation at end 6MWD (%) | 91 (84;94) | 93 (85;96) |
| Heart rate (bpm) | 75 (69;82) | 74 (65;80) |
| Mean pulmonary artery pressure (mmHg) | 38 (30;50) | 35(28;45) |
| Pulmonary artery wedge pressure (mmHg) | 12 (11; 13.5) | 12.5 (10.0;14.3) |
| Cardiac output (l/min) | 5.2 (4.4;6.3) | 5.5 (4.9;7.0) |
| Stroke volume (ml) | 65.9 (55.8;87.8) | 72.3 (63.5;113.4) |

*$p < 0.001$ non parametric test Mann–Whitney-*U*-Test between groups

study, the energy score assessed by a questionnaire and the average activity level by actigraphy, as well as activity bouts by actigraphy and the 6MWD were correlated [26]. Another study in prevalent PAH or CTEPH patients compared activity monitor data (measured with SenseWear) with quality of life (QoL), 6MWD and questionnaire of activity in daily living (activity diary). The study only found weak to moderate correlations of activity monitor parameters with the 6MWD and QoL measures [27]. Thus, available evidence about physical activity levels, its assessment and the correlation with other factors of disease severity in PH is scarce.

It remains unclear if physical activity should be used as an additional assessment in patients with PAH/CTEPH, especially because the 6MWD correlated well with the steps/day in the current study. The 6MWD is still a validated, useful and easily applicable tool, for the assessment of patients with PH, and not every center can provide measuring physical activity with an accelerometer.

Future studies should test whether accelerometers are a feasible tool to detect clinically important changes in these patients in the course of their disease or in response to therapeutic interventions and verify its prognostic relevance.

Limitations of our study were the relatively small number of patients and the fact that 12 patients had to be excluded due to invalid (recording too short: median/IQR 1 day 22 h 42 min (1 day 1 h 45 min; 2 days 17 h 17 min) physical activity measurements. Patients in the current trial suffered from mild to moderate PAH and CTEPH with a relatively preserved exercise capacity, whether the results would be the same in severe PAH and CTEPH remains unclear.

The current study focused on newly diagnosed patients in the rare diseases PAH and CTEPH in order to compare activity with invasive hemodynamics. As our cohort had activity only assessed at baseline, we do not know whether activity level would change with therapy during follow-up. Since physical inactivity is a known indicator for global mortality [5] and may also be relevant in patients with PAH and CTEPH [8], it may well be worth to study the prognostic value and therapeutic effects on physical activity during follow-up in PAH and CTEPH patients.

## Conclusion

Daily physical activity as steps/day assessed in patients newly diagnosed with PAH/CTEPH did not well correlate with invasive hemodynamics at rest nor exercise, but very well with the 6MWD. Whether daily activity assessments provide additional information to other known prognostic factors such as 6MWD during follow-up in patients with PAH/CTEPH remains to be clarified.

## Compliance with Ethical Standards

**Conflicts of interest** Prof. Dr. Ulrich reports grants from Zurich Lung League, grants from Swiss National Science Foundation, during the conduct of the study; grants and personal fees from Actelion SA, personal fees from Bayer SA, personal fees from MSD, grants and personal fees from Orpha Swiss, outside the submitted work. All other authors declare that they have no conflicts of interest.

**Research Involving Human Participants and/or Animals** All procedures performed in studies involving human participants were in accordance with the ethical standards of the local ethics committee (Zurich ethics committee KEK-ZH Nr. 2014–0214) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed Consent** Informed consent was obtained from all individual participants included in the study.

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