Title: **A study of clinical and physiological relations of daily physical activity in precapillary pulmonary hypertension.**

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Abstract

Daily physical activity becomes reduced in precapillary pulmonary hypertension (PH) but the underlying mechanisms are inadequately explored. We sought to investigate clinical and physiological relations of daily physical activity and profile differences between less and more active patients with precapillary PH. A prospective, cross-sectional study of 20 patients with precapillary PH who undertook a) a comprehensive clinical assessment, b) a preliminary treadmill test, c) 7-day monitoring of daily walking intensity with triaxial accelerometry and d) a personalized treadmill test corresponding to the individual patient mean daily walking intensity with real-time physiological measurements. Significant clinical correlations with individual patient mean walking intensity (1.71±0.27 m/s^2) were observed for log N-terminal pro-brain natriuretic peptide (log-NTproBNP: r=-.75, p=<.001), age (r=-.70, p=.001), transfer factor for carbon monoxide %predicted (r=.51, p=0.022) and 6-minute walk distance (r=.50, p=.026). Significant physiological correlations were obtained for heart rate reserve (r=.68, p=.001), quadriceps tissue oxygenation index (Q-StO_2: r=.58, p=.008), change in Q-StO_2 from rest (r=.60, p=.006) and ventilatory equivalent for oxygen uptake (r=-.56, p=.013). Stepwise multiple regression analyses retained log-NTproBNP (R^2=0.55), heart rate reserve (R^2=0.44) and Q-StO_2 (R^2=0.13) accounting for a significant variance in individual walking intensity. Less active patients had greater physical activity-induced cardiopulmonary impairment, worse quadriceps oxygenation profile and compromised health-related quality of life compared to more active patients. These preliminary findings suggest a significant relation between right ventricular and peripheral muscle oxygenation status and reduced daily physical activity in precapillary PH. Further

research is warranted to unravel the physiological determinants, establish clinical predictors, and identify beneficial interventions.

New & Noteworthy

Daily physical activity holds promise to be meaningful, patient-related outcome measure in pulmonary hypertension. Herein, novel findings in a representative sample of patients with precapillary pulmonary hypertension link reduced daily walking activity, as measured by triaxial accelerometry with compromised right ventricular and pulmonary vascular status, peripheral muscle oxygenation and health-related quality of life. Thus, this study provides preliminary insight into the physiological mechanisms and clinical predictors of daily physical activity in precapillary pulmonary hypertension.

Keywords: pulmonary arterial hypertension, daily physical activity, right ventricle, skeletal muscle oxygenation.

Introduction

Precapillary pulmonary hypertension (PH) comprises primarily pulmonary arterial hypertension (PAH; group 1) and chronic thromboembolic pulmonary hypertension (CTEPH; group 4) and is characterised by progressive elevation of vascular resistance in the precapillary pulmonary vasculature and right heart failure (13). Despite important advances in the understanding and targeted therapy to date, the morbidity and mortality in precapillary PH remain high: typically, patients suffer progressive dyspnoea, impaired exercise capacity and health-related quality of life (HRQoL), and premature death (1, 13, 37).

Physical activity is defined as the bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above the basal level and can be described by dimensions of intensity, frequency, duration, mode and context (14). Daily physical activity is an important dimension of HRQoL in cardiopulmonary disease (10, 43) and satisfies the core requirement of a meaningful patient-centered endpoint in clinical trials, defined to be a direct measure of how a patient "feels, functions or survives" where "function" refers to the ability to carry out normal daily activities (15). Accordingly, enhancement of daily physical activity is recommended in PH (13); however, research shows significantly reduced daily physical activity in patients with precapillary PH compared to healthy controls and poorer survival in more sedentary patients (21, 36, 39, 45).

The causes of reduced daily physical activity in PH are not adequately explored. Our perception on the underlying mechanisms remains intuitively focused on pulmonary vasculopathy and right ventricular dysfunction and limited to extrapolations from

79 standardized exercise testing (40), which may not correspond well to daily physical
80 activity (28, 47). Importantly, the role of peripheral muscles has not been investigated.
81 This is despite growing evidence on skeletal muscle abnormalities in PAH (31) and
82 recent findings suggesting that estimates of skeletal muscle oxygenation may reflect the
83 pathophysiology of PAH (32, 33). Importantly, the surrogate value of common clinical
84 tools in precapillary PH in the prediction of daily physical activity is not well established.

85 The purpose of this study was therefore to explore the physiological mechanisms and
86 predictors of reduced physical activity in precapillary PH. To this aim, we investigated
87 relations of patient daily walking intensity as measured by accelerometry with a) routine
88 clinical measures and b) cardiopulmonary and peripheral muscle physiological responses
89 during laboratory exercise corresponding to individual daily walking intensities. We also
90 explored profile differences between less and more active patients. We hypothesized that
91 along with pulmonary vasculature and right ventricular status, peripheral muscle function
92 might be a pertinent factor to reduce daily physical activity in precapillary PH.

93 **Materials & Methods**

94 Study Sample

95 Consecutive patients with stable PAH and technically non-operable (distal) CTEPH
96 who attended the Scottish Pulmonary Vascular Unit between November 2014 and
97 October 2015 were eligible. The diagnosis had been previously established by right heart
98 catheterisation as recommended (13). Clinical stability was defined as a) no
99 hospitalization for precapillary PH and b) no escalation in therapy for PH or diuretics
100 within 3 months. Exclusion criteria were pulmonary endarterectomy or comorbidities

interfering with physical activity and treadmill testing. Approval from the West of Scotland Research Ethics Committee (14/WS/1075) and written consent were obtained.

Initial evaluation

Subjects had determination of WHO functional class, maximum voluntary ventilation (MVV=FEV_1 x 35) (1) and transfer factor for carbon monoxide (TLCO) corrected for haemoglobin concentration. (19). They also completed the patient-reported Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) (25) and emPHasis-10 (48), two well-validated questionnaires for the assessment of HRQoL in PH. CAMPHOR is probably the most widely studied questionnaire in PH and has been shown to predict clinical deterioration in idiopathic PAH and CTEPH (24). However, neither CAMPHOR nor emPHasis-10 questionnaires have been validated against objective, accelerometry measures of daily physical activity to date.

Finally, N-terminal pro-brain natriuretic peptide (NTproBNP) and 6-minute walk distance (6MWD) were retrieved from the medical record (median interval: 30 days for both).

Preliminary treadmill test

Subjects performed an incremental treadmill test (RAM 770M; RAM Medical and Industrial Instruments & Supplies, Padova, Italy) at an initial speed of 1.4 km/h that increased by 0.8 km/h every 3 minutes to the limit of tolerance as previously described (17, 18). The treadmill speed was determined by a communicating ergospirometry testing system (CASE ES, GE Healthcare, Freiburg, Germany). Minute-by-minute walking intensity was measured concurrently in units of acceleration (m/s^2) using a triaxial

123 activity monitor (DynaPort MoveMonitor; McRoberts, Netherlands). In this manner, a
124 range of intensities was obtained at various speeds and a graph of walking intensity
125 against treadmill speed was plotted for each patient. This was used to calculate a
126 treadmill speed corresponding to each patient's mean daily walking intensity, as
127 described below.

128 Accelerometry

129 Subjects were fitted with DynaPort accelerometers attached to an elastic strap and
130 positioned over L2 vertebra (an approximation of body's center of mass) to record their
131 daily walking intensity continuously for 7 days, excluding sleep and water-based
132 activities. Measurements were considered sufficient if technically acceptable signal was
133 obtained daily for a minimum of 12 consecutive hours, during 5 consecutive days (18,
134 34).

135 The DynaPort is a validated accelerometer that provides reliable measures of physical
136 activity including postures, steps and movement intensities even under sedentary
137 conditions (5, 37, 46). The intensity with which a person carries out activities of daily
138 living is a fundamental part of recommendations for health maintenance (14) and an
139 important aspect of the overall physical activity (17, 18).

140 Personalized treadmill test

141 Within 2 weeks, patients underwent a final, three-stage treadmill protocol during
142 which they sequentially: a) stood still on treadmill, b) warmed up at a speed of 1.4 km/h,
143 and c) walked at a predetermined treadmill speed corresponding to their individual daily
144 walking intensity (calculated by using the data from the preliminary test and monitoring

of daily walking intensity). The duration of each stage was 4 minutes in order to reach steady physiological state (18). Continuous physiological measurements were obtained throughout as described below. The resting and exercise value for each variable was the average value obtained during the last minute of the first and third stage, respectively.

Metabolic profile

Oxygen uptake (VO_2), minute ventilation (V_E) and ventilatory equivalent ratio for oxygen uptake (V_E/VO_2) and carbon dioxide (V_E/VCO_2) were recorded breath-by-breath (CASE ES, GE Healthcare, Freiburg, Germany). Oxyhaemoglobin saturation (SpO_2) was recorded continuously by pulse oximetry (Oxywatch^{TM} MD300C63, Beijing Choice Electronic Tech. Co. Ltd, China). Electrocardiography was used to calculate heart rate (HR) reserve (HRR) defined as the difference between age-predicted maximal HR (220-age) and peak HR (1).

Central hemodynamics

Estimates of stroke volume and cardiac output were measured using impedance cardiography technology (PhysioFlow®, Manatec Biomedical, France). PhysioFlow uses variations in the transthoracic impedance to a high-frequency (75 kHz), low-amperage (1.8 mA) alternating current across the thorax during cardiac ejection to calculate stroke volume (4) and it has been previously validated (42) and used in PAH (12). Application of six transthoracic electrodes, autocalibration, verification of signal quality and artifact detection were performed as instructed by the manufacturer and described elsewhere (4).

Quadriceps oxygenation

Quadriceps tissue oxygenation index ($Q\text{-}StO_2$), as an expression of the local

167 microvascular oxygenation status, was measured using spatially resolved near infrared
168 spectroscopy (NIRO-200NX®, Hamamatsu Photonics KK, Japan). Tissue oxygenation
169 index is essentially the ratio of oxygenated to total tissue hemoglobin concentration
170 expressed as [oxyhaemoglobin/(oxyhaemoglobin + deoxyhaemoglobin)] × 100 (%) and
171 represents an index of the dynamic balance between local tissue oxygen delivery and
172 utilisation in health and disease (3, 23). We have previously shown strong correlations
173 between Q-StO_2 and mixed venous oxygen saturation measured at pulmonary artery in
174 PAH subjects, both at rest and exercise (32, 33).

175 To measure Q-StO_2, one transcutaneous probe (S-type) housed in a black rubber
176 holder and fixed using a double-sided adhesive tape, was placed on the belly of each
177 vastus lateralis muscle, 10-12 cm above the lateral epicondyle. The values shown for Q-
178 StO_2 are the average from both legs. Estimated systemic oxygen delivery was calculated
179 as the product of cardiac output and arterial oxygen content; the latter was calculated as
180 the product of 1.34 × hemoglobin concentration × %SpO_2. The systemic arteriovenous
181 oxygen content difference (a-vO_2 difference) was calculated by dividing oxygen uptake
182 by cardiac output (Fick principle) whereas the systemic oxygen extraction ratio was
183 calculated as the ratio of the a-vO_2 difference to arterial oxygen content (18).

184 **Statistical analysis**

185 Data are reported as means ± SD or median with 95% confidence interval of median.
186 NTproBNP was log-transformed due to positive skewing. Associations of mean daily
187 walking intensity were examined using the Pearson's correlation coefficient. Significant
188 parameters were further tested using stepwise multiple regression analysis. Patients were

dichotomised using the median daily walking intensity for an unpaired group comparison using the Mann-Whitney *U*-test. Data were analyzed using the SPSS statistical package (v 20, SPSS Inc., Chicago, IL). The level of significance was set at $p<.05$. On the basis of data from a previous study (18), the critical sample size to achieve a power of 80% for detection of differences between patient groups with two-sided level of significance <.05 was 16 patients (calculated using the Stata package; StataCorp LP, Texas, USA).

Results

Patient characteristics

Patients characteristics are presented in Table 1. Twenty patients enrolled, completed the protocol without adverse effects and included in the analysis (Figure 1). Stroke volume profile of 3 (15%) patients had to be excluded due to invalid impedance cardiography signal. Sixteen patients had PAH (9, idiopathic PAH; 6, connective tissue disease associated-PAH; 1, PAH after correction of congenital heart disease) and 4 patients had CTEPH. None of the patients had significant cardiac shunt detected at right heart catheterisation or follow-up echocardiograms. All patients were on PH-specific therapy: 10, monotherapy (7, phosphodiesterase-5 inhibitor (PDEi); 2, stimulator of soluble guanylate cyclase (sGC); 1, endothelin receptor antagonist (ERA)) and 10, combination therapy (6, PDE-i+ERA; 1, ERA+sGC; 3, PDEi+ERA+inhaled prostanoid). None of the patients was on heart rate-limiting medication.

Total and daily time of accelerometry monitoring were 6.4±0.94 days and 864±94 min, respectively. Mean and median daily walking intensity were 1.71±0.27 m/s^2 and 1.78 (1.55, 1.83) m/s^2, respectively. Daily walking time was 61±26 min and daily steps 4897±2209.

Correlations and predictors of daily walking intensity

Significant clinical correlations with mean daily walking intensity were observed for log-NTproBNP (r=-.75, p=<.001), age (r=-.70, p=.001) and 6MWD (r=.50, p=.026) (Table 1; Figure 2). Significant physiological correlations with mean daily walking intensity were observed for HRR (r=.68, p=.001), Q-StO_2, (r=.58, p=.008), change in Q-StO_2 from rest to mean daily walking intensity (r=.60, p=.006), V_E/VO_2 (r=-.56, p=.013) and TLCO %predicted (r=.51, p=0.022) (Table 2; Figure 2). There was no association between estimates of stroke volume at rest or exercise and mean daily walking intensity

Stepwise multivariate regression analysis of significant clinical measures retained log-NTproBNP (b=-.290±.068, β=-.554, p=.001) and age (b=-.008±.002, β=-.486, p=002) accounting for 55% and 20% of the variance in mean daily walking intensity, respectively. Repeated for the significant physiological measures, analysis retained HRR (b=.006±.002, β=.506, p=.015) and Q-StO_2 at activity (b=.01±.005, β=.395, p=.049) accounting for 44% and 13% of the variance in mean daily walking intensity, respectively.

Comparison between less and more active patients

There was no significant difference in VO_2 between less and more active patients. Less active patients had significantly increased age, log-NTproBNP, V_E/MVV, V_E/VO_2, CAMPHOR and emPHasis-10 scores and decreased TLCO %predicted, HRR, Q-StO_2 at mean daily walking intensity and Q-ΔStO_2; they also showed 100-meter reduction in 6MWD compared to more active patients (for all numerical values and P-values see Table 1 and 2).

Discussion

This exploratory study in a representative cohort with precapillary PH, reports on significant associations of indices of right ventricular (log-NTproBNP, HRR) and pulmonary vascular (TLCO %predicted) status with mean daily walking intensity. In exercise conditions reproducing individual daily physical activity levels, measures of quadriceps oxygenation ($Q\text{-}StO_2$ at activity, $\Delta Q\text{-}StO_2$) and ventilatory efficiency (V_E/VO_2) were also associated significantly with mean daily walking intensity. log-NTproBNP, HRR and $Q\text{-}StO_2$ at mean activity levels predicted a significant variance in mean daily walking intensity. Finally, the profile of less active patients comprised greater cardiorespiratory impairment, worse quadriceps oxygenation profile and compromised HRQoL compared to more active patients.

Walking intensity is an important aspect that a patient with lung disease adopts in daily living For example, numerous studies (Watz et al ERJ 2014; 44(6): 1521-1537) have emphasized the finding that the intensity of movement adopted by COPD patients during walking is reduced by an average 0f 17 to 33% compared to healthy age-matched individuals. Daily walking intensity in the present cohort (1.7 m/s^2) favorably compares with that adopted by older patients with moderate/severe COPD (spirometric classes II/III), typically corresponding to 1.8 m/s^2 (18, 34). Overall, the present population adopted a sedentary (most commonly) or low-active lifestyle defined as daily steps of <5000 and between 5000-7500, respectively (43). This adds to previous evidence (21, 36, 39, 45) on reduced measures of daily physical activity in precapillary PH.

The hemodynamic profile in precapillary PH depends mostly on the right ventricular

257 performance (16). NT-proBNP, a nonspecific marker of myocardial dysfunction, is
258 considered an indicator of the right ventricular status and a prognostic marker at
259 diagnosis and during follow-up in precapillary PH (13). Out of 35 variables, NT-proBNP
260 was also the strongest predictor of peak VO_2 and a significant predictor of 6MWD in
261 patients with chronic heart failure (11). In line, we observed a strong negative correlation
262 between log-NTproBNP and mean daily walking intensity whereas log-NTproBNP
263 predicted more than half of the variance in mean daily walking intensity and it was
264 significantly higher in less active patients.

265 Heart rate profiles in precapillary PH are though to reflect the burden of the right
266 ventricle (16). In the setting of right ventricular failure and ensuing fixed/reduced stroke
267 volume, patients with precapillary PH become dependent on compensatory increase in
268 HR responses to maintain or increase cardiac output and preserve tissue oxygenation (16).
269 Hence, the HR-VO_2 relationship in precapillary PH is left-shifted with submaximal HR
270 values trending higher than normal (1). Accordingly, chronotropic response (peak
271 walking HR minus resting HR) and resting HR in PAH, have been independently
272 associated with 6MWD (35) and prognosis (16), respectively. Here, we extend these
273 findings by showing a strong relation between HRR and mean daily walking intensity
274 and significantly reduced HRR in less active

275 patients compared to more active patients. HRR also predicted almost half of the
276 variance in individual mean daily walking intensity.

277 The higher HR accounted for the higher cardiac output in less active patients in the
278 present study; estimates of stroke volume did not differ between less and more active

patients and it was dissociated with daily walking activity. Cardiac output as such also did not correlate with daily walking intensity in the present cohort. Previous studies using right heart catheterisation data also failed to show correlation between cardiac output/index and daily physical activity levels in precapillary PH (21, 36). In contrast, TLCO %predicted, reflecting pulmonary capillary volume, was also negatively associated with mean daily walking intensity and 40% lower in less active patients. Collectively, our findings on NT-proBNP and HRR profiles and, TLCO %predicted speak for a significant relation between the right ventricular and pulmonary capillary volume status and daily physical activity in precapillary PH.

The ventilatory response becomes exaggerated in precapillary PH due to chemo/ergo/baro- receptor sensitivity, dead space ventilation and hypoxemic drive. Premature lactic acidosis at the peripheral muscles due to hypoxemia will also increase the ventilatory drive on activity. Physiologically, the ventilatory response to the metabolic requirement is reflected in the V_E/VO_2 relationship (1). Accordingly, we observed a negative correlation between V_E/VO_2 and mean daily walking intensity whereas V_E/VO_2 and V_E/MVV were significantly higher among less active patients (by almost 20% and 40%, respectively). V_E/VCO_2, ratio, another important index of ventilatory efficiency and of prognostic significance in precapillary PH, also differed between the 2 groups (58 vs. 44); however, it did not reached statistical significance, possibly, due to submaximal testing and small sample. Such an exaggerated ventilatory response is highly relevant to physical activity as it may promote dyspnoea and cessation of exercise.

Patients with PAH exhibit significant morphological and functional changes of

quadriceps muscle including alteration in the muscle fibre type, muscle atrophy, reduced capillarity and oxidative capacity, and endothelial dysfunction (31). These abnormalities may impair the local tissue oxygen delivery and utilization capacity, muscle strength and exercise capacity (20). Importantly, muscle characteristics were unrelated to the hemodynamic severity (20) and targeted exercise training reversed abnormalities and improved exercise capacity (6, 26), which suggest that peripheral muscle abnormalities may be implicated independently in the exercise pathophysiology of PAH. Here, Q-StO_2 at activity correlated with mean daily walking intensity, predicted a clinically significant amount of the variance in daily walking intensity, and was significantly lower in less active patients. Importantly, ΔQ-StO_2 responses opposed between patient groups: less active patients drop Q-StO_2 whereas more active patients benefited from increased Q-StO_2 at individual mean daily walking intensity.

Factors determining local muscle oxygenation are modulated by the rate of oxygen delivery and oxygen extraction (8). Whereas arterial oxygen content and systemic oxygen delivery did not differ between the present patient groups, less active patients had significantly reduced a-vO_2 difference and ~ 10% reduction in oxygen extraction ratio compared to more active patients. Collectively, our novel findings on estimates of muscle oxygenation suggest a strong relation between capacity to enhance local muscle oxygenation and better preserved daily physical activity and they provide support to the peripheral muscle hypothesis (29). They also add to previous evidence showing: a) impaired oxygen extraction rate during maximal exercise in PAH patients compared to patients with pulmonary venous hypertension (41); b) lower thenar muscle resting StO_2 in PAH compared to CHF and healthy subjects (9); c) greater quadriceps oxygen delivery-

to-utilization inequalities (Δ[Mb-HHb]; change in deoxygenated myoglobin from rest to exercise) in PAH compared to healthy subjects, which accounted for a slower rate of adaptation of aerobic metabolism at exercise (2); and d) reduced quadriceps oxygenation (lower Q-ΔStO2, higher Δ[Mb-HHb]) in PAH compared to normal subjects even during submaximal exercise (22); Δ[Mb-HHb] was also related to reduced quadriceps capillarity and strength, and lower VO_2 (22).

Certainly, our study design does not allow for proof of causality and further research is required before a primary impairment of peripheral muscle oxygenation is considered a true limiting factor rather than a mere consequence of deconditioning, or reflection of hypoxemia. Nonetheless, we found no association between Q-StO_2 and SpO_2 or arterial oxygen content at rest/exercise ($p>0.5$ for all). Furthermore, Q-ΔStO_2 and Δ[Mb-HHb] in PAH subjects have been previously shown to remain unchanged with oxygen supplementation (22).

A unified explanation may lie within the seemingly paradoxical absence of difference in VO_2 between less and more active patients. It is possible that the metabolic requirements of the increased workload (reduced HRR) of the stressed heart (increased log-NTproBNP) and increased/inefficient ventilation (increased V_E/MVV, V_E/VO_2) in less active patients had matched the oxygen requirements of increased daily walking intensity in more active patients. Teleologically, it may that both patient groups had adjusted their activity to a certain threshold of oxygen/energy cost that allowed for acceptable exertional symptoms such as muscle fatigue and breathlessness (as suggested by responses in ventilation and estimates of quadriceps oxygenation). Ultimately, less active patients showed convincingly compromised HQoL (worse CAMPHOR and

348 emPHasis-10 scores).

349 The current study is limited by its cross-sectional design, small sample and small
350 number of patients with advanced disease willing to undergo such a complex study
351 protocol. Stroke volume profile of 3 (15%) patients had to be excluded due to invalid
352 impedance cardiography signal but this limitation is inherent to impedance cardiography
353 and this figure is similar to previously published experience in precapillary PH (12).
354 Furthermore, the absence of direct measurement of peripheral muscle strength does not
355 allow for further exploration of the role of the peripheral muscle. Impedance
356 cardiography and Arterial oxygen content was estimated from using continuous SpO_2
357 readings at the expense of possible reduced accuracy in the hypoxaemic patients
358 compared to invasive arterial blood sampling. For patient comfort, measurements of
359 6MWD and NT-proBNP were retrospective in nature. However, we believe that in the
360 context of clinical stability (a prerequisite for patient inclusion in the study), an interval
361 of 30 days is an acceptable collection period for both measures. Finally, this study did not
362 investigate the possible impact of specific diseases and drug therapy on muscle function
363 or the effect of unmeasured variables such as environmental, social and personal factors
364 to daily physical activity. These factors might have accounted for the unexplained
365 variance in daily walking intensity and the moderate correlation of 6MWD with daily
366 walking intensity. Of note, neither CAMPHOR or emPHasis-10 scores correlated with
367 daily walking activity. Taken together with previously shown weak-to-moderate
368 correlations of accelerometry data with 6MWD and patient-reported questionnaire scores
369 (39), these findings question the surrogate value of routine clinical tools in the prediction
370 of daily physical activity in precapillary PH.

Conclusions

Daily physical activity holds promise to be meaningful, patient-related outcome measure in PH. Our preliminary findings suggest a significant relation between right ventricular and pulmonary vascular status, peripheral muscle oxygenation and HQoL with reduced daily physical activity in precapillary PH. However, further research is warranted to unravel the physiological determinants and establish the clinical predictors of this phenomenon. The role of muscle function in the natural history of precapillary PH merits particular focus as it offers a potential target for effective interventions.

Acknowledgements

We thank Val Pollock, Agnes Crozier, Karon Carson, Rachel Thomson, Kirsty Menzies and Veronica Ferry for their contribution to patient recruitment and administrative assistance.

Disclosures

Marios Panagiotou is the recipient of a European Respiratory Society PAH Long-Term Research fellowship n° LTRF 2014-3106 supported by an unrestricted grant by GSK. No conflicts exist for the rest of the authors.

Figure Captions

Figure 1: Study flow chart. BMI: body mass index; WHO FC: World Health Organization functional class; TLCO: transfer factor for carbon monoxide; 6MWD: 6-minute walk distance; log-NTproBNP: log-transformed N-terminal pro-brain natriuretic peptide. VO_2: oxygen uptake; V_E: minute ventilation; MVV: maximum voluntary ventilation; V_E/VO_2: ventilatory equivalent ratio for oxygen; V_E/VO_2: ventilatory equivalent ratio for carbon dioxide; SpO_2: oxyhaemoglobin saturation; HRR: heart rate reserve; SV: stroke volume; CO: cardiac output; Q-StO_2: quadriceps tissue oxygenation index; Q-ΔStO_2: change in Q-StO_2 from rest to exercise. * Retrospective data (median interval: 30 days); § Resting and exercise value was the average value obtained during the last minute of the first and third stage, respectively; # SV/CO profile of 3 patients was excluded due to invalid impedance cardiography signal.

Figure 2: Correlations (Pearson's r) between daily walking intensity recorded by triaxial accelerometer and log N-terminal pro-brain natriuretic peptide (log-NTproBNP) (A); age (B); heart rate reserve (HRR) (C); ventilatory equivalent ratio for oxygen uptake (V_E/VO_2) (D); quadriceps tissue oxygenation index (Q-StO_2) at activity (E); and change in Q-StO_2 from rest to activity (Q-ΔStO_2) (F) in 20 patients with precapillary pulmonary hypertension.

409 **Table 1**: Clinical characteristics and comparison between less and more active patients[1]

		Daily walking intensity, *m/s²*		**P-value**
Variable	**All (n=20)**	**< 1.78 (n=10)**	**≥ 1.78 (n=10)**	
Walking Intensity, *m/s²*	1.71 ± 0.27	1.54 (1.29-1.75)	1.86 (1.79-2.03)	<.001*
Treadmill speed, *km/hr*	2.27 ± .84	1.90 (1.00-2.90)	2.95 (1.80-3.20)	.037
Sex, *m/f*	8/12	4/6	4/6	N/A
Age, *yr*	54.1 ± 15.9	66.0 (44.0-73.0)	48.5 (24.0-56.0)	.045*
BMI, *kg/m²*	29.9 ± 5.7	28.1 (18.8-31.6)	25.5 (21.3-29.7)	.705
Diagnosis				
Idiopathic PAH	9	4	5	N/A
CTD-PAH	6	4	2	N/A
CHD-PAH	1	0	1	N/A
CTEPH	4	2	2	N/A
WHO FC, I/II/III	4/12/4	1/5/4	3/7/0	N/A
mean PAP, *mm Hg*	45.1± 13.3	46.0 (32.0-57.0)	40.0 (28.0-65.0)	.713

[1] Values are expressed as means ± SD or median and 95% confidence interval of median. BMI: body mass index; PAH: pulmonary arterial hypertension; CTD-PAH: connective tissue disease associated PAH; CHD-PAH: PAH after correction of congenital heart disease; WHO FC: World Health Organization functional class; PAP, CO and PVR: historical pulmonary arterial pressure, cardiac output and pulmonary vascular resistance, respectively, measured at diagnostic right heart catheterization, prior to the initiation of PH-specific therapy; 6MWD: 6-minute walk distance; log-NTproBNP: log-transformed N-terminal pro-brain natriuretic peptide; TLCO: transfer factor for carbon monoxide. *Significant statistical difference between patient groups.

CO, *L/min*	3.8 ± 1.0	3.6 (2.6-4.3)	4.3 (3.3-5.0)	.102
PVR, *Wood units*	11.1 ± 5.7	12.3 (6.0-13.5)	8.7 (4.8-15.2)	.369
6MWD*, m*	418 ± 106	361 (298-513)	469 (347-570)	.076
CAMPHOR	23.2 ± 16.8	36.5 (8.0-46.0)	11.5 (0-36.0)	.041*
emPHasis-10	21.9 ± 14.1	31.0 (12.0-38.0)	13.5 (0-32.0)	.089
log-NTproBNP, *pg/mL*	2.53 ± 0.53	2.99 (2.75-3.29)	2.10 (1.79-2.42)	<.001*
FEV1, %pred.	89.9 ± 19.1	93.0 (80.0-115.5)	91.0 (65.8-98.5)	0.26
FVC, %pred.	112.4 ± 23.2	115.5 (100.3-141.5)	108.0 (90.0-122.3)	0.34
FEV1/FVC	66.5 ± 8.5	69.0 (60.3-72.0)	66.5 (63.3-71.0)	0.62

410 **Table 2**: Physiological characteristics and comparison between less and more active patients[1].

		Daily walking intensity, m/s^2		**P-value**
Variable	**All (n=20)**	**< 1.78 (n=10)**	**≥ 1.78 (n=10)**	
SpO_2 activity, *%*	89.9 ± 7.1	86.0 (81.0-95.0)	95.0 (88.0-96.0)	.1
HRR, *beats/min*	61.8 ± 26.2	51.0 (9.0-57.0)	78.5 (67.0-91.0)	<.001*
SV rest/activity, *ml/beat*	66.5± 21.5/ 80.9 ± 21.6	59.2 (25.0-116.9)/ 74.1 (42.9-137.0)	63.6 (58.3-79.2)/ 78.9 (72.0-91.2)	.664/ .745
CO rest/activity, *l/min*	5.4 ± 1.2 8.9 ± 2.6	5.2 (3.3-7.1) 10.0 (6.8-16.1)	4.8 (4.2-6.7) 7.5 (6.8-9.3)	.495/ .045*
Q-StO_2 rest/activity, *%*	64.1 ± 7.4/ 65.4 ± 10.6	63.7 (54.6-68.6)/ 60.5 (43.4-74.5)	65.7 (57.9-74.4)/ 71.4 (62.0-76.4)	.496/ .028*
Q-ΔStO_2, *%*	1.3 ± 6.6	-2.3 (-6.0-1.8)	5.1 (3.2-7.8)	.003*
V_E/MVV, *l/min*	40.9 ± 14.3	48.9 (32.2-60.0)	30.5 (25.9-39.6)	.007*
V_E/VO_2	51.1 ± 18.8	55.8 (39.8-81.1)	40.6 (34.3-58.2)	.041*
VO_2, $ml \cdot kg^{-1} \cdot min^{-1}$	9.5 ± 1.4	9.4 (7.5-11.0)	9.7 (7.9-10.5)	.806
V_E/VCO_2	52.1 ± 13.6	57.7 (38.4-77.0)	44.0 (40.0-56.7)	.142
Arterial oxygen content,	18.1 ± 1.42	17.3 (16.3-19.1)	19.1 (17.7-19.3)	.1

[1] Values are expressed as means ± SD or median and 95% confidence interval of median. SpO_2: oxyhaemoglobin saturation; HRR: heart rate reserve; SV: stroke volume; CO: cardiac output; Q-StO_2: quadriceps tissue oxygenation index; Q-ΔStO_2: change in Q-StO_2 from rest to exercise; V_E: minute ventilation; MVV: maximum voluntary ventilation; V_E/VO_2: ventilatory equivalent ratio for oxygen; V_E/VO_2: ventilatory equivalent ratio for carbon dioxide; VO_2: oxygen uptake; a-vO2 difference: arterio-venous oxygen content difference. *Significant statistical difference between patient groups.

ml/dl				
Systemic oxygen delivery, *l/min*	1.4 ± .5	1.6 (1.1-2.6)	1.4 (1.2-1.6)	.556
Systemic a-vO_2 difference difference, *mlO_2/100 ml*	7.7 ± 1.6	5.9 (5.1-8.3)	8.6 (6.7-9.8)	.017*
Systemic oxygen extraction, *%*	42 ± 11	35 (28-51)	44 (34-52)	.239

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