

Northumbria Research Link

Citation: Panagiotou, Marios, Johnson, Martin, Louvaris, Zafeiris, Baker, Julien, Church, Alistair, Peacock, Andrew and Vogiatzis, Ioannis (2017) A study of clinical and physiological relations of daily physical activity in precapillary pulmonary hypertension. *Journal of Applied Physiology*, 123 (4). pp. 851-859. ISSN 8750-7587

Published by: American Physiological Society

URL: <https://doi.org/10.1152/jappphysiol.00986.2016>
<<https://doi.org/10.1152/jappphysiol.00986.2016>>

This version was downloaded from Northumbria Research Link:
<http://nrl.northumbria.ac.uk/id/eprint/31371/>

Northumbria University has developed Northumbria Research Link (NRL) to enable users to access the University's research output. Copyright © and moral rights for items on NRL are retained by the individual author(s) and/or other copyright owners. Single copies of full items can be reproduced, displayed or performed, and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided the authors, title and full bibliographic details are given, as well as a hyperlink and/or URL to the original metadata page. The content must not be changed in any way. Full items must not be sold commercially in any format or medium without formal permission of the copyright holder. The full policy is available online: <http://nrl.northumbria.ac.uk/policies.html>

This document may differ from the final, published version of the research and has been made available online in accordance with publisher policies. To read and/or cite from the published version of the research, please visit the publisher's website (a subscription may be required.)

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

3
4 **Authors:** Marios Panagiotou¹, Martin K. Johnson¹, Zafeiris Louvaris^{2,3}, Julien S.
5 Baker⁴, Alistair C. Church¹, Andrew J. Peacock¹, Ioannis Vogiatzis^{2,5}.

6 **Author contributions:** MP obtained all of the data in the study, performed data
7 analysis and wrote the manuscript. ZL performed accelerometry data analysis. MP, MKJ,
8 ZL, JSB, ACH, AJP and IV contributed substantially to the study design, data
9 interpretation, and editing of the manuscript.

10 **Affiliations:** ¹Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital,
11 Glasgow, UK; ²Faculty of Physical Education and Sports Sciences, National and
12 Kapodistrian University of Athens, Athens, Greece; ³Faculty of Kinesiology and
13 Rehabilitation Sciences, Department of Rehabilitation Sciences KU Leuven, Division of
14 Respiratory Rehabilitation, University Hospitals Leuven, Belgium; ⁴Institute of Clinical
15 Exercise and Health Sciences, University of the West of Scotland, Hamilton, UK;
16 ⁵School of Health and Life Sciences, Northumbria University Newcastle, Newcastle
17 Upon-Tyne, UK.

18 **Corresponding author:** Marios Panagiotou; Scottish Pulmonary Vascular Unit,
19 Golden Jubilee National Hospital, Agamemnon Street, Glasgow, G81 4DY, UK; +44 141
20 9515497; mariopanag@gmail.com.

21 **Abstract**

22 Daily physical activity becomes reduced in precapillary pulmonary hypertension (PH)
23 but the underlying mechanisms are inadequately explored. We sought to investigate
24 clinical and physiological relations of daily physical activity and profile differences
25 between less and more active patients with precapillary PH. A prospective, cross-
26 sectional study of 20 patients with precapillary PH who undertook a) a comprehensive
27 clinical assessment, b) a preliminary treadmill test, c) 7-day monitoring of daily walking
28 intensity with triaxial accelerometry and d) a personalized treadmill test corresponding to
29 the individual patient mean daily walking intensity with real-time physiological
30 measurements. Significant clinical correlations with individual patient mean walking
31 intensity (1.71 ± 0.27 m/s²) were observed for log N-terminal pro-brain natriuretic peptide
32 (log-NTproBNP: $r = -.75$, $p < .001$), age ($r = -.70$, $p = .001$), transfer factor for carbon
33 monoxide %predicted ($r = .51$, $p = 0.022$) and 6-minute walk distance ($r = .50$, $p = .026$).
34 Significant physiological correlations were obtained for heart rate reserve ($r = .68$,
35 $p = .001$), quadriceps tissue oxygenation index (Q-StO₂: $r = .58$, $p = .008$), change in Q-StO₂
36 from rest ($r = .60$, $p = .006$) and ventilatory equivalent for oxygen uptake ($r = -.56$, $p = .013$).
37 Stepwise multiple regression analyses retained log-NTproBNP ($R^2 = 0.55$), heart rate
38 reserve ($R^2 = 0.44$) and Q-StO₂ ($R^2 = 0.13$) accounting for a significant variance in
39 individual walking intensity. Less active patients had greater physical activity-induced
40 cardiopulmonary impairment, worse quadriceps oxygenation profile and compromised
41 health-related quality of life compared to more active patients. These preliminary
42 findings suggest a significant relation between right ventricular and peripheral muscle
43 oxygenation status and reduced daily physical activity in precapillary PH. Further

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

46 **New & Noteworthy**

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

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

56 **Introduction**

57 Precapillary pulmonary hypertension (PH) comprises primarily pulmonary arterial
58 hypertension (PAH; group 1) and chronic thromboembolic pulmonary hypertension
59 (CTEPH; group 4) and is characterised by progressive elevation of vascular resistance in
60 the precapillary pulmonary vasculature and right heart failure (13). Despite important
61 advances in the understanding and targeted therapy to date, the morbidity and mortality in
62 precapillary PH remain high: typically, patients suffer progressive dyspnoea, impaired
63 exercise capacity and health-related quality of life (HRQoL), and premature death (1, 13,
64 37).

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

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

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

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

Materials & Methods

Study Sample

Consecutive patients with stable PAH and technically non-operable (distal) CTEPH who attended the Scottish Pulmonary Vascular Unit between November 2014 and October 2015 were eligible. The diagnosis had been previously established by right heart catheterisation as recommended (13). Clinical stability was defined as a) no hospitalization for precapillary PH and b) no escalation in therapy for PH or diuretics 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 ($MVV = FEV_1 \times 35$) (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

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

Accelerometry

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

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

Personalized treadmill test

Within 2 weeks, patients underwent a final, three-stage treadmill protocol during which they sequentially: a) stood still on treadmill, b) warmed up at a speed of 1.4 km/h, and c) walked at a predetermined treadmill speed corresponding to their individual daily 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 (OxywatchTM 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 ($220 - \text{age}$) 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-StO_2), as an expression of the local

microvascular oxygenation status, was measured using spatially resolved near infrared spectroscopy (NIRO-200NX[®], Hamamatsu Photonics KK, Japan). Tissue oxygenation index is essentially the ratio of oxygenated to total tissue hemoglobin concentration expressed as $[\text{oxyhaemoglobin}/(\text{oxyhaemoglobin} + \text{deoxyhaemoglobin})] \times 100$ (%) and represents an index of the dynamic balance between local tissue oxygen delivery and utilisation in health and disease (3, 23). We have previously shown strong correlations between Q-StO₂ and mixed venous oxygen saturation measured at pulmonary artery in PAH subjects, both at rest and exercise (32, 33).

To measure Q-StO₂, one transcutaneous probe (S-type) housed in a black rubber holder and fixed using a double-sided adhesive tape, was placed on the belly of each vastus lateralis muscle, 10-12 cm above the lateral epicondyle. The values shown for Q-StO₂ are the average from both legs. Estimated systemic oxygen delivery was calculated as the product of cardiac output and arterial oxygen content; the latter was calculated as the product of $1.34 \times \text{hemoglobin concentration} \times \% \text{SpO}_2$. The systemic arteriovenous oxygen content difference (a-vO₂ difference) was calculated by dividing oxygen uptake by cardiac output (Fick principle) whereas the systemic oxygen extraction ratio was calculated as the ratio of the a-vO₂ difference to arterial oxygen content (18).

Statistical analysis

Data are reported as means \pm SD or median with 95% confidence interval of median. NTproBNP was log-transformed due to positive skewing. Associations of mean daily walking intensity were examined using the Pearson's correlation coefficient. Significant 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/s² and 1.78 (1.55, 1.83) m/s², 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-StO₂, ($r=.58$, $p=.008$), change in Q-StO₂ from rest to mean daily walking intensity ($r=.60$, $p=.006$), V_E/VO₂ ($r=-.56$, $p=.013$) 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 ($b=-.290\pm.068$, $\beta=-.554$, $p=.001$) and age ($b=-.008\pm.002$, $\beta=-.486$, $p=.002$) accounting for 55% and 20% of the variance in mean daily walking intensity, respectively. Repeated for the significant physiological measures, analysis retained HRR ($b=.006\pm.002$, $\beta=.506$, $p=.015$) and Q-StO₂ at activity ($b=.01\pm.005$, $\beta=.395$, $p=.049$) 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 VO₂ between less and more active patients. Less active patients had significantly increased age, log-NTproBNP, V_E/MVV, V_E/VO₂, CAMPHOR and emPHasis-10 scores and decreased TLCO %predicted, HRR, Q-StO₂ at mean daily walking intensity and Q-ΔStO₂; 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).

234

235 **Discussion**

236 This exploratory study in a representative cohort with precapillary PH, reports on
237 significant associations of indices of right ventricular (log-NTproBNP, HRR) and
238 pulmonary vascular (TLCO %predicted) status with mean daily walking intensity. In
239 exercise conditions reproducing individual daily physical activity levels, measures of
240 quadriceps oxygenation (Q-StO₂ at activity, Δ Q-StO₂) and ventilatory efficiency
241 (V_E/V_{O_2}) were also associated significantly with mean daily walking intensity. log-
242 NTproBNP, HRR and Q-StO₂ at mean activity levels predicted a significant variance in
243 mean daily walking intensity. Finally, the profile of less active patients comprised greater
244 cardiorespiratory impairment, worse quadriceps oxygenation profile and compromised
245 HRQoL compared to more active patients.

246 Walking intensity is an important aspect that a patient with lung disease adopts in
247 daily living. For example, numerous studies (Watz et al ERJ 2014; 44(6): 1521-1537)
248 have emphasized the finding that the intensity of movement adopted by COPD patients
249 during walking is reduced by an average of 17 to 33% compared to healthy age-matched
250 individuals. Daily walking intensity in the present cohort (1.7 m/s²) favorably compares
251 with that adopted by older patients with moderate/severe COPD (spirometric classes
252 II/III), typically corresponding to 1.8 m/s² (18, 34). Overall, the present population
253 adopted a sedentary (most commonly) or low-active lifestyle defined as daily steps of
254 <5000 and between 5000-7500, respectively (43). This adds to previous evidence (21, 36,
255 39, 45) on reduced measures of daily physical activity in precapillary PH.

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

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

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

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

The higher HR accounted for the higher cardiac output in less active patients in the 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, $Q\text{-StO}_2$ 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, $\Delta Q\text{-StO}_2$ responses opposed between patient groups: less active patients drop $Q\text{-StO}_2$ whereas more active patients benefited from increased $Q\text{-StO}_2$ 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 $a\text{-vO}_2$ difference and $\sim 10\%$ 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 ($\Delta[\text{Mb-HHb}]$; 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 $\text{Q-}\Delta\text{StO}_2$, higher $\Delta[\text{Mb-HHb}]$) in PAH compared to normal subjects even during submaximal exercise (22); $\Delta[\text{Mb-HHb}]$ 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 $\text{Q-}\Delta\text{StO}_2$ and SpO_2 or arterial oxygen content at rest/exercise ($p>0.5$ for all). Furthermore, $\text{Q-}\Delta\text{StO}_2$ and $\Delta[\text{Mb-HHb}]$ 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 $\text{V}_\text{E}/\text{MVV}$, $\text{V}_\text{E}/\text{VO}_2$) in less active patients had matched the oxygen requirements of increased daily walking intensity in more active patients. Teleologically, it may be 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 SpO₂
 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.

371

372

373 **Conclusions**

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

381 **Acknowledgements**

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

385 **Disclosures**

386 Marios Panagiotou is the recipient of a European Respiratory Society PAH Long-
387 Term Research fellowship n° LTRF 2014-3106 supported by an unrestricted grant by
388 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/VCO_2 : ventilatory equivalent ratio for carbon dioxide; SpO_2 : oxyhaemoglobin saturation; HRR: heart rate reserve; SV: stroke volume; CO: cardiac output; Q-StO₂: quadriceps tissue oxygenation index; Q- Δ StO₂: change in Q-StO₂ 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-StO₂) at activity (E); and change in Q-StO₂ from rest to activity (Q- Δ StO₂) (F) in 20 patients with precapillary pulmonary hypertension.

409 **Table 1:** Clinical characteristics and comparison between less and more active patients¹

		Daily walking intensity, m/s^2		P-value
Variable	All (n=20)	< 1.78 (n=10)	≥ 1.78 (n=10)	
Walking Intensity, m/s^2	1.71 \pm 0.27	1.54 (1.29-1.75)	1.86 (1.79-2.03)	<.001*
Treadmill speed, km/hr	2.27 \pm .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 \pm 15.9	66.0 (44.0-73.0)	48.5 (24.0-56.0)	.045*
BMI, kg/m^2	29.9 \pm 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 \pm 13.3	46.0 (32.0-57.0)	40.0 (28.0-65.0)	.713

¹ Values are expressed as means \pm 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, <i>L/min</i>	3.8 ± 1.0	3.6 (2.6-4.3)	4.3 (3.3-5.0)	.102
PVR, <i>Wood units</i>	11.1 ± 5.7	12.3 (6.0-13.5)	8.7 (4.8-15.2)	.369
6MWD, <i>m</i>	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, <i>pg/mL</i>	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 patients¹.

		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, <i>beats/min</i>	61.8 ± 26.2	51.0 (9.0-57.0)	78.5 (67.0-91.0)	<.001*
SV rest/activity, <i>ml/beat</i>	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, <i>l/min</i>	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, <i>l/min</i>	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 , <i>ml·kg⁻¹·min⁻¹</i>	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. SpO₂: oxyhaemoglobin saturation; HRR: heart rate reserve; SV: stroke volume; CO: cardiac output; Q-StO₂: quadriceps tissue oxygenation index; Q-ΔStO₂: change in Q-StO₂ from rest to exercise; V_E: minute ventilation; MVV: maximum voluntary ventilation; V_E/VO₂: ventilatory equivalent ratio for oxygen; V_E/VCO₂: ventilatory equivalent ratio for carbon dioxide; VO₂: oxygen uptake; a-vO₂ difference: arterio-venous oxygen content difference. *Significant statistical difference between patient groups.

<i>ml/dl</i>				
Systemic oxygen delivery, <i>l/min</i>	$1.4 \pm .5$	1.6 (1.1-2.6)	1.4 (1.2-1.6)	.556
Systemic a-vO ₂ difference difference, <i>mlO₂/100 ml</i>	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

References

1. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 167: 211-77, 2003.
2. Barbosa PB, Ferreira EM, Arakaki JS, Takara LS, Moura J, Nascimento RB, Nery LE, Neder JA. Kinetics of skeletal muscle O₂ delivery and utilization at the onset of heavy-intensity exercise in pulmonary arterial hypertension. *Eur J Appl Physiol*; 111 :1851-61, 2011.
3. Boushel R, Langberg H, Olesen J, Gonzales-Alonzo J, Bülow J, Kjaer M. Monitoring tissue oxygen availability with near infrared spectroscopy (NIRS) in health and disease. *Scand J Med Sci Sports* 11: 213-22, 2001.
4. Charloux A, Lonsdorfer-Wolf E, Richard R, Lampert E, Oswald-Mammosser M, Mettauer B, Geny B, Lonsdorfer J. A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *Eur J Appl Physiol* 82: 313-20; 2000.
5. de Groot S, Nieuwenhuizen MG. Validity and reliability of measuring activities, movement intensity and energy expenditure with the DynaPort MoveMonitor. *Med Eng Phys* 35: 1499-505, 2013.
6. de Man FS, Handoko ML, Groepenhoff H, van 't Hul AJ, Abbink J, Koppers RJ, Grotjohan HP, Twisk JW, Bogaard HJ, Boonstra A, Postmus PE, Westerhof N, van der Laarse WJ, Vonk-Noordegraaf A. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 34: 669-75, 2009.
7. Deboeck G, Niset G, Vachiery JL, Moraine JJ, Naeije R. Physiological response to the six-minute walk test in pulmonary arterial hypertension. *Eur Respir J* 26: 667-72, 2005.
8. DeLorey DS, Kowalchuk JM, Paterson DH. Relationship between pulmonary O₂ uptake kinetics and muscle deoxygenation during moderate-intensity exercise. *J Appl Physiol (1985)* 95: 113-20, 2003.
9. Dimopoulos S, Tzanis G, Manetos C, Tasoulis A, Mpouchla A, Tseliou E, Vasileiadis I, Diakos N, Terrovitis J, Nanas S. Peripheral muscle microcirculatory alterations in patients with pulmonary arterial hypertension: a pilot study. *Respir Care* 58: 2134-41, 2013.
10. Esteban C, Quintana JM, Aburto M, Moraza J, Egurrola M, Pérez-Izquierdo J, Aizpiri S, Aguirre U, Capelastegui A. Impact of changes in physical activity on health-related quality of life among patients with COPD. *Eur Respir J* 36: 292-300, 2010.
11. Felker GM, Whellan D, Kraus WE, Clare R, Zannad F, Donahue M, Adams K, McKelvie R, Piña IL, O'Connor CM; HF-ACTION Investigators. N-terminal pro-brain natriuretic peptide and exercise capacity in chronic heart failure: data from the Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study. *Am Heart J* 158(4 Suppl): S37-44, 2009.
12. Ferreira EM, Ota-Arakaki JS, Barbosa PB, Siqueira AC, Bravo DM, Kapins CE, Silva CM, Nery LE, Neder JA. Signal-morphology impedance cardiography

- during incremental cardiopulmonary exercise testing in pulmonary arterial hypertension. *Clin Physiol Funct Imaging* 32: 343-52, 2012.
13. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*; 46: 903-75, 2015.
 14. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2010.
 15. Gombert-Maitland M, Bull TM, Saggarr R, Barst RJ, Elgazayerly A, Fleming TR, Grimminger F, Rainisio M, Stewart DJ, Stockbridge N, Ventura C, Ghofrani AH, Rubin LJ. New trial designs and potential therapies for pulmonary artery hypertension. *J Am Coll Cardiol* 62(25 Suppl): D82-91, 2013.
 16. Henkens IR, Van Wolferen SA, Gan CT, Boonstra A, Swenne CA, Twisk JW, Kamp O, van der Wall EE, Schalij MJ, Vonk-Noordegraaf A, Vliegen HW. Relation of resting heart rate to prognosis in patients with idiopathic pulmonary arterial hypertension. *Am J Cardiol* 103: 1451-6, 2009.
 17. Kortianou EA, Louvaris Z, Vasilopoulou M, Nasis I, Kaltsakas G, Koulouris NG, Vogiatzis I. Activity monitoring reflects cardiovascular and metabolic variations in COPD patients across GOLD stages II to IV. *Respir Physiol Neurobiol* 189: 513-20, 2013.
 18. Louvaris Z, Kortianou EA, Spetsioti S, Vasilopoulou M, Nasis I, Asimakos A, Zakynthinos S, Vogiatzis I. Intensity of daily physical activity is associated with central hemodynamic and leg muscle oxygen availability in COPD. *J Appl Physiol (1985)* 115: 794-802, 2013.
 19. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 26: 720-35, 2005.
 20. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, Provencher S. Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. *Thorax* 65: 113-7, 2010.
 21. Mainguy V, Provencher S, Maltais F, Malenfant S, Saey D. Assessment of daily life physical activities in pulmonary arterial hypertension. *PLoS One* 6: e27993, 2011.
 22. Malenfant S, Potus F, Mainguy V, Leblanc E, Malenfant M, Ribeiro F, Saey D, Maltais F, Bonnet S, Provencher S. Impaired Skeletal Muscle Oxygenation and Exercise Tolerance in Pulmonary Hypertension. *Med Sci Sports Exerc* 47: 2273-82, 2015.

23. Mancini DM, Bolinger L, Li H, Kendrick K, Chance B, Wilson JR. Validation of near-infrared spectroscopy in humans. *J Appl Physiol* (1985) 77: 2740-7, 1994.
24. McCabe C, Bennett M, Doughty N, MacKenzie Ross R, Sharples L, Pepke-Zaba J. Patient-reported outcomes assessed by the CAMPHOR questionnaire predict clinical deterioration in idiopathic pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Chest* 144: 522-30, 2013.
25. McKenna SP, Doughty N, Meads DM, Doward LC, Pepke-Zaba J. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): a measure of health-related quality of life and quality of life for patients with pulmonary hypertension. *Qual Life Res* 15: 103-15, 2006.
26. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper MM, Halank M, Meyer FJ, Karger G, Buss J, Juenger J, Holzapfel N, Opitz C, Winkler J, Herth FF, Wilkens H, Katus HA, Olschewski H, Grünig E. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 114: 1482-9, 2006.
27. Morris NR, Seale H, Harris J, Hall K, Lin AC, Kermeen F. Gas exchange responses during 6-min walk test in patients with pulmonary arterial hypertension. *Respirology* (Aug 16, 2016). doi: 10.1111/resp.12868.
28. Myers J, Gullestad L, Bellin D, Ross H, Vagelos R, Fowler M. Physical activity patterns and exercise performance in cardiac transplant recipients. *J Cardiopulm Rehabil* 23: 100-6, 2003.
29. Naeije R. Breathing more with weaker respiratory muscles in pulmonary arterial hypertension. *Eur Respir J* 25:6-8, 2005.
30. Okumus G, Aslan GK, Arseven O, Ongen G, Issever H, Kıyan E. The role of an activity monitor in the objective evaluation of patients with pulmonary hypertension. *Clin Respir J* (May 5, 2016). doi: 10.1111/crj.12495.
31. Panagiotou M, Peacock AJ, Johnson MK. Respiratory and limb muscle dysfunction in pulmonary arterial hypertension: a role for exercise training? *Pulm Circ* 5: 424-34, 2015.
32. Panagiotou M, Vogiatzis I, Louvaris Z, Jayasekera G, MacKenzie A, McGlinchey N, Baker JS, Church AC, Peacock AJ, Johnson MK. Dynamic near-infrared spectroscopy assessment as an important tool to explore pulmonary arterial hypertension pathophysiology. *Eur Respir J*; 49: 1602161, 2017.
33. Panagiotou M, Vogiatzis I, Louvaris Z, Jayasekera G, MacKenzie A, McGlinchey N, Baker JS, Church AC, Peacock AJ, Johnson MK. Near infrared spectroscopy for the assessment of peripheral tissue oxygenation in pulmonary arterial hypertension. *Eur Respir J* 48: 1224-1227, 2016.
34. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 171: 972-7, 2005.
35. Provencher S, Chemla D, Hervé P, Sitbon O, Humbert M, Simonneau G. Heart rate responses during the 6-minute walk test in pulmonary arterial hypertension. *Eur Respir J* 27: 114-20, 2006.

36. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest* 142: 1391-8, 2012.
37. Rabinovich RA, Louvaris Z, Raste Y, Langer D, Van Remoortel H, Giavedoni S, Burtin C, Regueiro EM, Vogiatzis I, Hopkinson NS, Polkey MI, Wilson FJ, Macnee W, Westerterp KR, Troosters T; PROactive Consortium. Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J* 42: 1205-15, 2013.
38. Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Health-related quality of life in a national cohort of patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Arch Bronconeumol* 49: 181-8, 2013.
39. Saglam M, Vardar-Yagli N, Calik-Kutukcu E, Arikan H, Savci S, Inal-Ince D, Akdogan A, Tokgozoglu L. Functional exercise capacity, physical activity, and respiratory and peripheral muscle strength in pulmonary hypertension according to disease severity. *J Phys Ther Sci* 27: 309-12, 2015.
40. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 104: 429-35 2001.
41. Tolle J, Waxman A, Systrom D. Impaired systemic oxygen extraction at maximum exercise in pulmonary hypertension. *Med Sci Sports Exerc* 40: 3-8, 2008.
42. Tonelli AR, Alnuaimat H, Li N, Carrie R, Mubarak KK. Value of impedance cardiography in patients studied for pulmonary hypertension. *Lung*; 189: 369-75, 2011.
43. Tudor-Locke C, Craig CL, Thyfault JP, Spence JC. A step-defined sedentary lifestyle index: <5000 steps/day. *Appl Physiol Nutr Metab* 38: 100-14, 2013.
44. Tung HH, Jan MS, Lin CY, Chen SC, Huang HC. Mediating role of daily physical activity on quality of life in patients with heart failure. *J Cardiovasc Nurs* 27: 16-23, 2012.
45. Ulrich S, Fischler M, Speich R, Bloch KE. Wrist actigraphy predicts outcome in patients with pulmonary hypertension. *Respiration* 86: 45-51, 2013.
46. van Hees VT, van Lummel RC, Westerterp KR. Estimating activity-related energy expenditure under sedentary conditions using a tri-axial seismic accelerometer. *Obesity (Silver Spring)* 17: 1287-92, 2009.
47. Witham MD, Argo IS, Johnston DW, Struthers AD, McMurdo ME. Predictors of exercise capacity and everyday activity in older heart failure patients. *Eur J Heart Fail* 8: 203-7, 2006.
48. Yorke J, Corris P, Gaine S, Gibbs JS, Kiely DG, Harries C, Pollock V, Armstrong I. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J* 43: 1106-13, 2014.