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

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Abstract

Daily physical activity is 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 a meaningful, patient-related outcome measure in pulmonary hypertension. In this study, 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. This provides a 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). Regular engagement in 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 of the underlying mechanisms remains intuitively focused on pulmonary vasculopathy and right ventricular dysfunction and limited to extrapolations from

77 standardized exercise testing (40), which may not correspond well to daily physical
78 activity (28, 47). Notably, the role of peripheral muscles has not been investigated. This is
79 despite growing evidence of skeletal muscle abnormalities in PAH (31) and recent
80 findings suggesting that estimates of skeletal muscle oxygenation may reflect the
81 pathophysiology of PAH (32, 33). The ability of the usual clinical variables collected in
82 precapillary PH to predict daily physical activity is not well established.

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

91 **Materials & Methods**

92 Study Sample

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

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

101 Initial evaluation

102 Data were collected on WHO functional class, maximum voluntary ventilation
103 (MVV=FEV_1 x 35) (1) and transfer factor for carbon monoxide (TLCO) corrected for
104 haemoglobin concentration (19). They also completed the patient-reported Cambridge
105 Pulmonary Hypertension Outcome Review (CAMPHOR) (25), a well-validated
106 questionnaire for the assessment of HRQoL in PH. CAMPHOR is probably the most
107 widely studied questionnaire in PH and has been shown to predict clinical deterioration in
108 idiopathic PAH and CTEPH (24). However, CAMPHOR questionnaire has not been
109 validated against objective, accelerometry measures of daily physical activity to date.

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

113 Preliminary treadmill test

114 All subjects performed an incremental treadmill test (RAM 770M Treadmil; RAM
115 Medical and Industrial Instruments & Supplies, Padova, Italy operated through the CASE
116 ES Ergospirometry Testing System; GE Healthcare, Freiburg, Germany) at an initial
117 speed of 1.4 km/h that increased by 0.8 km/h every 3 minutes to the limit of tolerance.
118 During the test, minute-by-minute walking intensity was measured in units of
119 acceleration (m/s^2) using a triaxial activity monitor (DynaPort MoveMonitor; McRoberts,
120 Netherlands). In this manner, a range of individualised walking intensities were plotted

against treadmill speeds and a predicted equation for walking intensity and corresponding treadmill speed was generated for each patient.

Accelerometry

Subjects were fitted with DynaPort accelerometers attached to an elastic strap and positioned over the L2 vertebra (an approximation of the 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 a 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 during locomotion, and even under sedentary conditions (5, 37, 46). The intensity with which a person carries out activities of daily living is a unique measure of daily life activity, which is a fundamental part of recommendations for health maintenance (14) and an important aspect of the overall physical activity in chronic lung disease (34). Importantly, walking intensity can be easily and accurately reproduced on the treadmill, thus allowing the study of individual physiological responses during activity in the laboratory setting [17, 18].

Personalized treadmill test

Within 2 weeks, patients underwent a final, three-stage treadmill protocol during which they sequentially: 1) stood still on treadmill, 2) warmed up at a speed of 1.4 km/h, and 3) walked at a predetermined treadmill speed corresponding to their individual daily walking intensity (calculated by using the predicted equation for walking intensity and

treadmill speed generated during the preliminary treadmill test. The duration of each stage was 4 minutes in order to reach a steady physiological state.

Continuous physiological measurements were obtained throughout as described below. The resting and exercise value for all the physiological variables considered for the analysis was the average value of all the acquired data during the last minute of the first and third stage of the personalized treadmill protocol, respectively.

Metabolic profile

Oxygen uptake (VO_2), minute ventilation (V_E) and ventilatory equivalent ratios 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 (4). The PhysioFlow

principle is based on the assumption that variations in impedance to a high-frequency (75kHz), low-magnitude (1.8 mA) alternating current across the thorax during cardiac ejection result in a waveform from which stroke volume (SV) can be calculated. Initially, a SV index (SVI) is calculated at rest by evaluating 30 consecutive heart beats (autocalibration procedure) using the largest impedance difference during systole, the largest rate of change in the impedance signal (contractility index), the thoracic fluid inversion time, heart rate, and the pulse pressure (systolic minus diastolic arterial pressure). Cardiac output is then calculated by multiplying the SVI by body surface area and HR [R-R interval determined on the electrocardiographic (ECG) first derivative]. The system was auto-calibrated before exercise tests on the treadmill. Signal quality was verified by visualizing the ECG tracing and its first derivative (dECG/dt) and the impedance waveform (ΔZ) with its first derivative (dZ/dt). If unstable signal recording occurred, the system did not allow the test to proceed, and a new calibration was performed. After shaving and cleaning the skin, two pairs of electrodes were firmly positioned at the left base of the neck and on the back at the xiphoid level for transmitting and receiving electrical currents. Two electrodes were also placed on the chest (V1/V6 position) for the ECG signal. The auto calibration procedure was started after a period of at least 5 minutes during which patients were sitting immobile on a chair. Cardiac output values were stored beat-by-beat.

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 [oxyhaemoglobin/(oxyhaemoglobin + deoxyhaemoglobin)] × 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 quadriceps tissue oxygenation index (Q-StO_2) and mixed venous oxygen saturation measured in the pulmonary artery in PAH subjects, both at rest and exercise (32, 33).

To measure Q-StO_2, 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. Briefly, one fiber optic bundle carries the near-infrared light produced by the laser diodes to the tissue of interest, and a second fiber optic bundle returns the transmitted light from the tissue to a photodetector in the spectrometer. The intensity of incident and transmitted light was recorded continuously and, along with the relevant specific extinction coefficients, was used to measure changes in the oxygenation status of hemoglobin + myoglobin (Hb+Mb) and then covered with a black rubber holder and fixed using a double-sided adhesive tape, thus minimizing the intrusion of extraneous light and loss of near-infrared light. The values shown for Q-StO_2 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 × hemoglobin concentration × %SpO_2. The systemic arteriovenous oxygen content difference (a-vO_2 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-vO_2 difference to arterial oxygen content (18).

Statistical analysis

Data are reported as means ± 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 $p<.05$.

The critical sample size of the study was calculated using Q-StO2 as the primary variable, based on a previous study which investigated the association between daily walking intensity (also measured by the same activity monitor) and quadriceps muscle oxygenation in 18 COPD patients (18). On the basis of an expected effect size of 0.589 that had been calculated from the mean difference (14.95%) and the corresponding standard deviation (25.38%) of Q-StO2 (18), the calculated critical sample size to address the objectives of the present study using multiple regression analysis with power of 0.80 and 2-sided alpha significance level of 0.05 (calculated using GPower statistical software, v 3.1; Heinrich Heine University Düsseldorf, Germany) was 18 patients.

Results

Patient characteristics

Patients characteristics are presented in Table 1. Twenty patients were enrolled,

completed the protocol without adverse effects and were 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 previously had a significant cardiac shunt detected at transthoracic echocardiogram, cardiac magnetic resonance imaging or right heart catheterisation. 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.

In the preliminary test, the tolerated treadmill speeds ranged between 0.8 and 6.2 km/h corresponding to walking intensities ranged between 1.07 to 3.96 m/s^2. In the personalized test, the treadmill speeds ranged from 0.8 to 3.3 km/h corresponding to daily walking intensities between 1.08 and 2.22 m/s^s.

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 were 4897±2209 indicating a generally sedentary lifestyle [43].

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) (Figure 2) and 6MWD (r=.50, p=.026). 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) (Figure 2). There was no significant 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 and age accounting for 75% of the variance in mean daily walking intensity, (Table 3). Repeated for the significant physiological measures, analysis retained HRR and Q-StO_2 at activity accounting for 57% of the variance in mean daily walking intensity (Table 3).

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 score and decreased TLCO %predicted, HRR, Q-StO_2 at mean daily walking intensity and Q-ΔStO_2. They also showed a 100-metre reduction in 6MWD compared to more active patients (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-StO_2 at activity, ΔQ-StO_2) and ventilatory efficiency (V_E/VO_2) were also associated significantly with mean daily walking intensity. Log-

NTproBNP, HRR and Q-StO_2 at mean activity levels predicted a significant proportion of the 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.

Overall, the present population adopted either a sedentary lifestyle, defined as daily steps of <5000 (43) (12 out of 20 patients; 60%) or a low-active lifestyle, defined as daily steps between 5000 and 7500 (43) (8 out of 20 patients; 40%). Also, mean daily walking intensity in the present cohort (1.71 m/s^2) 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). This adds to previous evidence (21, 36, 39, 45) of reduced measures of daily physical activity in precapillary PH.

The hemodynamic profile in precapillary PH depends mostly on 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. It was significantly elevated in less active patients.

Heart rate profiles in precapillary PH are though to reflect the burden of the right ventricle (16). In the setting of right ventricular failure and fixed/reduced stroke volume response with exercise, patients with precapillary PH become dependent on a

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.

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 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 suggest 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 and 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, which is an important index of ventilatory efficiency and prognostic significance in precapillary PH, also differed between the 2 groups (58 vs. 44). However, it did not reach statistical significance, possibly, due to submaximal testing and small sample size. 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 the 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). Muscle characteristics were unrelated to the hemodynamic severity (20) and targeted exercise training reversed abnormalities and improved exercise capacity (6, 26). This suggests 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. Of significance, ΔQ-StO_2 responses contrasted sharply between the patient groups. Less active patients showed a fall in Q-StO_2 whereas more active patients experienced an increase in Q-StO_2 at individual mean daily walking intensity.

345 Factors determining local muscle oxygenation are modulated by the rate of oxygen
346 delivery and oxygen extraction (8). Whereas arterial oxygen content and systemic oxygen
347 delivery did not differ between the present patient groups, less active patients had
348 significantly reduced a-vO_2 difference and ~ 10% reduction in oxygen extraction ratio
349 compared to more active patients. Collectively, our novel findings on estimates of muscle
350 oxygenation suggest a strong relationship between the capacity to enhance local muscle
351 oxygenation and better preserved daily physical activity and they provide support to the
352 peripheral muscle hypothesis (29). They also add to previous evidence showing: a)
353 impaired oxygen extraction rate during maximal exercise in PAH patients compared to
354 patients with pulmonary venous hypertension (41), b) lower muscle resting StO_2 in PAH
355 compared to CHF and healthy subjects (9), c) greater quadriceps oxygen delivery-to-
356 utilization inequalities (Δ[Mb-HHb]; change in deoxygenated myoglobin from rest to
357 exercise) in PAH compared to healthy subjects, which accounted for a slower rate of
358 adaptation of aerobic metabolism at exercise (2) and d) reduced quadriceps oxygenation
359 (lower Q-ΔStO2, higher Δ[Mb-HHb]) in PAH compared to normal subjects even during
360 submaximal exercise (22). Δ[Mb-HHb] was also related to reduced quadriceps capillarity
361 and strength, and lower VO_2 (22).

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

supplementation (22).

A unifying 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 scores).

The current study is limited by its cross-sectional design, small sample and small number of patients with advanced disease willing to undergo such a complex study protocol. Stroke volume profile of 3 (15%) patients had to be excluded due to invalid impedance cardiography signal but this limitation is inherent to impedance cardiography and this figure is similar to previously published experience in precapillary PH (12). Furthermore, the absence of direct measurement of peripheral muscle strength does not allow for further exploration of the role of the peripheral muscle. Arterial oxygen content was estimated using continuous SpO_2 readings at the expense of possible reduced accuracy in the hypoxaemic patients compared to invasive arterial blood sampling. For patient comfort, measurements of 6MWD and NT-proBNP were retrospective in nature. However, in the context of clinical stability (a prerequisite for patient inclusion in the study), an interval of 30 days is a clinically acceptable collection period for both

391 measures. With regards to walking intensity, albeit an attractive measure of the most
392 important mode of human physical activity, it ignores physical activities not involving
393 walking. This may have introduced some limitations in the assessment, interpretation and
394 prediction of the overall physical activity. Finally, this study did not investigate the
395 possible impact of specific diseases and drug therapy on muscle function or the effect of
396 unmeasured variables such as environmental, social and personal factors to daily physical
397 activity. These factors might have accounted for the unexplained variance in daily
398 walking intensity and the moderate correlation of 6MWD with daily walking intensity. Of
399 note, CAMPHOR scores did not correlate with daily walking activity. Taken together
400 with previously shown weak-to-moderate correlations of accelerometry data with 6MWD
401 and patient-reported questionnaire scores (39), these findings question the surrogate value
402 of routine clinical tools in the prediction of daily physical activity in precapillary PH.

403 **Conclusions**

404 Daily physical activity holds promise to be a meaningful, patient-related outcome
405 measure in PH. Our preliminary findings suggest a significant relation between estimates
406 of right ventricular status (as assessed by NT-proBNP levels and heart rate responses)
407 pulmonary vascular status (as assessed by TLCO %predicted), peripheral muscle
408 oxygenation and HRQoL with reduced daily walking intensity in precapillary PH.
409 However, further research is warranted to unravel the physiological determinants and
410 establish the clinical predictors of this phenomenon. The role of muscle function in the
411 natural history of precapillary PH merits particular focus as it offers a potential target for
412 effective interventions.

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Figure Captions

Figure 1: Study flow chart. BMI: body mass index; WHO FC: World Health Organization functional class; PFT: pulmonary function testing; 6MWD: 6-minute walk distance; log-NTproBNP: log-transformed N-terminal pro-brain natriuretic peptide. VO_2: oxygen uptake; VE: minute ventilation; MI: movement intensity; VE/VO_2: ventilatory equivalent ratio for oxygen; VE/VO_2: ventilatory equivalent ratio for carbon dioxide; HRR: heart rate reserve; SpO_2: oxyhaemoglobin saturation; 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. The study protocol for each patient was concluded within 2 weeks. * Retrospective data (median interval: 30 days); § Resting and exercise value was the average value obtained during the last minute of the 1st and 3rd stage of the personalised treadmill test (see text for explanation), respectively; # SV and 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.

442 **Table 1**: Clinical 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)**	
Walking Intensity, m/s^2	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, *yrs*	54.1 ± 15.9	66.0 (44.0-73.0)	48.5 (24.0-56.0)	.045*
BMI, kg/m^2	29.9 ± 5.7	28.1 (18.8-31.6)	25.5 (21.3-29.7)	.705
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
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

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; FEV1: force expiratory volume in one second; FVC, forced vital capacity; TLCO: transfer factor for carbon monoxide. *Significant statistical difference between patient group.

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*
log-NTproBNP, *pg/mL*	2.53 ± 0.53	2.99 (2.75-3.29)	2.10 (1.79-2.42)	<.001*
FEV_1, %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
FEV_1/FVC	66.5 ± 8.5	69.0 (60.3-72.0)	66.5 (63.3-71.0)	0.62
TLCO, %	51.1 ± 19.2	62.5 (47.9-73.0)	38.0 (29.7-53.6)	0.025

443

444 **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, *ml/dl*	18.1 ± 1.42	17.3 (16.3-19.1)	19.1 (17.7-19.3)	.1
Systemic oxygen delivery, *l/min*	1.4 ± .5	1.6 (1.1-2.6)	1.4 (1.2-1.6)	.556

[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; VE: minute ventilation; MVV: maximum voluntary ventilation; VE/VO_2: ventilatory equivalent ratio for oxygen; VE/VO_2: ventilatory equivalent ratio for carbon dioxide; VO_2: oxygen uptake; a-vO_2 difference: arterio-venous oxygen content difference. *Significant statistical difference between patient groups.

Systemic a-vO_2 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

Table 3: Independent predictors of walking intensity in the two multivariate linear regression analyses[1].

	Unstandardised Regression coefficient		95% CI for	Standardised Regression coefficient			Change statistics	
Model 1	B	SE	B	B	P value	R^2	R^2 change	F change
Constant	2.901	.171	2.540 to 3.263	-				
log-NTproBNP	-.292	.068	-.436 to -.148	-.557	0.001	.555	-	22.45
Age	-.008	.002	-.013 to -.004	-.485	0.002	.755	.20	13.88
Model 2	B	SE	B	B	P value	R^2	R^2 change	F change
Constant	.679	.286	.070 to 1.288	-				
HRR	.006	.002	.001 to 0.11	.506	.015	.436	-	12.38
Q-StO_2	.010	.005	.000 to .020	.395	.049	.538	.132	9.87

[1] Model 1 contains clinical characteristics. Model 2 contains physiological characteristics. Log-NTproBNP: log-transformed N-terminal pro-brain natriuretic peptide; HRR: heart rate reserve; Q-StO_2: quadriceps tissue oxygenation index.

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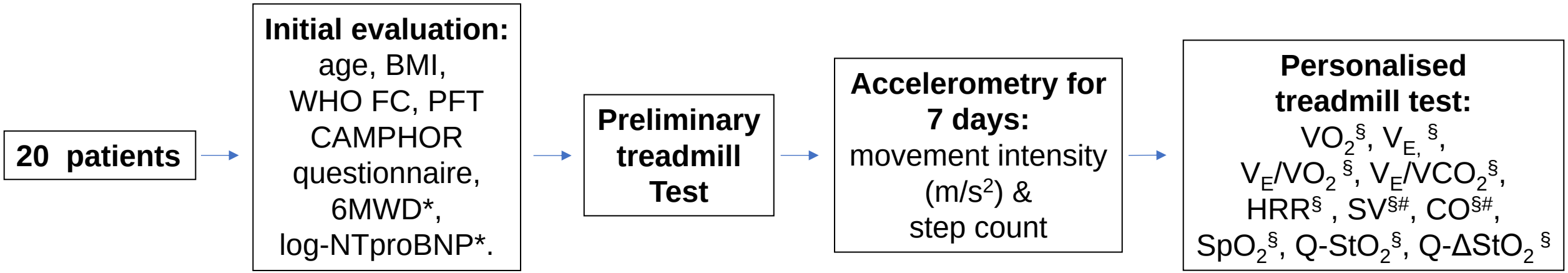
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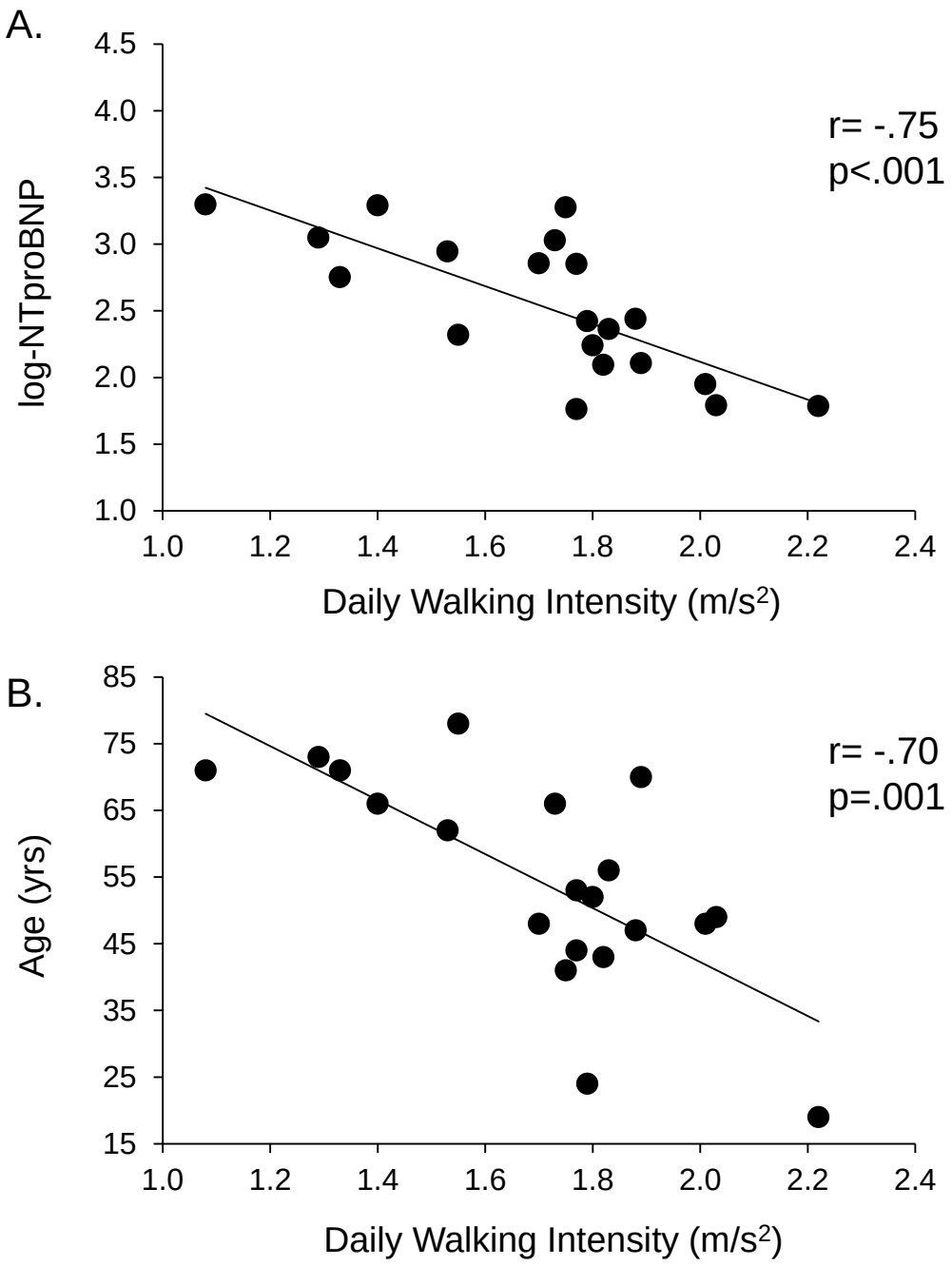
WHO FC, PFT
CAMPHOR
questionnaire,
6MWD*,
log-NTproBNP*.
Preliminary treadmill Test
Accelerometry for 7 days:
movement intensity (m/s²) &
step count
Personalised treadmill test:
VO2§, VE,§,
VE/VO2§, VE/VCO2§,
HRR§ , SV§#, CO§#,
SpO2§, Q-StO2§, Q-ΔStO2§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Daily Walking Intensity (m/s2)
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p<.001
B.
Age (yrs)
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45
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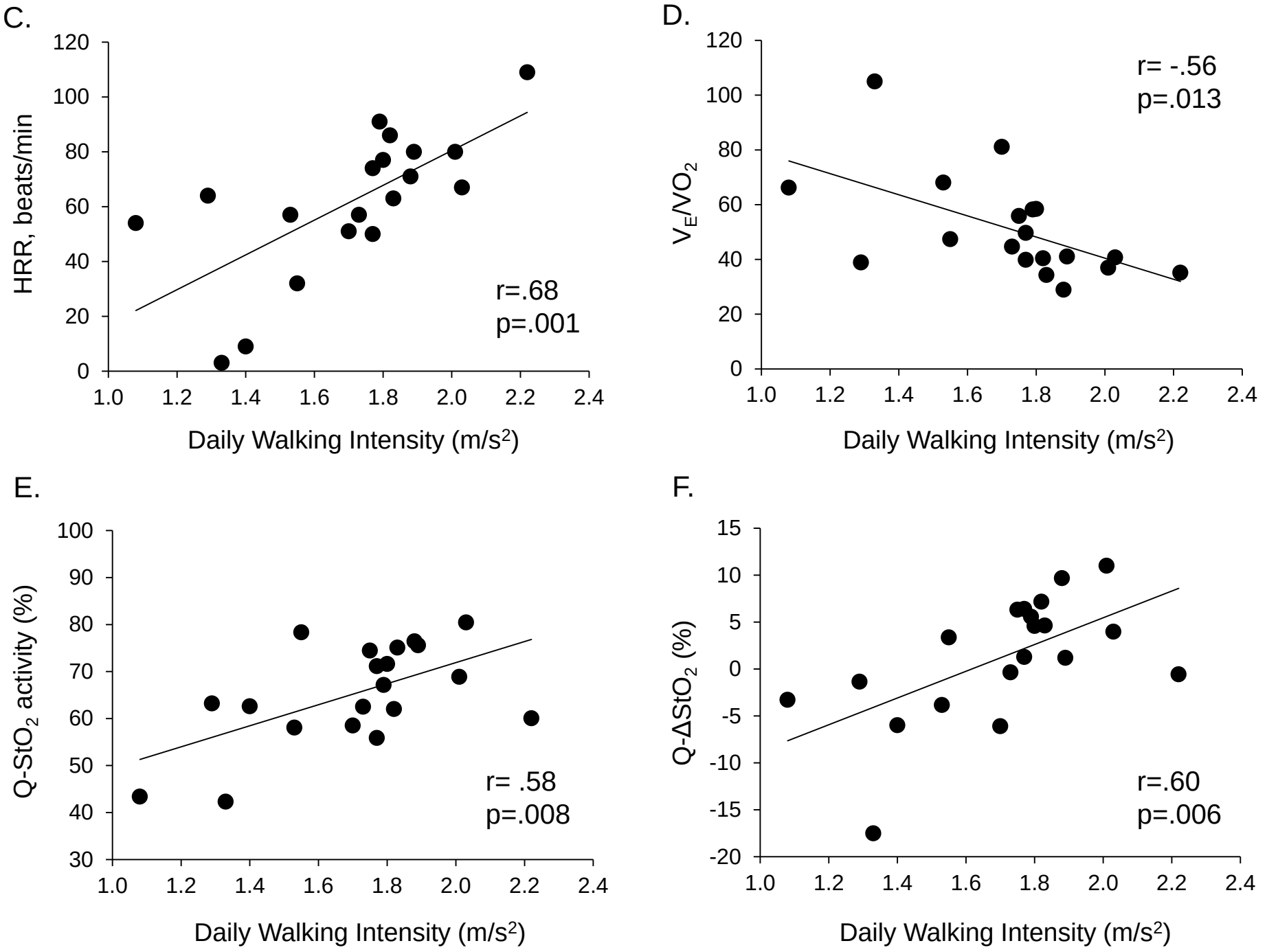
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80
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1.6
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2.0
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2.4
Daily Walking Intensity (m/s²)
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p=.001
D.
V_E/VO_2
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p=.013
Daily Walking Intensity (m/s²)
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Q-StO_2 activity (%)
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90
80
70
60
50
40
30
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Daily Walking Intensity (m/s²)
F.
Q-ΔStO_2 (%)
15
10
5
0
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-10
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-20
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Daily Walking Intensity (m/s²)