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1   Title: **A study of clinical and physiological relations of daily physical activity in**

2   **precapillary pulmonary hypertension.**

3

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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/s^2) 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-StO$_2$: r=.58, p=.008), change in Q-StO$_2$

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-StO$_2$ (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.

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 <u>Study Sample</u>

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

101 interfering with physical activity and treadmill testing. Approval from the West of

102 Scotland Research Ethics Committee (14/WS/1075) and written consent were obtained.

103 Initial evaluation

104 Subjects had determination of WHO functional class, maximum voluntary ventilation

105 (MVV=FEV_1 x 35) (1) and transfer factor for carbon monoxide (TLCO) corrected for

106 haemoglobin concentration. (19). They also completed the patient-reported Cambridge

107 Pulmonary Hypertension Outcome Review (CAMPHOR) (25) and emPHasis-10 (48),

108 two well-validated questionnaires for the assessment of HRQoL in PH. CAMPHOR is

109 probably the most widely studied questionnaire in PH and has been shown to predict

110 clinical deterioration in idiopathic PAH and CTEPH (24). However, neither CAMPHOR

111 nor emPHasis-10 questionnaires have been validated against objective, accelerometry

112 measures of daily physical activity to date.

113 Finally, N-terminal pro-brain natriuretic peptide (NTproBNP) and 6-minute walk

114 distance (6MWD) were retrieved from the medical record (median interval: 30 days for

115 both).

116 Preliminary treadmill test

117 Subjects performed an incremental treadmill test (RAM 770M; RAM Medical and

118 Industrial Instruments & Supplies, Padova, Italy) at an initial speed of 1.4 km/h that

119 increased by 0.8 km/h every 3 minutes to the limit of tolerance as previously described

120 (17, 18). The treadmill speed was determined by a communicating ergospirometry testing

121 system (CASE ES, GE Healthcare, Freiburg, Germany). Minute-by-minute walking

122 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   <u>Accelerometry</u>

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   <u>Personalized treadmill test</u>

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

145 of daily walking intensity). The duration of each stage was 4 minutes in order to reach

146 steady physiological state (18). Continuous physiological measurements were obtained

147 throughout as described below. The resting and exercise value for each variable was the

148 average value obtained during the last minute of the first and third stage, respectively.

149 ## Metabolic profile

150 Oxygen uptake (VO_2), minute ventilation (V_E) and ventilatory equivalent ratio for

151 oxygen uptake (V_E/VO_2) and carbon dioxide (V_E/VCO_2) were recorded breath-by-breath

152 (CASE ES, GE Healthcare, Freiburg, Germany). Oxyhaemoglobin saturation (SpO_2) was

153 recorded continuously by pulse oximetry (Oxywatch^{TM} MD300C63, Beijing Choice

154 Electronic Tech. Co. Ltd, China). Electrocardiography was used to calculate heart rate

155 (HR) reserve (HRR) defined as the difference between age-predicted maximal HR (220-

156 age) and peak HR (1).

157 ## Central hemodynamics

158 Estimates of stroke volume and cardiac output were measured using impedance

159 cardiography technology (PhysioFlow$^{®}$, Manatec Biomedical, France). PhysioFlow uses

160 variations in the transthoracic impedance to a high-frequency (75 kHz), low-amperage

161 (1.8 mA) alternating current across the thorax during cardiac ejection to calculate stroke

162 volume (4) and it has been previously validated (42) and used in PAH (12). Application

163 of six transthoracic electrodes, autocalibration, verification of signal quality and artifact

164 detection were performed as instructed by the manufacturer and described elsewhere (4).

165 ## Quadriceps oxygenation

166 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)] $\times$ 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 $Q\text{-}StO_2$ and mixed venous oxygen saturation measured at pulmonary artery in

174   PAH subjects, both at rest and exercise (32, 33).

175   To measure $Q\text{-}StO_2$, 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 $\times$ hemoglobin concentration $\times$ $\%SpO_2$. 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

189 dichotomised using the median daily walking intensity for an unpaired group comparison

190 using the Mann-Whitney *U*-test. Data were analyzed using the SPSS statistical package

191 (v 20, SPSS Inc., Chicago, IL). The level of significance was set at p<.05. On the basis of

192 data from a previous study (18), the critical sample size to achieve a power of 80% for

193 detection of differences between patient groups with two-sided level of significance <.05

194 was 16 patients (calculated using the Stata package; StataCorp LP, Texas, USA).

195 **Results**

196   Patient characteristics

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

198 the protocol without adverse effects and included in the analysis (Figure 1). Stroke

199 volume profile of 3 (15%) patients had to be excluded due to invalid impedance

200 cardiography signal. Sixteen patients had PAH (9, idiopathic PAH; 6, connective tissue

201 disease associated-PAH; 1, PAH after correction of congenital heart disease) and 4

202 patients had CTEPH. None of the patients had significant cardiac shunt detected at right

203 heart catheterisation or follow-up echocardiograms. All patients were on PH-specific

204 therapy: 10, monotherapy (7, phosphodiesterase-5 inhibitor (PDEi); 2, stimulator of

205 soluble guanylate cyclase (sGC); 1, endothelin receptor antagonist (ERA)) and 10,

206 combination therapy (6, PDE-i+ERA; 1, ERA+sGC; 3, PDEi+ERA+inhaled prostanoid).

207 None of the patients was on heart rate-limiting medication.

208   Total and daily time of accelerometry monitoring were 6.4±0.94 days and 864±94

209 min, respectively. Mean and median daily walking intensity were 1.71±0.27 m/s^2 and

210 1.78 (1.55, 1.83) m/s^2, respectively. Daily walking time was 61±26 min and daily steps

211 4897±2209.

212   Correlations and predictors of daily walking intensity

213   Significant clinical correlations with mean daily walking intensity were observed for

214   log-NTproBNP (r=-.75, p=<.001), age (r=-.70, p=.001) and 6MWD (r=.50, p=.026)

215   (Table 1; Figure 2). Significant physiological correlations with mean daily walking

216   intensity were observed for HRR (r=.68, p=.001), Q-StO$_2$, (r=.58, p=.008), change in Q-

217   StO$_2$ from rest to mean daily walking intensity (r=.60, p=.006), V$_E$/VO$_2$ (r=-.56, p=.013)

218   and TLCO %predicted (r=.51, p=0.022) (Table 2; Figure 2). There was no association

219   between estimates of stroke volume at rest or exercise and mean daily walking intensity

220   Stepwise multivariate regression analysis of significant clinical measures retained log-

221   NTproBNP (b=-.290±.068, β=-.554, p=.001) and age (b=-.008±.002, β=-.486, p=002)

222   accounting for 55% and 20% of the variance in mean daily walking intensity,

223   respectively. Repeated for the significant physiological measures, analysis retained HRR

224   (b=.006±.002, β=.506, p=.015) and Q-StO$_2$ at activity (b=.01±.005, β=.395, p=.049)

225   accounting for 44% and 13% of the variance in mean daily walking intensity,

226   respectively.

227   Comparison between less and more active patients

228   There was no significant difference in VO$_2$ between less and more active patients.

229   Less active patients had significantly increased age, log-NTproBNP, V$_E$/MVV, V$_E$/VO$_2$,

230   CAMPHOR and emPHasis-10 scores and decreased TLCO %predicted, HRR, Q-StO$_2$ at

231   mean daily walking intensity and Q-ΔStO$_2$; they also showed 100-meter reduction in

232   6MWD compared to more active patients (for all numerical values and P-values see

233   Table 1 and 2).

234

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-StO$_2$ at activity, ΔQ-StO$_2$) and ventilatory efficiency

241   (V_E/VO$_2$) were also associated significantly with mean daily walking intensity. log-

242   NTproBNP, HRR and Q-StO$_2$ 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 0f 17 to 33% compared to healthy age-matched

250   individuals. Daily walking intensity in the present cohort (1.7 m/s^2) favorably compares

251   with that adopted by older patients with moderate/severe COPD (spirometric classes

252   II/III), typically corresponding to 1.8 m/s^2 (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

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

279   patients and it was dissociated with daily walking activity. Cardiac output as such also

280   did not correlate with daily walking intensity in the present cohort. Previous studies using

281   right heart catheterisation data also failed to show correlation between cardiac

282   output/index and daily physical activity levels in precapillary PH (21, 36). In contrast,

283   TLCO %predicted, reflecting pulmonary capillary volume, was also negatively

284   associated with mean daily walking intensity and 40% lower in less active patients.

285   Collectively, our findings on NT-proBNP and HRR profiles and, TLCO %predicted

286   speak for a significant relation between the right ventricular and pulmonary capillary

287   volume status and daily physical activity in precapillary PH.

288   The ventilatory response becomes exaggerated in precapillary PH due to

289   chemo/ergo/baro- receptor sensitivity, dead space ventilation and hypoxemic drive.

290   Premature lactic acidosis at the peripheral muscles due to hypoxemia will also increase

291   the ventilatory drive on activity. Physiologically, the ventilatory response to the

292   metabolic requirement is reflected in the V_E/VO_2 relationship (1). Accordingly, we

293   observed a negative correlation between V_E/VO_2 and mean daily walking intensity

294   whereas V_E/VO_2 and V_E/MVV were significantly higher among less active patients (by

295   almost 20% and 40%, respectively). V_E/VCO_2, ratio, another important index of

296   ventilatory efficiency and of prognostic significance in precapillary PH, also differed

297   between the 2 groups (58 vs. 44); however, it did not reached statistical significance,

298   possibly, due to submaximal testing and small sample. Such an exaggerated ventilatory

299   response is highly relevant to physical activity as it may promote dyspnoea and cessation

300   of exercise.

301   Patients with PAH exhibit significant morphological and functional changes of

302 quadriceps muscle including alteration in the muscle fibre type, muscle atrophy, reduced

303 capillarity and oxidative capacity, and endothelial dysfunction (31). These abnormalities

304 may impair the local tissue oxygen delivery and utilization capacity, muscle strength and

305 exercise capacity (20). Importantly, muscle characteristics were unrelated to the

306 hemodynamic severity (20) and targeted exercise training reversed abnormalities and

307 improved exercise capacity (6, 26), which suggest that peripheral muscle abnormalities

308 may be implicated independently in the exercise pathophysiology of PAH. Here, Q-StO_2

309 at activity correlated with mean daily walking intensity, predicted a clinically significant

310 amount of the variance in daily walking intensity, and was significantly lower in less

311 active patients. Importantly, ΔQ-StO_2 responses opposed between patient groups: less

312 active patients drop Q-StO_2 whereas more active patients benefited from increased Q-

313 StO_2 at individual mean daily walking intensity.

314 Factors determining local muscle oxygenation are modulated by the rate of oxygen

315 delivery and oxygen extraction (8). Whereas arterial oxygen content and systemic oxygen

316 delivery did not differ between the present patient groups, less active patients had

317 significantly reduced a-vO_2 difference and $\sim 10\%$ reduction in oxygen extraction ratio

318 compared to more active patients. Collectively, our novel findings on estimates of muscle

319 oxygenation suggest a strong relation between capacity to enhance local muscle

320 oxygenation and better preserved daily physical activity and they provide support to the

321 peripheral muscle hypothesis (29). They also add to previous evidence showing: a)

322 impaired oxygen extraction rate during maximal exercise in PAH patients compared to

323 patients with pulmonary venous hypertension (41); b) lower thenar muscle resting StO_2 in

324 PAH compared to CHF and healthy subjects (9); c) greater quadriceps oxygen delivery-

325   to-utilization inequalities (Δ[Mb-HHb]; change in deoxygenated myoglobin from rest to

326   exercise) in PAH compared to healthy subjects, which accounted for a slower rate of

327   adaptation of aerobic metabolism at exercise (2); and d) reduced quadriceps oxygenation

328   (lower Q-ΔStO2, higher Δ[Mb-HHb]) in PAH compared to normal subjects even during

329   submaximal exercise (22); Δ[Mb-HHb] was also related to reduced quadriceps capillarity

330   and strength, and lower VO_2 (22).

331   Certainly, our study design does not allow for proof of causality and further research is

332   required before a primary impairment of peripheral muscle oxygenation is considered a

333   true limiting factor rather than a mere consequence of deconditioning, or reflection of

334   hypoxemia. Nonetheless, we found no association between Q-StO$_2$ and SpO$_2$ or arterial

335   oxygen content at rest/exercise (p>0.5 for all). Furthermore, Q-ΔStO$_2$ and Δ[Mb-HHb] in

336   PAH subjects have been previously shown to remain unchanged with oxygen

337   supplementation (22).

338   A unified explanation may lie within the seemingly paradoxical absence of difference

339   in VO$_2$ between less and more active patients. It is possible that the metabolic

340   requirements of the increased workload (reduced HRR) of the stressed heart (increased

341   log-NTproBNP) and increased/inefficient ventilation (increased V$_E$/MVV, V$_E$/VO$_2$) in

342   less active patients had matched the oxygen requirements of increased daily walking

343   intensity in more active patients. Teleologically, it may that both patient groups had

344   adjusted their activity to a certain threshold of oxygen/energy cost that allowed for

345   acceptable exertional symptoms such as muscle fatigue and breathlessness (as suggested

346   by responses in ventilation and estimates of quadriceps oxygenation). Ultimately, less

347   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.

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.

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385   **Disclosures**

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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/VO_2: ventilatory equivalent ratio for carbon dioxide; SpO_2: oxyhaemoglobin saturation; HRR: heart rate reserve; SV: stroke volume; CO: cardiac output; $Q\text{-}StO_2$: quadriceps tissue oxygenation index; $Q\text{-}\Delta StO_2$: change in $Q\text{-}StO_2$ 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 ($Q\text{-}StO_2$) at activity (E); and change in $Q\text{-}StO_2$ from rest to activity ($Q\text{-}\Delta StO_2$) (F) in 20 patients with precapillary pulmonary hypertension.

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

| Variable | All (n=20) | Daily walking intensity, m/s^2 | | P-value |
		< 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, yr	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
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)**	
SpO₂ 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-StO₂ 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-ΔStO₂, *%*	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$_E$/VO₂	51.1 ± 18.8	55.8 (39.8-81.1)	40.6 (34.3-58.2)	.041*
VO₂, *ml·kg^{-1}·min^{-1}*	9.5 ± 1.4	9.4 (7.5-11.0)	9.7 (7.9-10.5)	.806
V$_E$/VCO₂	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$_E$/VO₂: ventilatory equivalent ratio for carbon dioxide; VO₂: 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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