Physical Activity Limitation as Measured by Accelerometry in Pulmonary Arterial Hypertension

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Background: The 6-min walk test, commonly used to assess exercise capacity and response to therapy in pulmonary arterial hypertension (PAH), has many well-described limitations. Sedentary time is associated with adverse cardiovascular outcomes and reduced quality of life, and measuring sedentary time and physical activity using accelerometry is another potential way to quantify exercise capacity in PAH. Whether sedentary time is different in patients with PAH vs control subjects is unknown.

Methods: Physical activity was measured in 20 patients with PAH and 30 matched healthy control subjects using accelerometry for 7 consecutive days. Patients with PAH completed standard 6-min walk testing, and baseline demographics were recorded for all study participants. Total daily activity counts, sedentary time, and proportion of time at various activity levels were compared between groups.

Results: Sedentary time was significantly higher in patients with PAH (mean, 92.1% daily activity; 95% CI, 89.5-94.8%) than in control subjects (mean, 79.9% daily activity; 95% CI, 76.4%-83.5%; $P < .001$), and all levels of physical activity were reduced in the PAH group compared with the control group ($P < .01$ for all). Daily moderate to vigorous physical activity was reduced in the PAH group (7.5 min; 95% CI, 0.8-15.6 min) compared with the control group (mean, 64.7 min; 95% CI, 51.1-78.2 min; $P < .001$). Activity counts correlated with 6-min walk distance in the PAH group (Spearman rank correlation = 0.72, $P < .001$).

Conclusions: Sedentary time is increased in patients with PAH and may lead to increased risk for metabolic and cardiovascular morbidity. Quantitation of daily activity and sedentary time using accelerometry may be a novel end point for PAH management and clinical trials.

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Abbreviations: 6MWT = 6-min walk test; ERA = endothelin receptor antagonist; MET = metabolic equivalent; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase-5 inhibitor; r-s = Spearman rank correlation; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of pulmonary arterioles, leading to elevated pulmonary vascular resistance and right-sided heart failure. Despite the

availability of several therapies for PAH,¹⁻³ the morbidity and mortality of this disease remain high. Impaired exercise tolerance is a prominent feature of PAH and contributes significantly to reduced quality of life. Assessing exercise capacity is an integral part of the clinical evaluation of PAH⁴ and is an important primary end point for clinical trials in

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PAH.⁵ Exercise capacity is most commonly assessed using the 6-min walk test (6MWT),⁶ although this test has many limitations and may not demonstrate exercise intolerance in patients who are less severely ill.^{5,7,8} In addition, the 6MWT and other methods assessing exercise capacity cannot capture patterns of physical activity, including sedentary time (time at 1.0-1.5 metabolic equivalents [METs]), which has been associated with adverse cardiovascular health outcomes.⁹⁻¹¹ Because decreased total physical activity and increased sedentary behavior may contribute to reduced quality of life in patients with PAH, improved methods of accurately assessing physical activity and sedentary behavior are needed for clinical practice and trial end points.

Accelerometers are well-validated, easy-to-use instruments that quantitate patterns of physical activity in multiple planes.¹²⁻¹⁴ Accelerometry has been used in adults with left-sided heart failure to measure the effect of intervention on daily activity, and results suggest a correlation with survey-based quality of life.^{15,16} Accelerometry has been used to demonstrate reduced physical activity and energy expenditure in patients with PAH relative to healthy control subjects¹⁷; however, evaluation of daily sedentary time in patients with PAH compared with healthy control subjects has not been reported. We hypothesized that total daily physical activity as measured by a waist accelerometer would be lower in patients with PAH than in healthy control subjects and that patients with PAH would spend significantly more time per day in sedentary behaviors than healthy control subjects.

MATERIALS AND METHODS

Study Sample

Approval was obtained from the Vanderbilt University Institutional Review Board (protocol 090782), and written informed consent was obtained. Patients aged >18 years with established World Health Organization (WHO) functional class I PAH who were seen for routine follow-up in the pulmonary vascular clinic between December 2009 and April 2011 were eligible. Hemodynamic confirmation of PAH was established by right-sided heart catheterization in all patients according to published guidelines.⁴ Only those with stable PAH (defined as no hospitalization for PAH and no escalation in dose or addition of PAH therapy or diuretics within 2 months prior to enrollment or during the study) were included. Exclusion criteria were a pulmonary artery occlusion pressure of >15 mm Hg, mixed pulmonary hypertension, more than one etiology for pulmonary hypertension, portopulmonary hypertension, significant arthritis or conditions other than pulmonary vascular disease limiting ambulatory activities (eg, orthopedic injury, neurologic disease), or significant obstructive or restrictive lung disease (FEV₁/FVC <70%, total lung capacity <70% predicted). Patients with PAH who initiated a structured physical rehabilitation program within 2 months of study enrollment were not eligible to participate. Enrollment

was offered to eligible patients in clinic as accelerometer devices became available. During the study, additional devices (five devices total) were obtained to facilitate enrollment. Thirty healthy subjects matched by age, sex, and BMI to the patients with PAH were recruited from the community.

Participant Characteristics

For each study participant, age and sex were recorded, and measurement of height and weight was performed for calculation of BMI. For patients with PAH, the type of PAH and hemodynamic data (from right-sided heart catheterizations performed within 6 months of study enrollment) were obtained from the medical record. WHO functional classification was assigned by the treating provider at the time of study enrollment as part of routine clinic evaluation.

Accelerometry and Physical Activity Assessment

At study enrollment, patients with PAH underwent standard 6MWT according to protocol.⁶ Participants were then given an ActiGraph GT3X activity monitor (ActiGraph) to record physical activity for 7 consecutive days. The ActiGraph GT3X monitor is a small (3.8 × 3.7 × 1.8 cm), lightweight (27 g), triaxial accelerometer that measures physical activity as time-varying accelerations denoting locomotion. This device has been validated in numerous studies, including the National Health and Nutrition Survey,^{11,18-20} and provides accurate measurements of physical activity, including vector magnitude, activity counts, steps taken, energy expenditure, and activity intensity levels (METs). ActiGraph output can be used for estimating sedentary time and for ranking individuals by their level of sedentary time. Participants were instructed to wear the device on the waist over their dominant side for 7 consecutive days at all times except during sleep, bathing, or showering. They were encouraged to participate in their routine activities while completing the study. None of the patients with PAH or the control subjects were participating in a structured exercise program during this study.

On completion of data collection, ActiGraph monitors were returned to the study investigators in a self-addressed stamped envelope through US mail, and the data were downloaded using ActiLife (ActiGraph) software. Data were recorded in 60-s epochs for the duration of device wear. Days with at least 10 h of consecutive device wear were considered valid. Subjects with at least 4 valid days were included in the final analysis (all 50 enrolled subjects had ≥4 valid days). Total accelerometer counts were divided by time the device was worn (counts/min), and each 60-s period was classified into sedentary (1.0-1.5 METs), low-intensity (1.6-3.0 METs), moderate intensity (3.1-6.0 METs), and vigorous (>6.0 METs) activity levels, as reported elsewhere.¹⁸ Examples of routine household activities and their approximate intensity (METs) are shown in Table 1.^{21,22}

Statistical Analysis

The Mann-Whitney *U* test was used to assess the difference in activity counts and percentage of daily time spent at each activity level between patients with PAH and control subjects. Spearman rank correlation (*r*-s) and linear regression were used to examine correlations between activity count and 6MWT distance. Demographic data are presented as mean ± SD or percentages as appropriate. Activity counts are corrected for time of accelerometer wear and presented as mean values with 95% CIs. All *P* values are two sided, and a *P* < .05 was considered significant. Statistical analyses were performed using SPSS Statistics 19.0 (IBM) and Prism 4.0 (GraphPad Software, Inc) software.

Table 1—METs for Routine Household Activities

Activity Level (METs)	Examples of Activities
Rest/sedentary (<1.5)	Sitting quietly Watching television or listening to music
Low activity (1.6-3.0)	Sleeping Folding laundry Sweeping floors Cooking Bathing
Moderate activity (3.1-6.0)	Walking 2.0 mi/h on level surface Walking the dog Carrying < 15-lb load upstairs Food shopping Child care (feeding, bathing, changing)
Vigorous activity (>6.0)	Walking 3.0 mi/h on level surface Swimming Jogging/running Shoveling snow by hand Carrying groceries upstairs

MET = metabolic equivalent. Data from Ainsworth et al.²²

RESULTS

Participant Characteristics and Demographics

Twenty patients with PAH and 30 control subjects were enrolled and included in the analysis (Table 2). All participants were well matched by age, sex, and BMI. All patients were receiving PAH-specific therapy as follows: Six were receiving oral monotherapy (one, a calcium channel blocker; four, an endothelin receptor antagonist [ERA]; and one, a phosphodiesterase-5 inhibitor [PDE-I]), three were receiving IV prostaglandin monotherapy, two were receiving combination oral therapy (ERA + PDE-I), and nine were receiving combination oral and IV therapy (ERA, PDE-I, or both, plus IV prostaglandin).

Protocol Adherence

All participants completed the 7-day protocol, and there were no adverse events or discomfort complaints related to accelerometry. Patients with PAH had an average of 6.7 valid days (95% CI, 6.0-7.4 days) of accelerometer wear with an average of 683 min (95% CI, 628-739 min) of daily wear. Control subjects had more valid minutes of daily accelerometer wear (764 min, $P = .01$). Figure 1 shows representative single-day accelerometer graphical output from a patient with PAH.

Daily Physical Activity

Patterns of physical activity were different in patients with PAH and control subjects (Fig 2). Total daily activity counts were significantly reduced in the PAH group compared with the control group (Fig 3). Patients with PAH spent more time in sedentary

behaviors (mean, 92.1% daily activity; 95% CI, 89.5%-94.8%) than control subjects (mean, 79.9% daily activity; 95% CI, 76.4%-83.5%; $P < .001$) (Fig 4). Similarly, patients with PAH compared with control subjects had significantly less low (6.8% vs 11.4%, $P = .001$), moderate (1.1% vs 5.5%, $P < .001$), and vigorous (0.01% vs 3.1%, $P < .001$) daily activity (Fig 5). Daily moderate or vigorous activity (>3.0 METs) was significantly reduced in the PAH group (mean, 7.5 min; 95% CI, -0.8-15.6 min) compared with the control group (mean, 64.7 min, 95% CI, 51.1-78.2 min; $P < .001$). Vigorous activity (>6.0 METs) was rare in the PAH group: Only one patient with PAH, who was WHO functional class I treated with a calcium channel blocker, engaged in any vigorous activity during the study (average of 0.3% daily activity).

Physical Activity Level by WHO Functional Class in Patients With PAH

Total daily activity counts were significantly lower in patients with WHO class III/IV PAH (mean, 95.5 counts; 95% CI, 48.3-142.8 counts) compared with class I/II PAH (mean, 178.1 counts; 95% CI, 92.3-264.0 counts; $P = .02$) (Fig 6A). In addition, patients with PAH with more-severe heart failure

Table 2—Characteristics of Study Participants

Characteristic	PAH (n = 20)	Control Subjects (n = 30)
Age, y	53.7 ± 14.3	51.1 ± 15.4
Female sex, No. (%)	15 (75)	22 (73)
BMI, kg/m ²	29.0 ± 6.8	30.1 ± 8.6
Type of PAH		
Idiopathic	7	...
Heritable	3	...
CTD	7	...
CHD	2	...
HIV	1	...
Hemodynamics		
RAP, mm Hg	6.5 ± 4.4	...
PA systolic, mm Hg	72.9 ± 20.6	...
PA diastolic, mm Hg	29.3 ± 9.6	...
Mean PAP, mm Hg	46.4 ± 12.7	...
PAOP, mm Hg	8.4 ± 3.8	...
CO, L/min	5.5 ± 1.8	...
Cardiac index, L/min/m ²	3.0 ± 1.1	...
PVR, Wood units	8.4 ± 3.8	...
WHO functional class, No.		
I	1	...
II	10	...
III	7	...
IV	2	...

Data are presented as mean ± SD, unless otherwise indicated. CHD = congenital heart disease; CO = cardiac output; CTD = connective tissue disease; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PAOP = pulmonary artery occlusion pressure; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; WHO = World Health Organization.

FIGURE 1. Representative single-day ActiGraph output from a patient with World Health Organization (WHO) functional class III pulmonary arterial hypertension. Activity count (y-axis) is shown as a function of time of day (x-axis). Sedentary (< 1.5 metabolic equivalents [METs]), light (1.6–3.0 METs), moderate (3.1–6.0 METs), and vigorous (> 6.0 METs) activity levels are shown according to ActiGraph specifications.

(WHO functional class III/IV) had increased mean sedentary time per day (mean, 94.8% daily time; 95% CI, 91.1%–98.5%) compared with patients with functional class I/II PAH (mean, 90.0% daily time; 95% CI, 86.1%–93.8%; $P = .01$) (Fig 6B).

Activity Count and Conventional PAH Assessments

Total activity count correlated with 6MWT distance in patients with PAH ($r-s = 0.72$, $P < .001$) (Fig 7). Neither 6MWT distance nor activity count was correlated with hemodynamic parameters, including right atrial pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac output ($P > .07$ for all, data not shown). WHO functional class did correlate with 6MWT distance in this population ($r-s = -0.55$, $P = .01$).

DISCUSSION

The results show that assessment of physical activity in patients with PAH using accelerometry is well tolerated and that these patients have profound activity limitation and increased sedentary time relative to healthy control subjects. Determination of sedentary time and physical activity intensity is feasible in clinical practice, and accelerometer-derived variables may be important end points for future studies in PAH.

Accelerometers record physical activity as activity counts, a somewhat arbitrary value for a clinician. Sedentary time (minutes or proportion of daily awake time spent at ≤ 1.5 METs) may be a more clinically meaningful output. Sedentary behaviors are closely linked to all-cause mortality,^{10,23} cardiovascular mortality,²⁴ metabolic syndrome,^{11,25} inflammation,¹¹ and insulin resistance.^{26,27} The present finding that patients with PAH spend 92.1% of their awake time, on average 10.5 h per day, in sedentary activity denotes

FIGURE 2. Daily activity in patients with PAH and control subjects. Mean percentage of daily time spent at each activity level is shown for the control and PAH groups. PAH = pulmonary arterial hypertension. See Figure 1 legend for expansion of other abbreviation.

FIGURE 3. Activity counts are significantly reduced in patients with PAH compared with control subjects. For each group, the median is shown as the black bar; boxes represent the interquartile range. The open circle denotes an outlier value, and the asterisk denotes an extreme value. $P < .001$ by Mann-Whitney U test. See Figure 2 legend for expansion of abbreviation.

significant cardiopulmonary limitation that likely affects overall quality of life. Given the association of sedentary time with adverse cardiovascular outcomes,¹⁰ further studies examining the impact of sedentary time on PAH outcomes are needed. Decreasing sedentary time may be an important target of therapy in PAH. Reducing sedentary time may improve outcomes in left-sided heart failure^{28,29} as well as ameliorate the degree of insulin resistance,^{30,31} but this has not been studied in PAH.

Regimented exercise programs aimed at increasing moderate to vigorous activity, have been shown to improve 6-min walk distance,³² exercise endurance,

FIGURE 4. Sedentary time is increased in patients with PAH compared with control subjects. Sedentary time is shown as percentage of time per day at 1.0 to 1.5 METs for patients with PAH and control subjects. For each group, the median is shown as the black bar; boxes represent the interquartile range. The open circles denote outlier values. $P < .001$ by Mann-Whitney U test. See Figure 1 and 2 legends for expansion of abbreviations.

and quadriceps strength³³ in PAH. Efforts to decrease sedentary time complement exercise programs and cardiovascular training because sedentary time has deleterious effects, even in individuals who exercise.¹⁰ To date, no trial has used accelerometry to show an increase in physical activity or a reduction in sedentary time in PAH. Treatment with PAH therapy was shown to increase daily activity count in a subset of patients in a multicenter study using implantable hemodynamic monitors with movement-detection technology.³⁴ Noninvasive accelerometers, such as the ActiGraph used in this study, have complementary applicability given their availability and lower cost, and they do not require a procedure for placement. Whether currently approved therapies lead to reductions in sedentary time and changes in the profile of daily activity by this method of accelerometry in PAH is unknown.

The present results are similar to the findings of Mainguy et al,¹⁷ showing reduced total daily activity and reduced moderate and vigorous (> 3 METs) activity in patients with PAH compared with healthy control subjects. Increased sedentary time in PAH is a novel finding highlighted in the present study and may have important implications for disease management and patient quality of life. The ActiGraph device we used is one of the most widely validated monitors for assessing sedentary time in large population studies.³⁵ The inclusion of WHO functional classes I to IV in this study shows the range of physical activity across a wide spectrum of PAH disease severity, as typically encountered in outpatient practice.

The 6MWT is the current routine assessment of exercise capacity in PAH, and change in 6MWT distance remains an important objective end point in clinical trials.⁵ The present data and that of others¹⁷ show that 6MWT distance correlates with free-living total daily activity, suggesting that the 6MWT remains a useful test of submaximal exercise performance. Accelerometry has several advantages over the 6MWT for assessment of exercise performance. First, it shows patterns of activity across days at a time rather than at a single point in time. It can accurately quantify sedentary time and intensity of exercise, metrics with clinical relevance and potential application as novel end points for clinical trials. Increases in activity count and reduction in sedentary time as measured by accelerometry is a patient-centered outcome with direct application to patients' routine activities.

It has been suggested that the 6MWT may lack the ability to detect clinically significant changes in patients with PAH with less-severe heart failure symptoms (WHO class II),⁷ patients who are increasingly being enrolled in clinical trials. Given the greater breadth of data available with accelerometry, it is possible that this method will provide more-accurate

FIGURE 5. Low, moderate, and vigorous activity in patients with PAH and control subjects. Results are shown as mean percentage of daily activity. * $P = .001$ by Mann-Whitney U test. ** $P < .001$ by Mann-Whitney U test. See Figure 1 and 2 legends for expansion of abbreviations.

data regarding the efficacy of therapy. Accelerometry has been well validated in children³⁶⁻³⁹ and has significant promise as a potential clinical tool to assess functional status and response to therapy in younger children with PAH, where 6MWT and cardiopulmonary exercise testing are challenging and unreliable. Contrary to cardiopulmonary exercise testing, which is somewhat labor intensive to perform and requires interpretation by trained subspecialists, accelerometers are easy to use and require minimal additional technology to analyze and interpret data.

Submaximal exercise testing, which requires less specialty expertise to perform than traditional cardiopulmonary exercise testing, is gaining momentum as a useful tool in PAH.⁴⁰ Whether accelerometer-derived activity measures correlate with physiologic variables derived from exercise testing (ie, ventilatory equivalent for CO_2) is not known but is an important question to address in future studies.

The present study has several limitations. First, this was a single-center study, and the PAH population may not be representative of other centers. Despite this, the mean age, types of PAH, and WHO functional classes included in this study were similar to other large PAH studies.⁴¹ We did not see a correlation between 6MWT distance and hemodynamic variables as reported by others,⁴² which may be due to the small sample size. Consecutive clinic patients were not enrolled; thus, the study population may be subject to sampling bias. We did not collect simultaneous journals of physical activity in each patient, so we cannot relate activity intensity to specific behaviors. Although we did exclude patients with neurologic and musculoskeletal disease-limiting mobility, we acknowledge that other conditions, including depression, anxiety, and other psychosocial stressors, not specifically assessed for prior to study enrollment could also limit activity. None of the participants had clinical evidence for severe depression or anxiety, however. We did not perform quality-of-life assessments in the participants, so we cannot determine the relationship of sedentary activity and quality of life in PAH from this study. Whether increased sedentary time is associated with poorer quality of life, assessed with a validated instrument for patients with

FIGURE 6. Physical activity by WHO functional classification. A, Total daily activity count in patients with WHO class I/II compared with class III/IV pulmonary arterial hypertension. B, Percentage of time per day at 1.0 to 1.5 MET (sedentary/rest time) in patients with WHO class I/II compared with class III/IV pulmonary arterial hypertension. The open circle denotes an outlier value, and the asterisks denote extreme values. P values shown are for comparison between groups using Mann-Whitney U test. See Figure 1 and 2 legends for expansion of abbreviations.

FIGURE 7. Daily activity count correlates with 6-min walk distance in patients with pulmonary arterial hypertension.

PAH (eg, CAMPHOR [Cambridge Pulmonary Hypertension Outcome Review]^{43,44}), is unknown and a focus of future study. The small samples size also precludes subgroup analysis, so it is unknown whether sedentary time is significantly different between patients with idiopathic PAH and those with associated PAH, for example. Although the ActiGraph device is one of the most well-validated activity monitors, a limitation of this device is that it uses body motion for the prediction of sedentary time without assessing body position (eg, sitting, lying down, standing), which may provide more-precise information about sedentary behaviors.³⁵

In conclusion, we report the feasibility of using accelerometry in a population of adults with PAH and show increased sedentary time in patients with PAH compared with matched control subjects. Quantitation of sedentary time and daily activity levels is a novel patient-centered approach to functional assessment in PAH and may be a highly useful tool for clinical care and assessing response to therapy, particularly in less-severe heart failure and in children. Whether current PAH-specific therapies reduce sedentary time and whether reductions in sedentary time in PAH improve quality of life are uncertain.

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Dr Pugh: contributed to the study design, data collection, data analysis, and manuscript preparation.

Dr Buchowski: contributed to the study design, data analysis, data collection, and manuscript preparation.

Dr Robbins: contributed to the study design, data collection, and manuscript preparation.

Dr Newman: contributed to the study design, data analysis, and manuscript preparation.

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