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Early View

Research letter

Physical activity and quality of life in patients with pulmonary hypertension

Thomas M. Cascino, Vallerie V. McLaughlin, Caroline R. Richardson, Nilofar Behbahani-Nejad, Victor M. Moles, Scott H. Visovatti, Elizabeth A. Jackson

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Title: Physical activity and quality of life in patients with pulmonary hypertension

Authors: Thomas M. Cascino, MD[a], Vallerie V. McLaughlin, MD[a], Caroline R. Richardson, MD[b], Nilofar Behbahani-Nejad, BS, MS[c], Victor M. Moles, MD[a], Scott H. Visovatti, MD[a], Elizabeth A. Jackson, MD, MPH[d]

[a]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan

[b]Department of Family Medicine, University of Michigan, Ann Arbor, Michigan

[c]Oakland University William Beaumont School of Medicine, Auburn Hills, Michigan

[d]Division of Cardiovascular Medicine, University of Alabama at Birmingham, Birmingham, Alabama

Corresponding author: Thomas M. Cascino, MD; Tel: (734) 936-8214; Email: tcascino@med.umich.edu; 2381 CVC SPC 5853, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5853

Take Home Message

In a longitudinal study of stable pulmonary hypertension patients, there was a non-linear association between 6MWD and step counts at higher levels of exercise capacity and average step counts were associated with disease-specific and global HRQOL.

To the editor:

Pulmonary arterial hypertension (PAH) is a progressive, non-curable disease with significant associated comorbidity, including reduced exercise capacity [1] and poor health-related quality of life (HRQOL) [2]. Exercise capacity is frequently measured by the six-minute walk test (6MWT) [3]. The 6MWT is easy to perform and correlates with disease severity and HRQOL [4]. However, the 6MWT has limitations such as the need for a clinic visit to perform [4] and ceiling effects which reduce the sensitivity to changes among patients [5].

Commercially available activity trackers have the potential to monitor ambulatory function continuously beyond onetime measures of exercise capacity. For the PAH population, data on ambulatory activity may provide a more sensitive means to assess changes in clinical status [4] and be informative to the assessment of new therapies; however, an understanding of the long-term correlation between physical activity and both 6MWD and patient-centered outcomes such as HRQOL is needed as prior studies were limited to short-term follow-up [6-9].

The primary aims of this prospective cohort study were to assess the correlation between 6MWD and physical activity (step counts) and to examine associations between physical activity and HRQOL among patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) over an extended period.

We enrolled patients ≥18 years-old from the University of Michigan Medical Center between June and November 2016 at the time of a PAH clinic visit and followed them until their next scheduled appointment. Participants were included if they had a diagnosis of PAH or CTEPH according to World Health Organization (WHO) Criteria [10] and WHO functional class I to III symptoms [3] on stable PAH medications for ≥ 3 months without comorbid conditions that limited activity. The study was approved by the Institutional Review Board and informed consent was obtained (HUM00110649).

At each visit, a 6MWT was performed and physical activity quantified using average daily step counts for two weeks acquired with the Fitbit Zip™ accelerometer. Days with <200 steps were excluded and weeks with ≥4 excluded days were considered non-valid. Participants were instructed to wear the Fitbit Zip™ during waking hours and to continue their usual level of activity. HRQOL measured using the emPHasis-10 questionnaire, a PAH-specific instrument used to determine the impact of PAH symptoms on patients' lives [11], and several non-disease specific Patient-Reported Outcomes Measurement Information System (PROMIS) short form domain measures (physical function-v1.2, fatigue-v1.0, illness impact-v1.0, satisfaction with roles-v1.0 and ability to participate in social roles-v2.0) [12].

The primary outcomes of the study were (1) correlation of 6MWT and physical activity, (2) association between physical activity and HRQOL, and (3) association between physical activity change and HRQOL change between baseline and follow-up. Visual inspection of scatterplots suggested a curvilinear relationship between step counts and 6MWD. The inclusion of step count as a second-order term (quadratic) improved the model fit. A p-value of <0.05 was used to determine significance. Analyses were conducted using STATA 14 (College Station, TX).

Of the 87 consecutive patients screened, 36 either didn't meet inclusion criteria or met exclusion criteria, 11 were eligible but did not participate, and 1 enrolled but elected not to participate, leaving 39 participants in the study [mean age 61±12, 85% (n=33) female, 90% PAH (n=35), 10% CTEPH (n=4)]. A total of 34 participants (87%) had valid mean step counts for the initial visit, 69% (n=27) for the follow-up visit, and 64% (n=25) for both and were included in the change between visits analysis. Participants were followed for a median (interquartile range) of 6.1 (4.6, 6.4) months between visits.

The mean (±SD) steps and 6MWD were 4391 (±2442) steps and 460 (±107) meters. Average daily step count was significantly associated with 6MWD (R=0.71, R^2=0.51, p<0.001) (Figure 1a). Average daily step counts and HRQOL measures remained stable between visits. Higher average daily step counts were positively associated with lower PH symptoms burden (EmPHasis-10 score) and PROMIS domains including higher self-reported function, lower fatigue, higher satisfaction with social roles, and decreased psychosocial illness impact (Figure 1b). The adjusted analyses examining the association between change in step counts and change in HRQOL measures are also reported in Table 1 and reflect the clinical stability in all measures between visits.

Our findings support the stability and reliability of continuous long-term monitoring of physical activity in PAH and CTEPH patients. Over a median follow-up of about 6 months in clinically stable participants, physical activity measured by average daily step counts did not change and was strongly associated with 6MWD. The current use of 6MWD to monitor exercise capacity is well-established. Thus, 6MWD is frequently used as an efficacy outcome in clinical trials [13]. However, given the limitations, there has been increasing interest in using continuous device monitoring to assess ambulatory function [4]. The confirmation of the stability and reliability of physical activity using measures over an extended period builds on prior work of shorter duration and is a necessary first step in understanding if physical activity monitoring adequately addresses these limitations [6-9].

Additionally, there was a high correlation between physical activity and 6MWD which has been previously described [6-8]. However, we observed this relationship to be non-linear suggesting that at higher ambulatory activity (daily step counts), the 6MWD lost discriminatory value. This may represent the previously reported ceiling effect where the 6MWT was unable to differentiate response to therapies in participants with higher exercise capacity [5]. With the use of early combination therapies, participants enrolling in clinical trials are changing and tend to have improved exercise tolerance limiting the ability to use 6MWD in these patients [14]. Our findings suggest that ambulatory step count monitoring has the potential to be more sensitive to changes in functional capacity among active individuals.

Ambulatory step count monitoring in our study was associated with HRQOL including the EmPHasis-10 survey and several general health domains. These findings are particularly important given the evolving emphasis at the World Symposium on PH on translating clinical trial results into meaningful outcomes for participants rather than less patient-centered outcomes such as 6MWD [15]. As a result, home activity monitoring has the potential to offer a more complete understanding of ambulatory activity and should be considered as an exploratory patient-centered outcome in clinical trials.

Our study has limitations. Participants overall found using the Fitbit Zip™ to be acceptable, wearing the device for 77% of eligible days. Despite this, 36% of participants

(14/39) did not provide step count data at both visits. Involving patients in the research design may better elucidate the optimal strategy to improve compliance. Although our median follow-up was 6-months, the duration was too short in this clinically stable group to detect changes in physical activity and HRQOL. A larger, longer study or a study aimed at increasing physical activity is necessary to determine if physical activity is sensitive to change or if improving physical activity improves clinically important outcomes.

Our results suggest step counts provide a clinically useful method for measuring ambulatory function among patients with PAH and CTEPH which correlated with 6MWD and HRQOL. It is recommended that investigators using devices which measure step counts examine their data for non-linear correlations with other measures. Lastly, given the relationship of daily physical activity and HRQOL, future studies which promote regular physical activity for a goal of improving HRQOL are warranted.

References

1. Delcroix M, Howard L. Pulmonary arterial hypertension: The burden of disease and impact on quality of life. *European Respiratory Review* 2015: 24(138): 621-629.
2. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related Quality of Life and Survival in Pulmonary Arterial Hypertension. *Annals of the American Thoracic Society* 2016: 13(1): 31-39.
3. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M, Aboyans V, Vaz Carneiro A, Achenbach S, Agewall S, Allanore Y, Asteggiano R, Paolo Badano L, Albert Barbera J, Bouvaist H, Bueno H, Byrne RA, Carerj S, Castro G, Erol C, Falk V, Funck-Brentano C, Gorenflo M, Granton J, Iung B, Kiely DG, Kirchhof P, Kjellstrom B, Landmesser U, Lekakis J, Lionis C, Lip GY, Orfanos SE, Park MH, Piepoli MF, Ponikowski P, Revel MP, Rigau D, Rosenkranz S, Voller H, Luis Zamorano J. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016: 37(1): 67-119.
4. McLaughlin V, Bacchetta M, Badesch D, Benza R, Burger C, Chin K, Frantz R, Frost A, Hemnes A, Kim NH, Rosenzweig EB, Rubin L. Update on pulmonary arterial hypertension research: proceedings from a meeting of experts. *Current medical research and opinion* 2018: 34(2): 263-273.
5. Frost AE, Langleben D, Oudiz R, Hill N, Horn E, McLaughlin V, Robbins IM, Shapiro S, Tapson VF, Zwicke D, DeMarco T, Schilz R, Rubenfire M, Barst RJ. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascular pharmacology* 2005: 43(1): 36-39.
6. Mainguy V, Provencher S, Maltais F, Malenfant S, Saey D. Assessment of daily life physical activities in pulmonary arterial hypertension. *PLoS One* 2011: 6(11): e27993.
7. Pugh ME, Buchowski MS, Robbins IM, Newman JH, Hemnes AR. Physical activity limitation as measured by accelerometry in pulmonary arterial hypertension. *Chest* 2012: 142(6): 1391-1398.
8. Matura LA, Shou H, Fritz JS, Smith KA, Vaidya A, Pinder D, Archer-Chicko C, Dubow D, Palevsky HI, Sommers MS, Kawut SM. Physical Activity and Symptoms in Pulmonary Arterial Hypertension. *Chest* 2016: 150(1): 46-56.

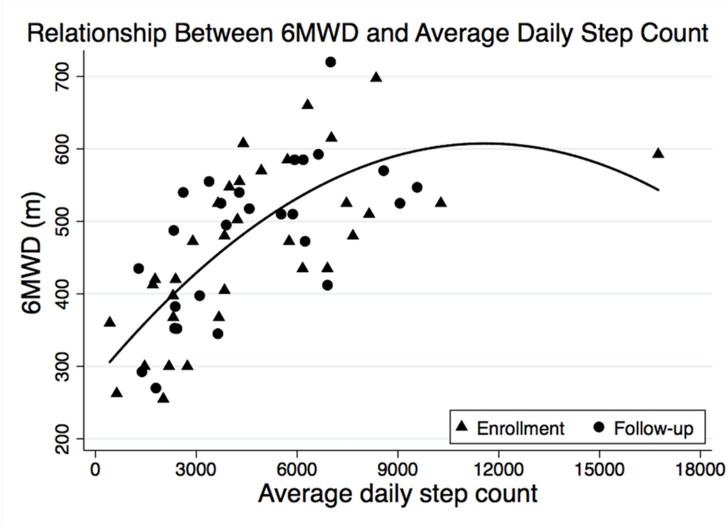
9. Okumus G, Aslan GK, Arseven O, Ongen G, Issever H, Kiyan E. The role of an activity monitor in the objective evaluation of patients with pulmonary hypertension. *The clinical respiratory journal* 2018: 12(1): 119-125.
10. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J, Documents ACoCFTFoEC, Association AH, Physicians ACoC, American Thoracic Society Ic, Association PH. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009: 53(17): 1573-1619.
11. Yorke J, Corris P, Gaine S, Gibbs JS, Kiely DG, Harries C, Pollock V, Armstrong I. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. *Eur Respir J* 2014: 43(4): 1106-1113.
12. Cella D, Yount S, Rothrock N, Gershon R, Cook K, Reeve B, Ader D, Fries JF, Bruce B, Rose M, Group PC. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care* 2007: 45(5 Suppl 1): S3-S11.
13. Demir R, Kucukoglu MS. Six-minute walk test in pulmonary arterial hypertension. *Anatolian journal of cardiology* 2015: 15(3): 249-254.
14. McLaughlin VV. Has the 6-min walk distance run its course? *Chest* 2012: 142(6): 1363-1365.
15. McGoon MD, Ferrari P, Armstrong I, Denis M, Howard Luke S, Lowe G, Mehta S, Murakami N, Wong Brad A. The importance of patient perspectives in pulmonary hypertension. *European Respiratory Journal* 2018: 1801919.

Figure 1 legend.

a. Scatter plot with regression line showing the relationship between 6MWD and average daily step counts. Average daily step count was significantly associated with 6MWD (R=0.63, R^2=0.39, p<0.001). Model fit improved when step counts included as a second order variable (R=0.71, R^2=0.51, p<0.001) (shown in figure).

b. Results of the multivariable linear regressions adjusting for age and sex. HRQOL and change in HRQOL were the dependent variables with average daily step counts and change in average daily step counts the primary independent variables. Regression coefficient with standard errors in parentheses, p-value and R^2 displayed for each model. The emPHasis-10 score ranges from 0 – 50 with higher scores representing worse symptom burden and QOL [12]. PROMIS results are transformed using a T-score metric with a mean of 50 and a standard deviation of 10 for the general United States population. A higher score indicates more of the domain being evaluated [13]. PROMIS = Patient-Reported Outcomes Measurement Information System.

a)



b)

	emPHasis-10	PROMIS Domains Physical Function	Participate in social roles	Fatigue	Psychosocial Illness Impact	Satisfaction with social roles
Baseline & follow-up						
Step count (per 1000 steps)	-1.690 (0.463)	1.425 (0.373)	0.826 (0.538)	-1.534 (0.521)	-1.020 (0.398)	1.419 (0.520)
p-value	0.001	0.001	0.133	0.006	0.015	0.010
R^2	0.24	0.32	0.10	0.19	0.17	0.19
Change between visits						
Step count (per 1000 steps)	0.008 (0.534)	-0.107 (0.256)	-0.465 (0.543)	0.859 (0.692)	1.361 (0.744)	-0.058 (0.717)
p-value	>0.20	>0.20	>0.20	>0.20	0.081	>0.20
R^2	0.05	0.44	0.15	0.13	0.16	0.04