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Clinical Investigation

Correlation Between Right Ventricular Echocardiography Measurements and Functional Capacity in Patients With Pulmonary Arterial Hypertension

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***Background**: Accelerometry is an emerging option for real-time evaluation of functional capacity in patients with pulmonary arterial hypertension (PAH). This prospective pilot study assesses the relationship between functional capacity by accelerometry and right ventricular measurements on echocardiography for this high-risk cohort.*

***Methods**: Patients with PAH were prospectively enrolled and underwent 6-Minute Walk Test and cardiopulmonary exercise testing. They were given a Fitbit, which collected steps and sedentary time per day. Echocardiographic data included right ventricular global longitudinal, free wall, and septal strain; tricuspid regurgitant peak velocity; tricuspid annular plane systolic excursion; tricuspid annular plane systolic velocity; right ventricular myocardial performance index; and pulmonary artery acceleration time. Pairwise correlations were performed.*

***Results:** The final analysis included 22 patients aged 13 to 59 years. Tricuspid regurgitant peak velocity had a negative correlation with 6-Minute Walk Test ($r = -0.58$, $P = .02$), peak oxygen consumption on exercise testing ($r = -0.56$, $P = .03$), and average daily steps on accelerometry ($r = -0.59$, $P = .03$), but a positive correlation with median sedentary time on accelerometry ($r = 0.64$, $P = .02$). Pulmonary artery acceleration time positively correlated with peak oxygen consumption on exercise testing ($r = 0.64$, $P = .002$). There was no correlation between right ventricular strain measurements and functional capacity testing.*

Conclusion:** In this pilot study, tricuspid regurgitant jet and pulmonary artery acceleration time were the echocardiographic variables that correlated most with accelerometry data. With further echocardiographic validation, accelerometry can be a useful, noninvasive, and cost-effective tool to monitor disease progression in patients with PAH. **(Tex Heart Inst J. 2022;49(6):e217719)

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Echocardiographic evidence of right ventricular (RV) dysfunction has long been regarded as a main determinant of morbidity and mortality in patients with pulmonary artery hypertension (PAH).[1-3] Echocardiography is often used in conjunction with functional capacity testing in the monitoring of patients with PAH via the 6-Minute Walk Test (6MWT) and cardiopulmonary exercise testing (CPET).[4,5] However, the 6MWT may not accurately assess patients with less-severe disease,[6,7] and CPET does not reflect daily activity.[5,7-9] Accelerometry is an emerging technology to accurately measure exercise capacity in real time, with early data demonstrating fewer steps per day and greater sedentary time in patients with PAH than in those without PAH.[10-12] Although speckle-tracking RV strain echocardiography has shown a strong association with mortality[3,13,14] and 6MWT performance[15,16] in these patients, the relationships between RV echocardiographic measurements and accelerometry remain poorly understood.[12]

This pilot prospective observational study was conducted in adult and pediatric patients with PAH of varying severity to assess the relationship between RV echocardiography measurements, including RV global longitudinal strain, and functional capacity measurements, including accelerometry.

Patients and Methods

Participant Enrollment

Patients with PAH presenting for routine follow-up at the Pulmonary Hypertension Comprehensive Care Center at Columbia University Irving Medical Center between September 1, 2016, and July 31, 2017, were recruited during routine visits. Inclusion criteria included patients with group 1 PAH, defined as having a mean pulmonary artery pressure of greater than 25 mm Hg with pulmonary artery wedge pressure less than 15 mm Hg by cardiac catheterization and hemodynamic studies. Participants were aged at least 13 years at the time of enrollment and spoke English. Patients' World Health Organization (WHO) functional class (FC) was required to be I to III at the time of enrollment. Participants were excluded if they had a history of noncompliance with follow-up visits, reported use of any wearable physical activity tracker in the last 6 months, had WHO FC IV disease, or were unable to provide informed consent/assent. Participants provided informed consent or assent (based on age) and completed a Health Insurance Portability and Accountability Act of 1996 (HIPAA) form as required by the Columbia University Human Research Protection Office. Before the initial visit, each patient was given a Fitbit Charge HR activity monitor (Fitbit, Inc) with instructions on usage and synchronization to the patient's smartphone device or computer. The Fitbit Charge HR is a wireless, wrist-worn, triaxial accelerometer. A proprietary algorithm translates raw acceleration signals into steps and activity levels. It estimates steps, heart rate, activity level, and energy expenditure each minute.[17]

The Fitbit device was chosen given its ease of use, easy availability, and greater accuracy than that of other commercially available activity monitors.[18] Patients were given instructions on how to upload data to a cloud interface. These data were downloaded by research personnel to a deidentified spreadsheet. The study protocol was approved by the institutional review board at Columbia University (protocol No. AAAQ9188).

Patient Characteristics and Functional Capacity Variables

Date of birth, sex, ethnicity, race, weight in kilograms, body mass index (BMI), WHO FC, and WHO diagnostic classification were charted for each patient. At the initial visit, all patients underwent a CPET and 6MWT. Peak oxygen consumption (VO_2 max) (in mL/kg/min), percentage predicted VO_2, and meters walked on 6MWT were used in the final analysis.

Steps per day and sedentary time per day (in minutes) were obtained from each Fitbit device, beginning from the day after the initial visit. Sedentary activity, which includes activities such as sitting quietly, sleeping, and watching television, is defined by Fitbit as 1.0 to 1.5 metabolic equivalents. These 2 variables were used, given their relative accuracy compared with other Fitbit data, such as distance walked per day, which may vary by stride, or calories consumed per day, which may vary by patient weight. Only days on which more than 500 steps were recorded were included for statistical analysis, as descriptive analysis of steps per day suggested that days with fewer than 500 steps might represent substantial outliers from technical factors of the device (eg, insufficient detection of steps, errors in uploading, or failure to wear the device) that did not truly reflect the patient's disease burden. For each patient, 7 consecutive compliant days of activity were used in the final analysis to maximize the likelihood of consistent wear time.

Transthoracic Echocardiography Variables

At the initial visit, patients underwent a clinically indicated transthoracic echocardiogram (Phillips iE33, Philips Healthcare). Qualitative global RV function (normal or mild, moderate, or severe dysfunction) was obtained from the echocardiogram report. If technical limitations or image resolution precluded any of the echocardiographic measurements being made, that participant was excluded from the study.

Tricuspid regurgitant peak velocity (in m/s), tricuspid annular plane systolic excursion (TAPSE; in cm), and tricuspid annular peak systolic velocity (TAPSV) by tissue Doppler (in cm/s; Fig. 1A); RV myocardial performance index by tissue Doppler (myocardial performance index [MPI], Fig. 1A); and pulmonary artery acceleration time (PAAT; in ms; Fig. 1B) were measured by one of the authors (J.L.W.), who was blinded to previous measurements and clinical data. These previously validated measurements are abnormal in patients with PAH as a result of abnormal RV myocardial dynamics.[19] In addition, PAAT uses the flow velocity characteristics through the RV outflow tract for a quantifiable measure of pulmonary circulatory mechanics, and PAAT has been shown to be inversely proportional to both mean pulmonary artery pressure and indexed pulmonary vascular resistance on cardiac catheterization for both adults and children.[20,21] All parameters were measured in triplicate and averaged.

Right ventricular global longitudinal strain (GLS) and strain rate (SR) were measured retrospectively using TomTec multivendor software version 4.6 (TomTec Imaging Systems). A standard 2-dimensional image of the apical 4-chamber view was used to assess RV longitudi-

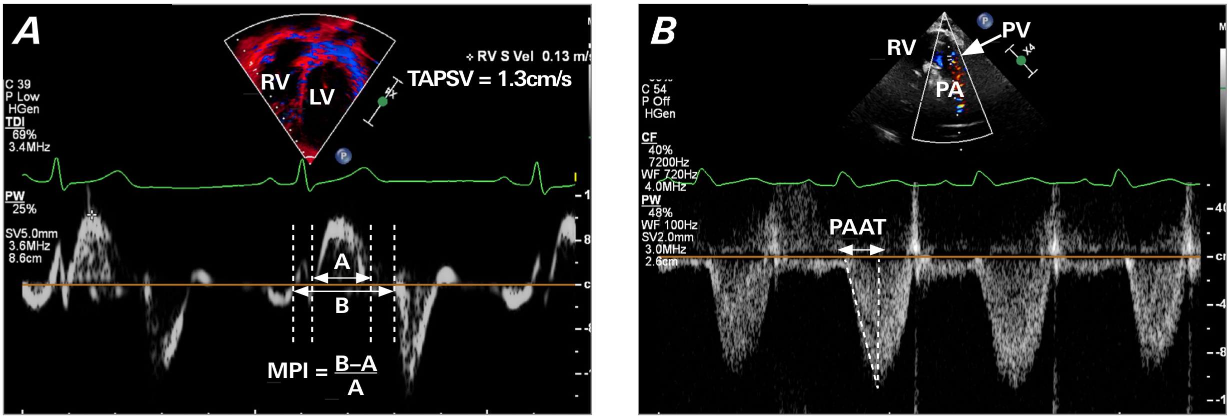

Fig. 1 A*) A tissue Doppler echocardiogram is used to calculate right ventricular MPI, where A = ejection time and B = isovolumetric contraction time + isovolumetric relaxation time.* ***B****) A pulsed-wave Doppler echocardiogram (parasternal short-axis view, with the cursor placed over the pulmonary valve) is used to measure PAAT.*

CF, color flow mapping; LV, left ventricle; MPI, myocardial performance index; PA, pulmonary artery; PAAT, pulmonary artery acceleration time; PV, pulmonary valve; PW, pulsed-wave Doppler; RV, right ventricle; RV S Vel, lateral tricuspid annulus peak systolic velocity; TAPSV, tricuspid annular peak systolic velocity; TDI, tissue Doppler imaging; WF, wall filter

nal strain. The quality of the tracking was ensured for each segment and adjusted as necessary. The peak longitudinal strain and SR were recorded. All measurements were performed by 1 author (J.L.W.) on 3 separate occasions separated by several weeks, and this author was blinded to previous measurements and clinical data. Ten studies were chosen at random, and measurements were performed by a second reader (N.P.) to determine interobserver reliability.

Statistical Analysis

Data are presented as mean (SD) or median (interquartile range [IQR]) for continuous variables and frequency counts (percentage) for categorical variables. Comparisons of echocardiographic data with WHO FC groups were conducted using analysis of variance or Kruskal–Wallis tests, depending on the distribution of the data. Pearson (*r*) and Spearman (r) correlations were calculated for continuous variables. Intraclass correlation was used to assess intraobserver reliability for MPI and PAAT and both intra- and interobserver reliability for RV GLS/SR. An intraclass correlation threshold of 0.75 was used to indicate good intraobserver and interobserver reliability.[22] If the intraclass correlation exceeded 0.75, the primary reader's (J.L.W.) measurements were used for statistical analysis, including those instances in which the 2 readers disagreed. Significant *P* values were defined as < .05. Statistical analyses were performed using Stata14 (StataCorp).

Results

Patient Characteristics

Thirty-two patients were initially enrolled in the study, 22 patients of which had complete data for analysis. One participant withdrew after enrollment because of developing a rash, and 3 patients did not have 7 consecutive compliant days of Fitbit data. One participant did not have an exercise study at the time of enrollment. One participant did not have images suitable for MPI or PAAT measurements, and 4 participants did not have images that were suitable for strain analysis.

There were equal numbers of males and females in the cohort (Table I). The median (IQR) age of the cohort was 27 (15-46) years, with 59% of patients older than 30 years. The mean (SD) BMI was 23.4 (6.2) kg/m^2. Nearly half of the patients were White (n = 9 [41%]), and half had WHO FC II symptoms (n = 11 [50%]). The mean (SD) number of steps per day for the entire cohort was 6,237 (3,498) steps. The median (IQR) sedentary time per day for the entire cohort was 962 (676-1,262) minutes.

Echocardiography Data by WHO Functional Class

Average peak tricuspid regurgitant (TR) velocity increased by WHO FC and was nearly 50% higher in the WHO FC III than the WHO FC I group (2.9 [0.74] m/s in WHO FC I, 3.8 [0.52] m/s in WHO FC II, 4.5 [0.59] in WHO FC III; *P* < .01; Fig. 2A). Average RV GLS worsened by WHO FC (–20.6% [3.8%] in WHO FC I, –16.3% [5.2%] in WHO FC II, –14.1% [3.3%] in WHO FC III groups), although this did not reach statistical significance (*P* = .07; Fig. 2B). Similarly, average RV septal strain worsened with higher WHO FC (–23.8% [5.1%] in WHO FC I, –19.3% [5.6%] in WHO FC II, –16.5% [6.8%] in WHO FC III groups), although this did not reach statistical significance (*P* = .07). In considering a potential confounding effect of posterior bowing of the interventricular septum on the relationship between WHO FC and strain, although

TABLE I. Patient Demographics and Clinical Characteristics

Sex, No. (%)	
Male	11 (50)
Female	11 (50)
Age, median (IQR), y	27 (15-46)
Age group, No. (%), y	
13-18	6 (27)
19-30	3 (14)
31-60	13 (59)
BMI, mean (SD), kg/m^2	23.4 (6.2)
Race, No. (%)	
White	9 (41)
Black	4 (18)
Asian	5 (23)
Native American or Native Alaskan	1 (5)
Missing data/did not wish to report	3 (14)
Ethnicity, No. (%)	
Non-Hispanic	18 (82)
Hispanic	2 (9)
Unknown	2 (9)
WHO FC	
I	5 (23)
II	11 (50)
III	6 (27)
Diagnosis, No. (%)	
Idiopathic PAH	10 (45)
PAH associated with other conditions	12 (55)
EuroSCORE II, %	4.1 (0.8-24.5)
STS score, %	4.0 (0.8-31.4)
Mean hemoglobin, g/dL	11.8 (8.0-17.4)
Mean creatinine, mg/dL	1.0 (0.4-10.1)

BMI, body mass index; FC, functional class; IQR, interquartile range; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

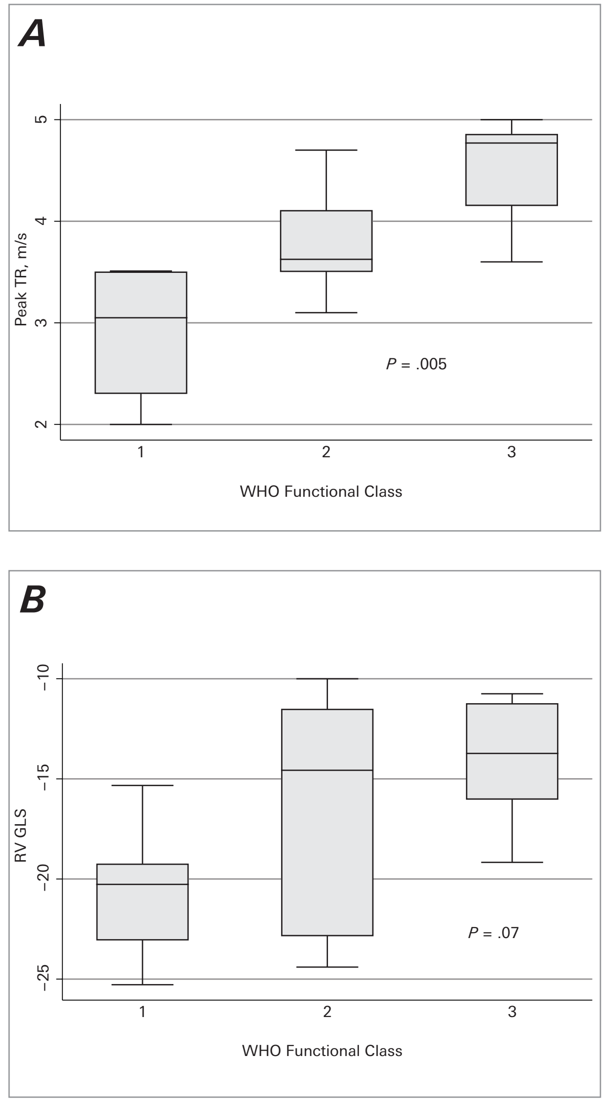

Fig. 2 *Box-and-whisker plots show* ***A****) the average peak TR and* ***B****) average RV GLS based on WHO functional class.* P *< .05 was considered statistically significant.*

Peak TR, tricuspid regurgitant peak velocity; RV GLS, right ventricular global longitudinal strain; WHO, World Health Organization

there was an association between increasing posterior bowing and worsening septal strain ($P = .04$), an association was not found with WHO FC ($P = .86$) or RV GLS ($P = .09$). TAPSE, TAPSV, RV MPI, PAAT, and RV free wall strain did not significantly change across WHO FC groups.

Correlation Between Echocardiography Data and Functional Capacity

Tricuspid regurgitant peak velocity had a negative correlation with 6MWT performance ($r = -0.58$, $P = .02$; Fig. 3A), average steps per day ($r = -0.59$, $P = .03$; Fig. 3B), and VO_2 max on exercise testing ($r = -0.55$, $P = .03$). Conversely, TR peak velocity had a positive correlation with median sedentary time on Fitbit ($r = 0.64$, $P = .02$; Fig. 3C). Pulmonary artery acceleration time positively correlated with VO_2 max on CPET ($r = 0.63$, $P < .01$; Fig. 3D). Right ventricular TAPSE, TAPSV, MPI, GLS, free wall strain, septal strain, and global SR were not significantly correlated with accelerometry or functional capacity testing (Table II).

Intraobserver and Interobserver Reliability

Intraclass correlation for intraobserver reliability was 0.82 for MPI (95% CI, 0.63-0.92), 0.91 for PAAT (95% CI, 0.76-0.96), and 0.86 for RV GLS and SR (95% CI,

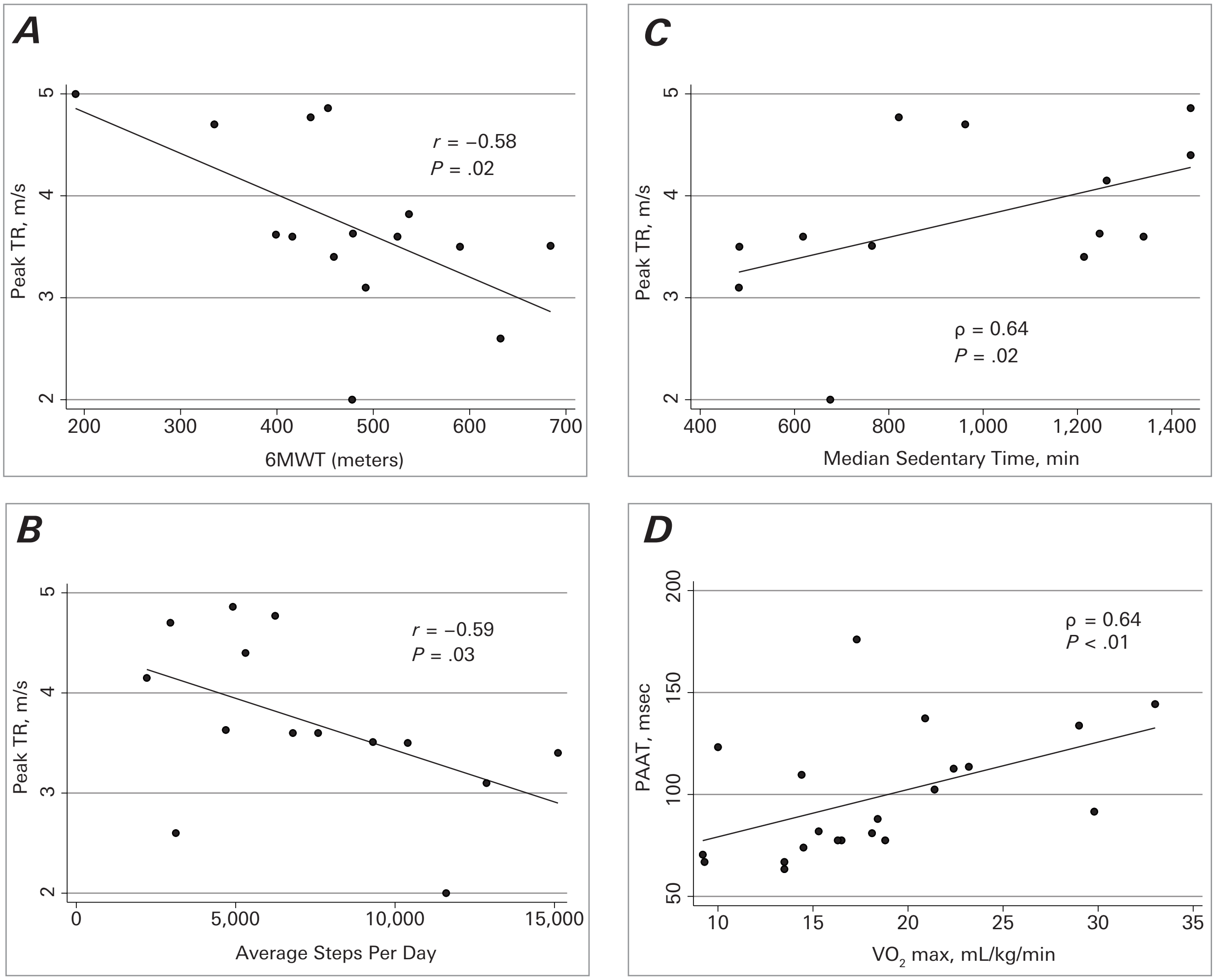

Fig. 3 *Scatter plot graphs show correlation between peak TR and* ***A****) 6MWT results,* ***B****) average steps per day, and* ***C****) median sedentary time per day.* ***D****) PAAT and* VO_2 *max were also correlated.* P *< .05 was considered statistically significant.*

6MWT, 6-Minute Walk Test; PAAT, pulmonary artery acceleration time; peak TR, tricuspid regurgitant peak velocity; VO_2 *max, peak oxygen consumption*

0.52-0.89). Intraclass correlation for interobserver reliability for RV GLS was 0.78 (95% CI, 0.51-0.92).

Discussion

In this prospective pilot study, TR and PAAT were found to be the echocardiographic variables that were most closely correlated with accelerometry data and that average RV GLS worsened by WHO FC, although this finding did not achieve statistical significance. Interestingly, RV strain measurements were not correlated with accelerometry measurements. This may be a reflection of the influence of increased RV load on TR jet and PAAT, but not on strain, which is less sensitive to RV load by comparison and more closely related to the RV–pulmonary artery decoupling that occurs before RV failure.[23] It is therefore plausible that functional impairment is associated more with the load introduced by pulmonary hypertension than with RV failure.

This is one of the first studies of dedicated investigation into RV echocardiographic measurements and their relationship with CPET or accelerometry data in a cohort that includes pediatric patients. The correlations of RV echocardiographic measurements with 6MWT in patients with PAH—specifically, TR peak gradient, RA size,[24] systolic to diastolic duration ratio,[25] RV GLS,[15] and free wall strain[15,16]—have been described. Sehgal et al[12] also used a pilot cohort and prospective design to investigate the relationship between hemodynamics by cardiac catheterization, N-terminal pro-brain natriuretic peptide, TAPSE, and 6-wall RV strain with accelerometry data. Among 17 patients, the researchers found no relationship between patients' echocardiographic measurements and steps or sedentary time per day, although they did find a positive correlation between steps per day and 6MWT as well as a negative correlation between sedentary time per day and quality-of-life scoring.

TABLE II. Correlation Among RV Echocardiographic Measurements, Accelerometry, and Functional Capacity Testing[a]

	Average steps/d on Fitbit	Median sedentary time on Fitbit	6MWT	Peak oxygen consumption on CPET
RV global longitudinal strain	*r* = −0.02 (.93)	r = −0.14 (.60)	*r* = −0.37 (.10)	*r* = −0.13 (.57)
RV free wall strain	*r* = 0.30 (.21)	*r* = −0.41 (.1)	*r* = −0.29 (.22)	*r* = −0.22 (.35)
RV septum strain	*r* = 0.04 (.88)	*r* = −0.22 (.39)	*r* = −0.30 (.20)	*r* = 0.06 (.80)
RV global strain rate	*r* = 0.04 (.86)	*r* = −0.02 (.94)	r= −0.25 (.29)	r= −0.03 (.91)
Tricuspid regurgitant peak velocity	*r* = −0.59[b] (.03)	*r* = 0.64[b] (.02)	*r* = −0.58[b] (.02)	*r* = −0.55[b] (.03)
Tricuspid annulus peak systolic velocity	r = −0.26 (.23)	*r* = 0.12 (.62)	r= 0.06 (.80)	r= −0.49 (.02)
Tricuspid annular plane systolic excursion	r = −0.01 (.95)	*r* = −0.08 (.74)	r= 0.29 (.20)	r= −0.40 (.06)
RV myocardial performance index	*r* = 0.18 (.42)	*r* = −0.04 (.88)	*r* = −0.04 (.86)	*r* = 0.02 (.94)
Pulmonary artery acceleration time	r = 0.46 (.06)	*r* = −0.35 (.14)	r = 0.27 (.21)	r= 0.64[b] (<.01)

6MWT, 6-Minute Walk Test; CPET, cardiopulmonary exercise testing; RV, right ventricular.

[a] *P* values are shown in parentheses.
[b] Statistically significant at $P < .05$.

The findings from this study were similar to those of Sehgal et al in that there also was not a significant correlation between RV GLS, free wall strain, or septal strain and accelerometry data. However, similar to what is found in existing literature, RV GLS and free wall strain worsened with increasing WHO FC in this study and approached statistical significance; the lack of statistical significance of this finding was likely secondary to the small sample size of this cohort, which resulted in an underpowered study. The team hypothesizes that the lack of relationship between RV strain and accelerometry could be from differences in the temporal onset of strain changes, which result from myocardial deformation and RV–pulmonary artery decoupling that occur later in the disease process.[23] Given that this was a cross-sectional study measuring a cohort of patients at a discrete time point in their disease rather than a longitudinal study of the disease course of this cohort, the team cannot make conclusions about the temporal relationships between RV strain and functional capacity changes based on the team's analysis. A longitudinal study may further delineate the true relationship between RV strain and functional capacity changes and determine which is a more-sensitive marker of disease severity.

It was found that a higher TR peak gradient was inversely correlated with steps per day and positively correlated with sedentary time per day. Pulmonary artery acceleration time was positively correlated with steps per day and VO_2 on CPET. Interestingly, while TR peak velocity and PAAT are directly related to pulmonary artery pressure, the remaining echocardiographic measurements that were unrelated to accelerometry data (strain, TAPSE, TAPSV, MPI) reflect RV performance, suggesting a closer relationship between pulmonary artery pressure and steps per day. Future studies with larger cohort sizes and invasive hemodynamic data would be useful to validate this hypothesis.

This study had several limitations that were mostly related to low power in the setting of a pilot study. Some of the results (eg, RV GLS and free wall strain improving with increasing WHO FC) were clearly clinically significant but did not reach statistical significance. Other statistical limitations include the inability to perform multivariable analysis given too few events.[26] A follow-up study might include a greater sample size with a longitudinal evaluation of the relationship between accelerometry and echocardiographic findings using a matched control group. The findings could subsequently inform the design of a randomized control trial of accelerometry use as an adjunct to echocardiography for this high-risk population. Ultimately, accelerometry may provide an adjunct to detect early or impending worsening of clinical status or disease. Second, additional RV functional assessments, such as RV fractional area change and 3-dimensional volumetric assessments, were not included as study variables. A choice to evaluate RV strain rather than RV fractional area change was made, given that strain is a less-load-dependent measurement. Given that echocardiogram measurements were done post hoc, reliable 3-dimensional volumetric measurements could not be performed. Finally, there is a risk of selection bias within the cohort: Those who agreed to enroll in the study may have had greater health literacy or higher medication compliance rates, which could also be associated with echocardiographic and/or functional capacity variables.

The emergence of accelerometry as a tool for real-time evaluation of functional capacity could save substantial time and resources for patients with PAH. However, accelerometry requires further validation with known markers of disease progression. In this pilot study, positive correlations were found between known echocardiographic markers of PAH and accelerometry data. Future studies will evaluate the reproducibility of the findings in this pilot study, as well as cost-effectiveness compared with currently validated functional capacity testing, to better understand how this new tool can be used in the long-term monitoring of patients with PAH.

Conclusion

In this pilot study, tricuspid regurgitation and pulmonary artery acceleration time were the echocardiographic variables that correlated most with accelerometry data. With further echocardiographic validation, accelerometry can be a useful and potentially cost-effective tool to monitor disease progression in patients with PAH.

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