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RESEARCH ARTICLE

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Cardiac effort and 6-min walk distance correlate with stroke volume measured by cardiac magnetic resonance imaging

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Abstract

Right ventricular (RV) dysfunction in pulmonary arterial hypertension (PAH) is associated with poor outcomes. Cardiac magnetic resonance imaging (cMRI) is the gold standard for volumetric assessment, and few reports have correlated 6-min walk distance (6MWD) and cMRI parameters in PAH. Cardiac Effort, (the number of heart beats used during 6-min walk test)/(6MWD), incorporates physiologic changes into walk distance and has been associated with stroke volume (SV) measured by nuclear imaging and indirect Fick. Here, we aimed to interrogate the relationship of Cardiac Effort and 6MWD with SV measured by the gold standard, cMRI. This was a single-center, observational, prospective study in Group 1 PAH patients. Subjects completed 6-min walk with heart rate monitoring (Cardiac Effort) and cMRI within 24 h. cMRI was correlated to Cardiac Effort and 6MWD using Spearman Correlation Coefficient. Twenty-five participants with a wide range of RV function completed both cMRI and Cardiac Effort. There was a strong correlation between left ventricle SV index and both Cardiac Effort ($r = -0.70$, $p = 0.0001$) and 6MWD ($r = 0.67$, $p = 0.0002$). Cardiac Effort and 6MWD were statistically separated in patients at prognostically significant thresholds of left ventricle SV index (>31 ml/m^2), RV Ejection Fraction (>35%), and SV/End Systolic Volume (> 0.53). Cardiac Effort and 6MWD are noninvasive ways to gain insight into those with impaired SV. 6MWD may correlate better with SV than previously thought and heart rate monitoring provides physiologic context to the walk distance obtained.

Abbreviations: 6MWD, 6-min walk distance; 6MWT, 6-min walk test; CE, Cardiac Effort; cMRI, Cardiac magnetic resonance imaging; ESV, End Systolic Volume; ESVI, End Systolic Volume Index; IQR, Interquartile range; LV, left ventricle; ROC, Receiver operator curve; RV, Right ventricular; SV, stroke volume; SVI, stroke volume index.

All authors approve the manuscript.

KEYWORDS
6-min walk test, Cardiac Effort, cardiac MRI, stroke volume

INTRODUCTION

Right ventricular (RV) dysfunction attributable to increased afterload is associated with symptoms and predicts adverse outcomes in pulmonary arterial hypertension (PAH).[1] Quantifying RV and left ventricle (LV) volumes and function with echocardiogram in PAH can be difficult, although some echo-derived measures clearly have prognostic value.[2] Cardiac magnetic resonance imaging (cMRI) is the gold standard for volumetric assessment of the RV, but cost, availability, and patient acceptance has limited clinical use.[3] Multiple cMRI parameters[4–7] and invasive LV stroke volume (SV) index (SVI) at first follow-up[8] have been associated with outcomes. Developing novel, inexpensive assessments that provide insight into these important cardiac parameters in PAH could help improve serial clinical assessment and allow earlier identification of patients who need further therapy intensification or transplant evaluation.

The 6-min walk test (6MWT) is a submaximal exercise test[9] included as an endpoint in many pivotal trials[10] and a core variable in risk assessment.[11] It is inexpensive and easy to perform during routine clinic visits. Although 6MWD has been shown to correlate with resting cardiac output,[12] the variability in longer 6-min walk distance (6MWD)[13] (especially with distances >400 m, what has often been called ceiling effect[14]), has lessened enthusiasm for the 6MWT. To account for intrinsic variability in 6MWD (especially related to effort or pain), we developed Cardiac Effort, ([number of heart beats during 6MWT]/6MWD).[15–17] Cardiac Effort is more reproducible than 6MWD[16,17] and correlates strongly with resting stroke volume (SV) measured by nuclear ventriculography and indirect Fick during right heart catheterization.[15,16]

In this study, we aimed to (1) confirm the previously observed relationship between Cardiac Effort and SV (now measured by the gold standard cMRI) in PAH; (2) explore the relationship of cMRI parameters (RV Ejection Fraction, end systolic volumes, and end diastolic volumes) with Cardiac Effort, 6MWD, and NT-proBNP in PAH and subgroups (idiopathic, male, female); (3) evaluate whether Cardiac Effort and 6MWD thresholds might discriminate patients who are already known to have poor prognosis based on established parameters (RV ejection fraction <35% and LV SVI < 31 ml/m^2); and (4) finally, examine the relationship between Cardiac Effort and 6MWD in those with early clinical worsening after the cMRI. We hypothesized that Cardiac Effort would provide more insight into cardiac function than 6WMD in isolation and would be associated with 1-year clinical outcomes.

METHODS

This was a single-center, prospective, observational study at the University of Rochester with IRB approval. Group 1 PAH[18] patients on therapy and with a range of RV function (by echocardiography or right heart catheterization) were recruited from our PHA-accredited Comprehensive Care Center between 2021 and 2022. Testing included 6MWD[9] without a mask, Cardiac Effort,[15–17] NT-pro-BNP, and REVEAL Lite 2 score.[19] MC10 Biostamp nPoint provided continuous electrocardiogram monitoring to calculate Cardiac Effort as previously described, (heart beats during 6MWT)/6MWD).[16,17] cMRI was completed on Siemens Aera 1.5 T scanner within 24 h of 6MWT. A chest radiologist not affiliated with the study team (therefore blinded to walk distance) with expertise in cMRI reported right and left ventricle volumes. Using the MRI manufacturer's software, semi-automated analysis with contour smoothing in the long axis was performed to obtain volumes. Clinical worsening was defined as need to initiate parenteral prostacyclin or hospitalization for decompensated heart failure; for this report, we censored all individuals 12 months after testing was completed.

Statistical analysis

Categorical variables are reported as counts and percentages. Continuous variables are reported as mean with standard deviation or median with interquartile range (IQR). RV-Pulmonary Artery (RV-PA) coupling was estimated with RV SV/RV End Systolic Volume (ESV).[1] cMRI parameters (RV and LV end-diastolic and end-systolic measurements and those indexed for body surface area) were compared to Cardiac Effort, 6MWD, and NT-proBNP using Spearman correlation coefficient; we also generated regression equations. We were particularly interested in 1) whether Cardiac Effort would correlate better with MRI parameters than 6MWD, 2) determining values for Cardiac Effort, 6MWD, and NT-proBNP that would discriminate previously described favorable thresholds for RV ejection fraction (EF) > 35% vs <35%,[20] RV PA coupling > 0.53 vs <0.53,[21,22] and LV SVI > 31 ml/m^2 vs <31 ml/m^2[28] measured

on cMRI, and 3) the relationship between Cardiac Effort, 6WMD, and clinical outcomes at 12 months. Non-parametric testing was used for comparisons because of the sample size. GraphPad Prism 9 was used for statistical analysis.

RESULTS

Demographics

Twenty-five participants enrolled and completed both cMRI and Cardiac Effort. Three patients who pre-screened were willing to do the Cardiac Effort portion of the study but uninterested in cMRI and therefore did not sign consent. Most subjects were female (72%) with idiopathic PAH (17/25, 68%), a mean age of 52 and functional class II (84%, Table 1). All subjects were on combination therapy with the majority on prostacyclin therapy (60%). None of the subjects had atrial fibrillation; one person was on chronic low dose beta blocker therapy for resting tachycardia and another was on verapamil for cluster headache. The median (IQR) Cardiac Effort was 1.7 (1.4, 1.9) beats/m, 6MWD was 444 (370, 505) m, REVEAL Lite 2 was 4,[2,7] and NT-proBNP was 161 (106, 584) pg/ml. Interestingly, in this small sample of men ($n = 7$), men walked substantially further (514 *vs.* 421 m) and used fewer heart beats to do so such that Cardiac Effort was also markedly different (1.3 *vs.* 1.8 beat/m, Table 1). Consistent with a wide range of RV dysfunction, there was a wide range of heart rate expenditure during 6MWT; as we have previously reported, peak heart rate during 6MWT was consistently higher than heart rate at 6-min (Table 1). By design, there was a

TABLE 1 Demographics and clinical variables.

	All $n = 25$	**IPAH** $n = 18$	**Female** $n = 18$	**Male** $n = 7$
Age, mean	55 ± 14	54 ± 16	55 ± 13	56 ± 18
Female Sex (%)	18 (72%)	12 (67%)		
BMI (kg/m^2)	31 ± 9	26 (23, 36)	31 (25, 39)	23 (23, 30)
Type of PAH				
Idiopathic/Heritable	18 (72%)	18 (100%)	12 (67%)	6 (86%)
Connective Tissue Disease	6 (24%)	0	5 (27%)	1 (14%)
Portopulmonary	1 (4%)	0	1 (6%)	0
Vasodilator Therapy				
Monotherapy	1 (4%)	1 (6%)	1 (6%)	0
Combination Therapy	9 (36%)	5 (27%)	6 (33%)	2 (29%)
Prostacyclin	15 (60%)	12 (67%)	11 (62%)	5 (71%)
Reveal 2.0 Lite	5 ± 3	5 ± 3	5 ± 3	4 ± 2
NT-proBNP (pg/ml)	161 (106, 584)	252 (96, 956)	160 (105, 768)	303 (100, 321)
Hemoglobin (g/dl)	13.9 ± 1.7	13.9 ± 1.7	13.4 ± 1.7	15 ± 1
Functional Class (II/III)	21/4	15/3	14/4	7/0
6WMD (m)	444 (370, 505)	437 (358, 514)	421 (338, 469)*	514 (497, 544)*
Heart Rate During 6MWT				
Cardiac Effort, Beats/m	1.7 (1.4, 1.9)	1.7 (1.4, 2.1)	1.8 (1.4, 2.6)*	1.3 (1, 1.6)*
Resting Heart Rate, Beats/min	83 ± 12	84 ± 13	87 ± 11	76 ± 12
Peak Heart Rate, Beats/min	129 ± 20	129 ± 23	132 ± 20	120 ± 19
Heart Rate at 6 min, Beats/min	124 ± 19	125 ± 22	128 ± 19	116 ± 18
Heart Rate Expenditure, Beats	715 ± 92	718 ± 105	729 ± 89	680 ± 95
Heart Rate Reserve, Beats/m	45 ± 21	45 ± 25	46 ± 21	45 ± 25
Heart Rate Recovery, Beats/m	22 ± 15	23 ± 17	20 ± 13	27 ± 21

*significant difference between females and males.

strong correlation between Cardiac Effort and 6MWD, but there was no correlation with 6MWD and other heart rate parameters, age, or BMI (Fig. 1).

Cardiac MRI

Cardiac MRI parameters are in Table 2; we achieved our goal of recruiting participants with a range of RV function (RV ejection fraction mean 40%, range 13-55). There was no significant difference between RV and LV SV nor the indexed SVI values, $p = 0.21$ and $p = 0.24$, respectively; however, the numeric values were higher based on the RV SVI/LV SVI ratio (Table 2). Females had lower right and left ventricle volumes and SV compared to males (Table 2), but as expected, the differences became smaller when considering the indexed values in each case. For LV end-systolic volume index, males remained larger than females (31 *vs.* 24 ml/m^2). RV Ejection Fraction was identical in males and females.

Cardiac MRI comparison

Cardiac Effort and 6MWD both correlated strongly with LV SV measured by cMRI (Table 3 and Fig. 2). Indexing values for body surface area strengthened the relationship, especially in idiopathic PAH patients (Fig. 2). LV SV had a stronger correlation than RV SV with Cardiac Effort and 6MWD (Table 3). NT-proBNP correlated with RV but not LV end-diastolic and end-systolic volumes (Table 3). Cardiac Effort and 6MWD did not correlate as strongly with RVEF (Fig. 3).

RV ejection fraction, stoke volume index, SV/ESV

Using thresholds previously identified to be associated with clinical outcomes (RVEF > 35%, SVI > 31 ml/m^2, and SV/ESV > 0.53), we found Cardiac Effort and 6MWD were statistically different in those above and below all three thresholds (Fig. 4). NT-proBNP did not track with SVI threshold groups (Fig. 4c) but did track with RVEF and SV/ESV thresholds. In a receiver operator curve (ROC) analysis to distinguish those above and below RVEF 35%, Cardiac Effort was slightly better than 6MWD [Supporting information: (Fig. 1), Cardiac Effort, 1.8 beats/m, area = 0.88 (0.71, 1.0); 6MWD, 370 m, area = 0.85 (0.61, 1.0)]. For SV/ESV, the area values were similar and for LV SVI, area was slightly better for 6MWD than Cardiac Effort (Supporting information: (Fig. 1). Remarkably, the ROC threshold for LV

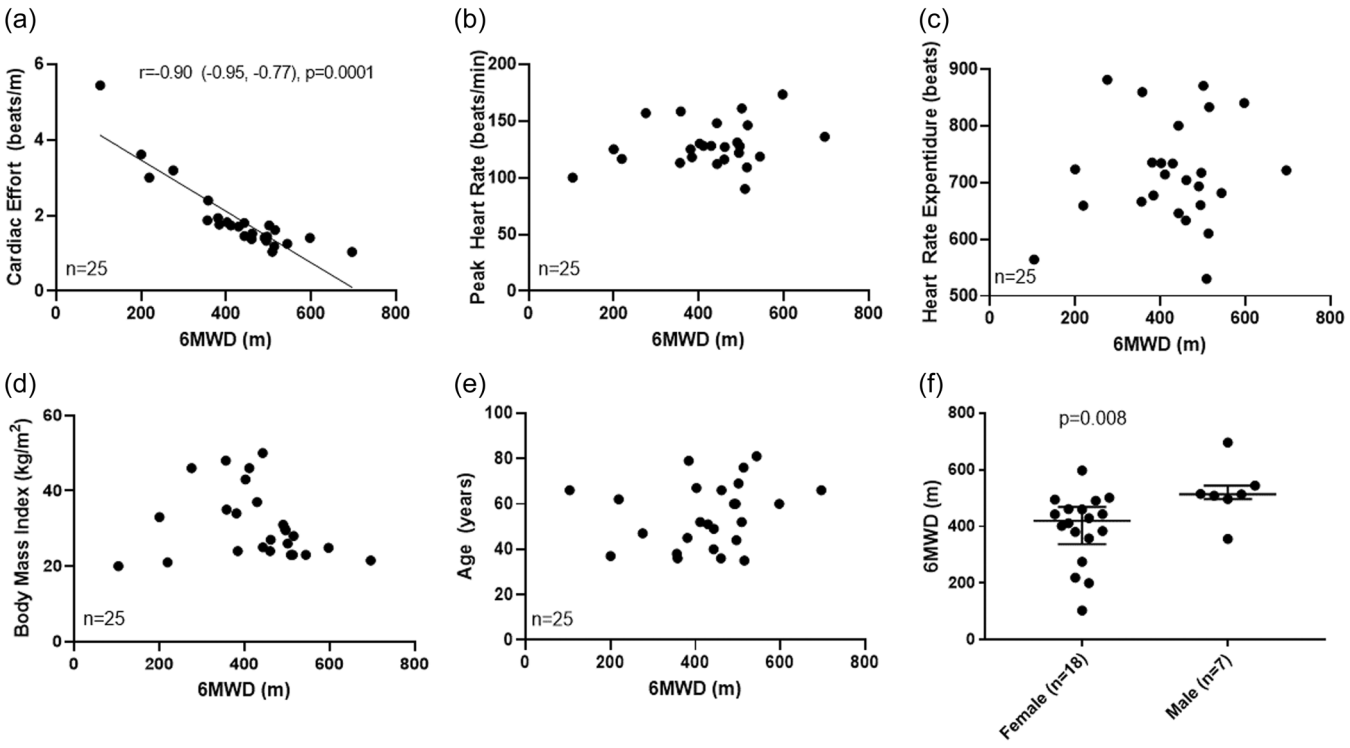

FIGURE 1 *6-min Walk Distance (6MWD) was associated* with a) Cardiac Effort but had no association with (b–e) peak heart rate, heart rate expenditure, body mass index, or age. f) There was a difference in 6MWD between females and males with PAH in this small sample of men.

TABLE 2 Cardiac MRI parameters.

Cardiac MRI	All $n = 25$	IPAH $n = 18$	Female $n = 18$	Male $n = 7$	p
Right Ventricle					
End Diastolic Volume, mL	205 ± 63	221 ± 64	188 ± 59	251 ± 48	0.01
End Diastolic Volume Index, mL/m^2	104 ± 30	112 ± 31	97 ± 31	120 ± 19	0.08
End Systolic Volume, mL	126 ± 52	141 ± 52	115 ± 53	154 ± 35	0.09
End Systolic Volume Index, mL/m^2	63 ± 24	71 ± 24	59 ± 27	74 ± 12	0.19
Stroke Volume, mL	79 ± 28	80 ± 31	73 ± 26	97 ± 28	0.05
Stroke Volume Index, mL/m^2	40 ± 15	41 ± 17	38 ± 15	47 ± 14	0.18
Ejection Fraction, %	40 ± 10	37 ± 11	40 ± 12	40 ± 7	0.88
Left Ventricle					
End Diastolic Volume, mL	121 ± 37	118 ± 35	112 ± 33	148 ± 34	0.02
End Diastolic Volume Index, mL/m^2	62 ± 18	60 ± 18	58 ± 17	72 ± 17	0.07
End Systolic Volume, mL	51 ± 18	50 ± 17	46 ± 17	64 ± 17	0.03
End Systolic Volume Index, mL/m^2	26 ± 8	25 ± 8	24 ± 7	31 ± 8	0.04
Stroke Volume, mL	70 ± 23	67 ± 24	64 ± 23	85 ± 19	0.05
Stroke Volume Index, mL/m^2	36 ± 12	34 ± 13	34 ± 12	41 ± 10	0.17
Ejection Fraction, %	59 ± 7	58 ± 6	59 ± 7	57 ± 4	0.43
Cardiac Output	5.0 ± 1.8	4.8 ± 1.8	4.7 ± 1.8	5.7 ± 1.6	0.20
Cardiac Index	2.5 ± 0.8	2.5 ± 0.9	2.5 ± 0.9	2.8 ± 0.8	0.44
Other					
RV SV/RV ESV	0.71 ± 0.29	0.64 ± 0.28	0.74 ± 0.31	0.65 ± 0.22	0.49
RV SVI/LV SVI	1.16 ± 0.31	1.23 ± 0.37	1.17 ± 0.36	1.13 ± 0.17	0.85
Pulmonary Artery Diameter, cm	3.6 ± 0.51	3.6 ± 0.57	3.6 ± 0.5	3.4 ± 0.5	0.34

Comparison is between females and males only.

SVI > 31 ml/m^2 was 436 m (>440 m being the low-risk prognostic threshold).

Clinical worsening

After baseline testing, three participants required hospitalization for decompensated heart failure and three others initiated parenteral therapy within the first 12 months. Subjects with worsening events had higher Cardiac Effort, 3.1 (1.8, 4.1) beats/m vs 1.4 (1.3, 1.8) beats/m, $p = 0.001$; lower 6MWD, 248 (176, 396) m vs 462 (412, 509) m, $p = 0.007$; higher NT-proBNP, 771 (317, 7,790) pg/ml vs 157 (83, 201) pg/ml, $p = 0.002$; higher REVEAL Lite 2 score, 8 (4, 11) vs 3 (2, 4), $p = 0.001$; higher RV ESVI, 86 (73, 101) ml/m^2 vs 56 (38, 74) ml/m^2, $p = 0.009$; lower RV SV/RV ESV, 0.40 (0.24, 0.60) vs 0.84 (0.60, 1.01), $p = 0.004$; lower RV EF, 28 (19, 37) % vs 45 (39, 50) %, $p = 0.003$; and lower LV SVI, 26 (13, 34) ml/m^2 vs 36 (31, 45) ml/m^2, $p = 0.03$.

DISCUSSION

This report uses the gold standard measure to validate our previous reports that Cardiac Effort is an easy, noninvasive way to identify those with low resting SV based on dynamic heart rate changes relative to walk distance achieved. 6MWD had a similarly strong relationship with SV, an observation that has not been emphasized in recent studies. Previously, we had significant data loss with a wrist worn heart rate monitor and used inferior measurements for SV estimates[15,16]; the present dataset with electrocardiogram heart rate monitor and cMRI volume measurements strengthens our prior reports substantially. Our findings show both Cardiac Effort and 6MWD provide insight into cardiac function assessed by cMRI and outcomes in PAH.

Cardiac Effort and 6WMD both have a strong correlation with LV SVI measured by cMRI; LV SVI has been shown to have prognostic significance in PAH,[8] and this new data strengthens the idea that Cardiac Effort may be a

TABLE 3 Correlation between Cardiac Effort, 6MWD, and NT-PROBNP and cMRI RV parameters.

	CE		6MWD		NT-proBNP	
	***R* (95% CI)**	***P***	**R (95%)**	***P***	***R***	***P***
Right Ventricle						
End Diastolic Volume, mL	0.008 (−0.40, 0.41)	0.97	0.07 (−0.35, 0.46)	0.75	**0.39 (−0.01, 0.69)**	**0.05**
End Diastolic Volume Index, mL/m^2	−0.12 (−0.51, 0.29)	0.54	0.19 (−0.23, 0.55)	0.36	**0.41 (0.01, 0.70)**	**0.04**
End Systolic Volume, mL	0.14 (−0.28, 0.52)	0.14	−0.08 (−0.47, 0.33)	0.70	**0.49 (0.11, 0.75)**	**0.01**
End Systolic Volume Index, mL/m^2	0.15 (−0.27, 0.53)	0.47	−0.05 (−0.44, 0.36)	0.83	**0.57 (0.21, 0.79)**	**0.003**
Stroke Volume, mL	**−0.46 (−0.73, −0.07)**	**0.02**	**0.48 (0.09, 0.74)**	**0.01**	−0.17 (−0.54, 0.26)	0.42
Stroke Volume Index, mL/m^2	**−0.55 (−0.78, −0.19)**	**0.004**	**0.59 (0.25, 0.81)**	**0.001**	−0.16 (−0.53, 0.26)	0.45
Ejection Fraction, %	−0.38 (−0.68, 0.03)	0.06	0.31 (−0.10, 0.64)	0.13	**−0.49 (−0.75, −0.10)**	**0.01**
Left Ventricle						
End Diastolic Volume, mL	**−0.50 (−0.75, −0.13)**	**0.009**	**0.50 (0.12, 0.75)**	**0.01**	−0.024 (−0.59, 0.19)	0.26
End Diastolic Volume Index, mL/m^2	**−0.65 (−0.83, −0.32)**	**0.0005**	**0.63 (0.31, 0.83)**	**0.007**	−0.25 (−0.59, 0.18)	0.24
End Systolic Volume, mL	−0.37 (−0.67, 0.04)	0.06	0.35 (−0.06, 0.66)	0.09	−0.11 (−0.50, 0.31)	0.59
End Systolic Volume Index, mL/m^2	**−0.52 (−0.76, −0.14)**	**0.008**	**0.46 (0.07, 0.73)**	**0.02**	−0.15 (−0.52, 0.27)	0.47
Stroke Volume, mL	**−0.62 (−0.82, −0.28)**	**0.001**	**0.58 (0.23, 0.80)**	**0.002**	−0.39 (−0.69, 0.02)	0.06
Stroke Volume Index, mL/m^2	**−0.70 (−0.86, −0.42)**	**0.0001**	**0.68 (0.37, 0.85)**	**0.0002**	−0.27 (−0.61, 0.15)	0.19
Ejection Fraction, %	−0.05 (−0.45, 0.36)	0.82	0.09 (−0.33, 0.50)	0.66	−0.04 (−0.44, 0.37)	0.84
Cardiac Output	**−0.40 (−0.70, 0.01)**	**0.05**	0.34 (−0.08, 0.65)	0.11	−0.23 (−0.58, 0.20)	0.29
Cardiac Index	**−0.54 (−0.77, −0.17)**	**0.005**	**0.47 (0.08, 0.74)**	**0.02**	−0.16 (−0.53, 0.26)	0.44
Other						
RV SV/RV ESV	−0.37 (−0.67, 0.04)	0.06	0.30 (−0.11, 0.63)	0.14	**−0.50 (−0.75, −0.11)**	**0.01**

Note: Bold values are statistically significant.

cost-effective way to do serial measurements which give insight into cardiac function (and have prognostic value). In this small, single-center study, both Cardiac Effort and raw 6WMD had reasonable ROC predictive value for three key cardiac functional thresholds: RVEF < 35%,[20] RV SV/RV ESV < 0.53,[21,22] and LV SVI < 31 ml/m^2.[8] Our previous reports indicate that there is less day–day variability in Cardiac Effort, which we propose as an advantage for Cardiac Effort over 6MWD; this same feature makes Cardiac Effort more sensitive to change (improvement or worsening). Cardiac Effort and 6MWD were substantially different in patients who experienced clinical worsening within 12 months of testing.

There has been renewed interest in 6MWD in PAH, likely because of its prognostic significance as a core component of risk scores.[19,23] The 6MWT is easy to perform without expensive equipment. Our findings update and extend those from Miyamoto et al.[12] who reported a correlation of cardiac output with 6WMD. Prior elegant cMR studies in clinically advanced PAH patients demonstrated that SV did not increase with exercise, making a faster heart rate the only way to augment cardiac output.[24,25] Cardiac Effort helps identify SV limitations during the 6MWT by highlighting exaggerated heart rate response (CE ≥ 1.8 beats/m) for a given walk distance, thus adding further information beyond 6MWD alone. We cautiously hypothesize that for those with very low Cardiac Effort (≤1.3 beats/m), the wide range of LV SV and RVEF (Figs. 2a, 3a) may indicate that some of these minimally symptomatic, intensely treated patients can increase SV with exercise (as in normals) and therefore have a more blunted heart rate response. Studies of RVEF or LV SV at rest and during exercise with minimally symptomatic patients (and low Cardiac Effort) would be necessary to test this intriguing idea.

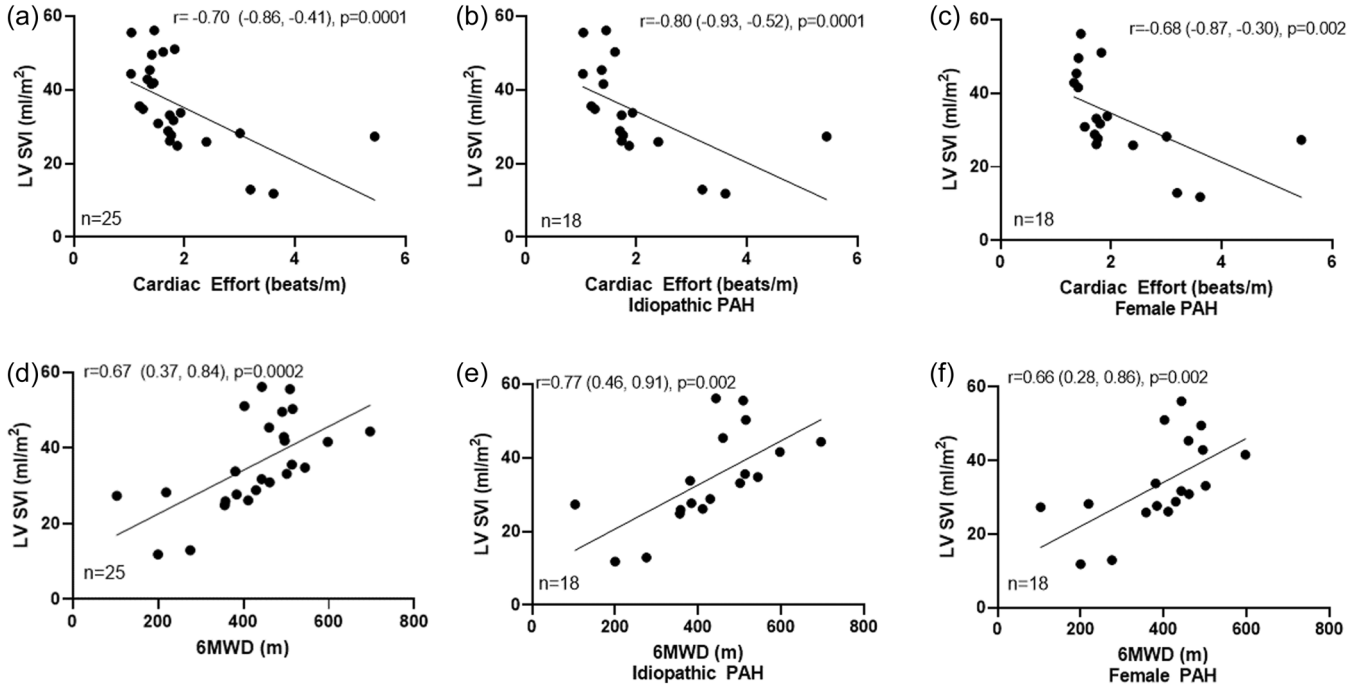

FIGURE 2 Left ventricle stroke volume index correlated with Cardiac Effort and 6-min walk distance. (a, b) Cardiac index has a very strong correlation with left ventricle stroke volume index and the relationship becomes stronger in patients with idiopathic PAH. (c) There is a strong correlation with stroke volume index and Cardiac Effort in female patients with PAH. (d, e) 6-min walk distance has a strong correlation with left ventricle stroke volume index that increases in patients with idiopathic PAH. (f) There is a strong correlation with left ventricle stroke volume index and 6-min walk distance in female patients.

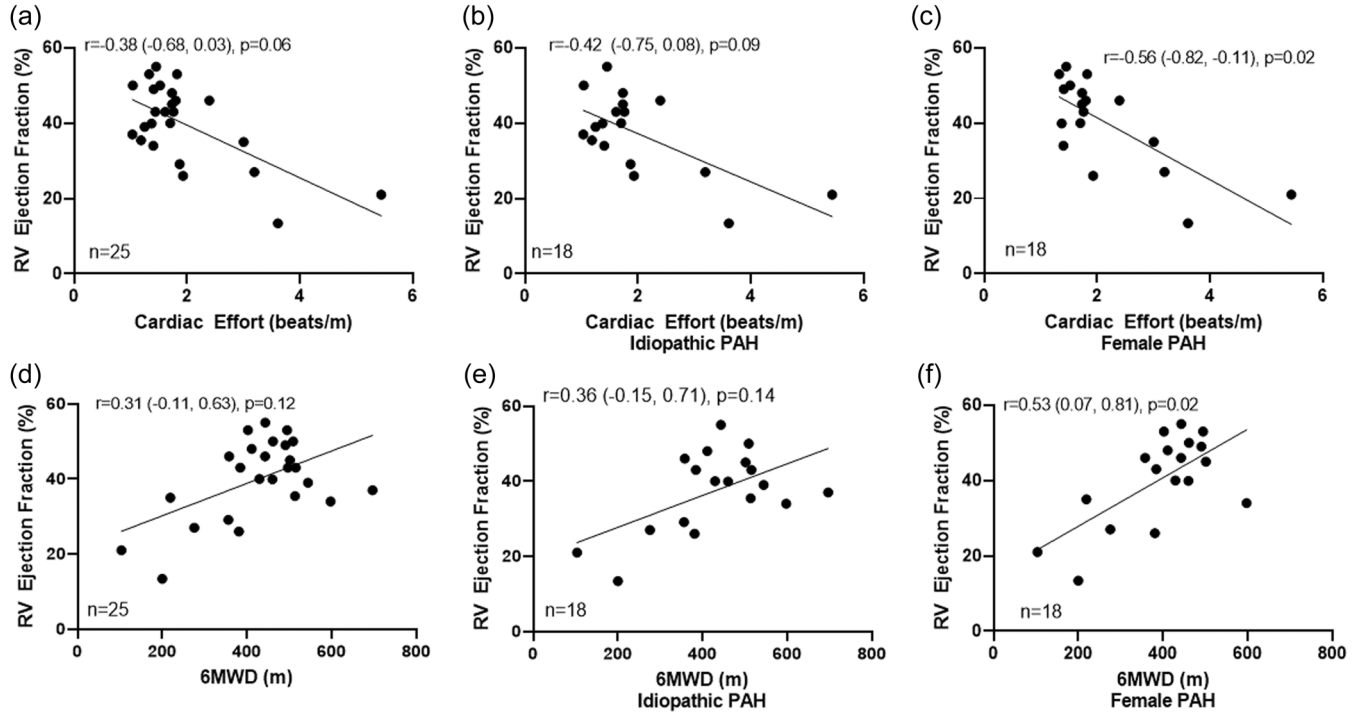

FIGURE 3 Right ventricular ejection fraction and its association with Cardiac Effort and 6-min walk distance. (a–c) Right ventricular ejection fraction in females with PAH correlates with Cardiac Effort. (d–f) Similar to Cardiac Effort, 6-min walk distance had a moderate correlation with right ventricular ejection fraction in female patients with PAH.

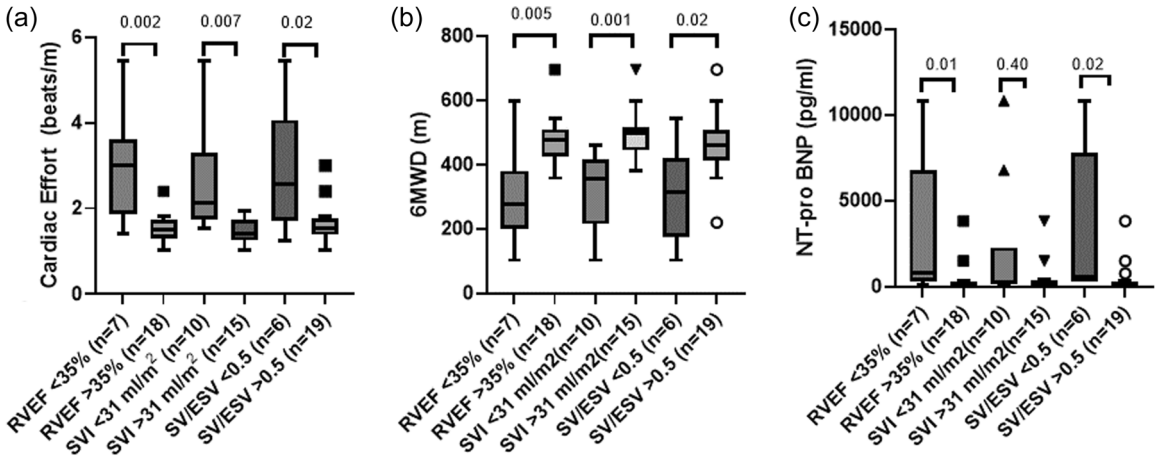

FIGURE 4 Cardiac Effort, 6-min walk distance, and NT-proBNP discriminated between right ventricular ejection fraction >35%, left ventricle stroke volume >31 ml/m^2, and stroke volume/end systolic volume >0.53. (a, b) Cardiac Effort and 6MWD were significantly different for all three thresholded parameters. (c) NT-proBNP was different for right ventricle ejection fraction and stroke volume/end systolic volume, while it was not different for the thresholds of left ventricle stroke volume index.

We previously found Cardiac Effort is more reproducible than 6MWD, probably because heart rate helps "index" 6MWD for other variables like effort and pain (Supporting information: (Fig. 2).[15,16] Cardiac Effort performed well in the home setting[17] and both Cardiac Effort and 6MWD have correlated strongly with SV assessed by MUGA[15] and right heart catheterization.[16] To our surprise, the present analyses do not argue that Cardiac Effort adds much to 6MWD in terms of indicating impaired SV or RVEF, perhaps because the participants gave a near maximal effort. However, in our previous work, continuous electrocardiogram recording adds value by providing physiologic insight and stabilizing the 6MWD measure against changes in motivation or musculoskeletal pain (also highlighted in the Supporting information). Importantly, electrocardiogram heart rate recording has significantly better data quality and acquisition compared to photoplethysmography (wrist or finger-based devices).[15,17] In our first attempts to measure Cardiac Effort, we had >25% data loss with photoplethysmography[15]; we did not lose any data here, and at this time, electrocardiogram heart rate monitoring is necessary for accurate Cardiac Effort. It is also critical to interrogate signal quality (visualize raw electrocardiogram data), as artifact can be misinterpreted by algorithms and report incorrect heart rates.

It has been shown previously that LV SV measured by cMRI correlated better with SV measured by direct Fick compared to RV SV,[26] and more recent work on the prognostic significance of cMRI measures in PAH reported LV SV as "the" SV measured by cMRI.[27] In the setting of RV dysfunction in PAH, LV volumes assessed by cMRI are also reduced,[28–30] a finding we also observed (Table 2). These prior reports and our data correlating LV SV with 6MWD suggest that measuring LV SV as an outcome in PAH is reasonable even though the RV is more directly impaired by the diseased pulmonary circulation.

The importance of right heart function in PAH and its association with symptoms, morbidity, and mortality has been established.[2] cMRI is the gold standard for assessment of right ventricle size and function in PAH,[31,32] and cMRI parameters have been shown to be reproducible,[33–35] associated with long term outcomes,[4–7] and treatment responsive in PAH.[36,37] Surprisingly, there is very little reported on 6MWD and its direct relationship with cMRI parameters or outcomes. In our prevalent, heavily-treated and relatively low-risk PAH cohort, we found Cardiac Effort and 6MWD both correlated strongly with LV SV. In a treatment naïve PAH cohort, both RV EF ($r = 0.325$) and RV SV ($r = 0.509$) were associated with 6WMD[21]; followup relationship between SV and 6MWD was not reported. Similar to our data, LV SV had a stronger correlation with 6WMD than RV SV in a mixed pulmonary hypertension cohort.[38] In our data, it is particularly noteworthy that the 6MWD ROC threshold (436 m) for predicting a LV SVI (>31 ml/m^2, Supporting information: (Fig. 1) lines up almost exactly with the >440 m threshold which predicts low mortality risk. We hope that future cMRI studies would study the relationship between LV SV and 6MWD or Cardiac Effort.

Additionally, while cMRI undoubtedly has a clear role in the evaluation of PAH patients, cost, limited availability, patient acceptance, and manual

imputation when calculating volumes[39] are limitations to cMRI. In resource limited settings, alternative tests that provide insight into cardiac function (and especially highlighting those with impaired SV) in a cost-effective manner are desperately needed. Cardiac Effort potentially helps fill this gap and can put frequent, serial testing in easy reach of all clinicians, including within the home setting.[17]

There are limitations to our study. Although prospective, it is a small, single center with only one observation; our primary purpose (and funding) was to interrogate the relationship between Cardiac Effort and cMRI measured ventricular volumes. We did not measure a treatment response for cMRI or Cardiac Effort (nor a delta-delta correlation), but our previous work has shown CE to be both treatment responsive and stable (reproducible).[15,16] This highly motivated PAH study population and the coordinators were experts with 6MWT, which likely contributed to 6MWD correlating better with cMRI parameters than others have reported. The distribution of our Cardiac Effort measurements was skewed towards low-risk values (7/25 ≤ 1.4 beats/m) despite our efforts to recruit across a range of RV dysfunction; a stronger study would have had more values between 1.6 and 2.5 beats/m, the range where the metric probably provides the most useful discriminatory information.

In summary, Cardiac Effort and 6MWD are simple, noninvasive assessments that correlate strongly with SV, now determined by three different modalities including cMRI. The present report suggests that a Cardiac Effort of ≥1.8 beats/m may identify a patient for whom SV is a critical limitation for walking distance. Our data align with others in that LV volumes provide useful information even though the RV is the 'culprit' ventricle in PAH. Prospective, multicenter studies are needed to evaluate the performance of Cardiac Effort in terms of predicting response to therapy and long-term outcomes.

AUTHOR CONTRIBUTION

Daniel J. Lachant: Study design, data analysis, interpretation, and writing of the manuscript. Michael D. Lachant: data acquisition, data analysis. Deborah Haight: data acquisition, data analysis. R. James White: Study design, data analysis, interpretation, and writing of the manuscript.

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DJL is the guarantor of the data. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

DJL: receives consulting and speaking fees from United Therapeutics. United Therapeutics also provides University of Rochester with research funding for industry and investigator sponsored studies. ML: none, DH: non, RJW: none.

ETHICS STATEMENT

The University of Rochester RSRB approved the protocol before the research was completed.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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