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RESEARCH ARTICLE

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Right ventricular stroke work index in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: A retrospective observational study

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Abstract

The right ventricular stroke work index (RVSWI) reflects the active work of the right ventricle (RV), but its clinical usefulness is not yet fully known in pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). We aimed to evaluate the correlation of RVSWI to clinical parameters, the presence of comorbidities and response to therapy. We performed a retrospective observational study of 54 patients (PAH: $N = 30$, CTEPH: $N = 24$) and control patients ($N = 11$), and collected clinical data including RVSWI and comorbidities at baseline. We also compared changes in the parameters of the four-strata mortality risk score at follow-up (median time of 12 months) after the initiation of therapy between patients with low- (<1450 mmHg*mL/m^2, $N = 18$) and high-RVSWI values (≥ 1450 mmHg*mL/m^2, $N = 19$). RVSWI at diagnosis was higher in PAH/CTEPH compared to control subjects (1408 ± 391 vs. 704 ± 140 mmHg*mL/m^2, $p < 0.001$, mean $\pm$ standard deviation, t-test), but did not differ between PAH and CTEPH patients (1406 ± 342 vs. 1409 ± 470 mmHg*mL/m^2, $p = 0.98$). Patients without comorbidities had higher RVSWI than those with comorbidities ($N = 23$: 1522 ± 400 vs. $N = 31$: 1323 ± 384 mmHg*mL/m^2,

Abbreviations: 6MWD, 6-min walk distance; BSA, body surface area; CI, cardiac index; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; FC, functional class; GFR, glomerular filtration rate; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; Hgb, hemoglobin; NA, not applicable; NS, nonsignificant; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide; PAC, pulmonary arterial compliance; $PaCO_2$, Arterial carbon dioxide pressure,; PAH, pulmonary arterial hypertension; PaO_2, arterial oxygen pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RHC, right heart catheterization; RV, right ventricle; RVOT VTI, right ventricular outflow tract velocity-time integral; RVSWI, right ventricular stroke work index; SPAPe, estimated systolic pulmonary arterial pressure by echocardiography; SV, stroke volume; SvO_2, mixed venous oxygen saturation; s/d/mPAP, systolic/mean/diastolic pulmonary arterial pressure by right heart catheterization; TAPSE, tricuspid annular plane systolic excursion; Vmax, maximal velocity.

Zsófia Lázár and Kristóf Karlócai are contributed equally to this study.

$p = 0.04$), which was also found in PAH ($p < 0.001$), but not in CTEPH ($p = 0.37$). A greater improvement in the four-strata mortality risk score ($p < 0.05$) and a trend for a larger reduction in N-terminal proB-type natriuretic peptide concentration ($p = 0.06$) were observed in the high-RVSWI subgroup than in the low-RVSWI patients at follow-up. In PAH and CTEPH, RVSWI provides additional information on RV function in comorbidities, and it may predict response to specific therapy. Regular monitoring of RVSWI may aid in optimizing therapy selection and timing.

KEYWORDS
chronic thromboembolic pulmonary hypertension, mortality risk, pulmonary arterial hypertension, right ventricular stroke work index

INTRODUCTION

Pulmonary hypertension (PH) is a debilitating disease, but appropriate treatment may reduce the rate of progression in some forms.[1] According to current guidelines, specific therapy is available for pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH).[1] Although these options may slow disease progression significantly, the actual response to therapy shows great interindividual variability. Furthermore, the relationship between right heart function and the patient's functional state is not linear. This is partly explained by the fact that the adaptation of the right heart is quite complex during the disease course.[2–4] In addition to the severity and extent of vascular abnormalities, the size of the right ventricle (RV), and the contractility of the myocardium are also influenced. Comorbidities can also alter the function of the myocardium or interfere with RV/pulmonary artery (PA) coupling.[5]

The active work of the RV myocardium during a contraction is described by the right ventricular stroke work (RVSW), which characterizes the ability of the RV to deliver blood volume (stroke volume, SV) into the pulmonary circulation by generating mean pulmonary arterial pressure (mPAP) against a given resistance of pulmonary circulation.[6] The gold standard method to determine this parameter is measuring the area of the pressure-volume loop.[7] The stroke work can well be expressed as the product of the blood volume delivered during systole (SV) and the pressure gradient. In this connection, the pressure gradient can be determined most precisely as the difference between the x1.25 mean RV pressure or - in the absence of pulmonary stenosis—mPAP and the right atrial mean pressure (RAP as RV end-diastolic pressure equivalent).[6] Instead, RVSW index (RVSWI) may be calculated from these hemodynamic parameters (RVSWI = (1.25 x mPAP-RAP) x SV index).[6,8] However, the clinical usefulness of RVSWI has remained uncertain in the routine clinical management of precapillary PH.

In the present study, we aimed to determine RVSWI in different PH groups compared to controls. Additionally, we aimed to assess the correlation of RVSWI with other echocardiographic and clinical parameters, the presence of comorbidities and response to therapy.

METHODS

Study design

We performed a retrospective observational study of patients undergoing right heart catheterization (RHC) due to suspected PH. Eligible patients were divided into diagnostic groups based on hemodynamic measurements: PAH, CTEPH, other or normal hemodynamic group. Patients from the PAH, CTEPH, and the normal hemodynamic (control) group were enrolled in the study after obtaining written informed consent. After enrollment, we collected baseline clinical data of echocardiography, pulmonary function test, 6-min walking test, arterial blood gas analysis and laboratory tests from our electronic database. Furthermore, we collected follow-up data from patients in the PAH and CTEPH groups from a re-evaluation at 12 (median:12; range: 3−17) months after the baseline assessment.

We compared baseline RVSWI in the PAH, CTEPH, and control groups and analyzed the correlation of baseline RVSWI to clinical parameters. We created subgroups based on the presence of comorbidities (comorbidities vs. no comorbidities), coupling and uncoupling in the total PH group, and mortality risk according to the four strata model (low, intermediate-low, intermediate-high, high mortality risk), and baseline

RVSWI values (low vs. high RVSWI) for further comparisons in follow-up patients. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Semmelweis University, Budapest, Hungary (protocol code 84/2023).

Study patients

Patients undergoing (RHC) due to suspected PH at the Cardiopulmonary Unit (Department of Pulmonology, Semmelweis University Clinical Center) between January 2020 and August 2023 were eligible for the study.

Suspected PH was defined as increased maximal velocity of tricuspid regurgitation (Vmax > 3.4 m/s) or moderately elevated maximal velocity (2.9 m/s < Vmax < 3.4 m/s) with other signs of right heart dysfunction (RV > 32 mm, D sign, and tricuspid annular plane systolic excursion [TAPSE] < 18 mm) on echocardiography.

Precapillary PH was defined as mPAP > 20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, and PVR > 2 WU. PAH was diagnosed after the exclusion of other possible causes.[1] CTEPH was defined as precapillary PH with thromboembolic origin based on imaging (chest CT scan and lung perfusion scan). Patients with normal hemodynamic parameters were defined as "normal" (serving as the control group). Patients with abnormal hemodynamic parameters, not fulfilling PAH or CTEPH criteria (postcapillary PH based on PAWP ≥ 15 mmHg, or precapillary PH due to lung disease and/or hypoxia, or PH with unclear or multifactorial mechanism based on clinical data, lung function test, and chest CT scan) were defined as "other" and excluded from the study. In the case of PAH, we evaluated the proportion of specific subsets, and in the CTEPH group, with the involvement of a radiologist expert, we evaluated the extent of thromboembolism and the involvement of the pulmonary branches of the proximal and distal arteries based on the guideline criteria.[1]

Data collection

General data

We collected demographic data (age, body surface area, and sex), results from RHC, echocardiography, and laboratory examinations (see below in detail), 6-min walk distance (6MWD), and functional classes were also recorded. In addition, mortality risk was evaluated based on the four-strata model at baseline and follow-up.[6,7]

Assessment of comorbidities

The presence of specific comorbidities that are often linked with left heart disease, especially heart failure with preserved ejection fraction, that is, arterial hypertension, diabetes mellitus, coronary heart disease, and obesity (defined by a body mass index > 30 kg/m^2) were recorded according to Rosenkranz et al.[5] These comorbidities had been diagnosed before the diagnostic workup due to suspected PH.

RHC

RHC was performed with Corodyn 7 F catheters (B Braun SE) under standard conditions.[1] We measured right atrial pressure (RAP), RV pressure, pulmonary arterial pressure (PAP), and PAWP. Cardiac output (CO) was determined by the thermodilution method, while mixed venous oxygen saturation (SvO_2) was measured from a PA blood sample by a blood gas analyzer (Roche Cobas b 221). In idiopathic PAH, the vasoreactivity test was performed with intravenous iloprost, according to the international guideline.[1] Further parameters were calculated including cardiac index (CI = CO/body surface area), stroke volume (SV = CO/heart rate), SV index (SVI = SV/body surface area), pulmonary vascular resistance (PVR = (mPAP-PAWP)/CO) and pulmonary arterial compliance (PAC = SV/[systolic PAP—diastolic PAP]).[1] In addition, the right ventricular stroke work (RVSWI) index was determined according to Chemla et al. (RVSWI = [1.25 x mPAP—RAP] x SVI).[6]

Echocardiography

Echocardiography was performed with the Mindray DC-70 X-Insight instrument (Shenzhen Mindray Bio-Medical Electronics Co.). We evaluated the right ventricular outflow tract velocity-tome integral (RVOT VTI) using the pulsatile doppler curve in the parasternal short axis view. From the apical 4-chamber view, we measured the right atrial area. TAPSE was acquired by placing an M-mode cursor through the tricuspid lateral annulus and measuring the amount of maximal longitudinal motion of the annulus. We calculated the right atrial-ventricular pressure gradient from the peak velocity of TR tracings. We estimated the systolic pulmonary pressure (SPAPe) by adding the right atrial pressure to the pressure gradient according to the ASE recommendation based on the size and the change of the inferior vena cava during respiration.[1,9,10] Right ventricular-pulmonary arterial coupling was determined from echocardiographic parameters as a ratio of TAPSE/SPAPe. The cut-off value of 0.32

separates the normal coupling group (TAPSE/SPAPe > 0.32) from the uncoupling group (TAPSE/SPAPe ≤ 0.32).[11,12]

Blood tests

Venous and arterial sampling was performed according to clinical standards. Serum N-terimal pro-B-type natriuretic peptide (NT-proBNP) concentration, laboratory indices of the liver (glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, gamma-glutamyl transferase), the kidney (glomerular filtration rate), and blood count were measured in the Central Laboratory of the Clinical Center. Arterial blood gas values and mixed venous oxygen saturation were determined with a blood gas analyzer (Roche Cobas b 221).

6-min walk test

6MWT was performed—based on international standards and the recommendations of the PH guideline—along a 20-m-long corridor, with continuous monitoring of oxygen saturation and heart rate in addition to blood pressure measurement and evaluation of the Borg 0–10 dyspnea scale before and after the test.[1,13]

Statistical analysis

Results are expressed as mean and standard deviation (SD). The normality of data was determined using the Shapiro-Wilk test and homogeneity of variances was assessed using the Levene test. Groups and subgroups were compared with the Student *t*-test, the Mann–Whitney *U*-test, analysis of variance or the one-way Kruskal–Wallis test with Bonferroni correction. Paired nominal data were assessed using a contingency table and Pearson chi-square test. The Spearman method was used to assess correlations. Missing data were not used in the calculations. We performed a two-sided analysis with significance level set at $\alpha = 0.05$ (SPSS 28.0 IBM SPSS Statistics). Follow-up time was calculated according to Schemper and Smith.[14]

RESULTS

Patient characteristics

One hundred seventeen patients were screened for the study and 65 were enrolled (Figure 1.). Out of the enrolled patients, 30 had PAH (idiopathic: $N = 20$, associated with portal hypertension: $N = 2$, drug-induced: $N = 1$, associated with congenital heart disease: $N = 5$, associated with connective tissue disease: $N = 2$), 24 had CTEPH (proximal obstruction: $N = 11$, distal obstruction: $N = 13$), and 11 were ascribed to the control group. The median time between diagnosis and the end of clinical observation was 12 months (min–max: 3–17 months). PAH and CTEPH patients had higher hemoglobin and NT-proBNP values compared to control patients ($p < 0.05$) (Table 1). SvO_2 was markedly higher in the PAH group than in CTEPH (Table 2). We did not find vasoreactivity in any PAH patients. RVSWI was higher in both PAH and CTEPH patients compared to the control group, but RVSWI showed no difference between the PAH and CTEPH groups (Table 2).

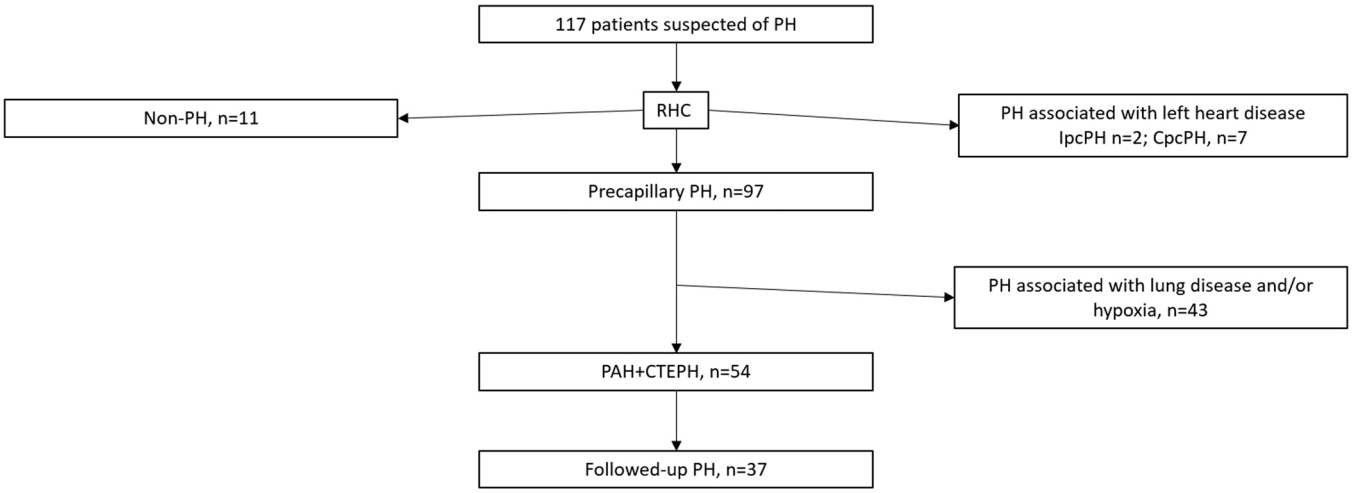

FIGURE 1 Patient selection algorithm. CpcPH, combined post- and precapillary pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; IpcPH, isolated postcapillary pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

TABLE 1 Patient characteristics.

Variables	Control $N = 11$	PAH + CTEPH $N = 54$	p Value	PAH $N = 30$	CTEPH $N = 24$	p Value
Male %	18%	40%	$p < 0.05$	27%	50%	$p < 0.05$
Age, years	60 ± 11	59 ± 13	0.47	63 ± 13	58 ± 10	0.10
BSA, kg/m^2	1.9 ± 0.4	1.9 ± 0.2	0.49	1.8 ± 0.2	2.0 ± 0.2	$p < 0.05$
6MWD, m	322 ± 181	311 ± 189	0.36	295 ± 171	360 ± 184	0.09
Echocardiographic parameters						
SPAPe, mmHg	39 ± 13	66 ± 20.2	$p < 0.001$	65 ± 16.8	68.5 ± 23.5	0.14
RV diameter, mm	30.6 ± 3.8	40.6 ± 8.6	$p < 0.001$	40.6 ± 8.6	40.4 ± 8.4	0.35
RA area, cm^2	19.4 ± 4.7	25.5 ± 8.1	$p < 0.05$	25.4 ± 8.4	25.7 ± 7.3	0.31
TAPSE, mm	23.6 ± 4.2	18.6 ± 5.8	$p < 0.05$	19.1 ± 6.4	18.1 ± 4.7	0.56
RVOT VTI, cm	13.4 ± 2.8	12.7 ± 5.4	0.09	14.0 ± 6.2	11.4 ± 3.6	0.14
Laboratory tests						
NT-proBNP, pg/ml	323 ± 117	2344 ± 2959	$p < 0.05$	2335 ± 3401	2354 ± 2312	0.48
GFR, ml/min	84 ± 14	72 ± 19	0.07	71 ± 19	73 ± 19	0.43
Hgb, g/L	128 ± 16	152 ± 19	$p < 0.05$	151 ± 20	152 ± 17	0.33
GOT, U/L	32 ± 20	27 ± 13	0.14	28 ± 10	27 ± 15	0.11
GPT, U/L	26 ± 17	27 ± 25	0.44	27 ± 19	27 ± 31	0.47
Art. pH	7.43 ± 0.02	7.41 ± 0.04	0.14	7.41 ± 0.03	7.41 ± 0.04	0.31
PaO_2, mmHg	64 ± 12	62 ± 15	0.5	63 ± 16	62 ± 13	0.48
$PaCO_2$, mmHg	35 ± 5	35 ± 7	0.44	35 ± 6	35 ± 7	0.37

Note: Data are presented as mean ± standard deviation. Control versus Total PH and PAH versus CTEPH groups were compared with *T* test.

Abbreviations: Art. PCO2, Arterial carbon dioxide pressure; Art. PO2, arterial oxygen pressure; BSA, body surface area; CTEPH, chronic thromboembolic pulmonary hypertension; GFR, glomerular filtration rate; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; Hgb, hemoglobin; NA, not applicable; NS, nonsignificant; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; RA, right atrium; RV, right ventricle; RVOT VTI, right ventricular outflow tract velocity-time integral; SPAPe, estimated pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion; 6MWD, 6-min walk distance.

Association of RVSWI with clinical parameters, comorbidities and mortality risk-score at diagnosis

We found no correlation between RVSWI and hemodynamic (PVR, PAC, and SvO_2), echocardiographic (TAPSE, RV diameter, right atrial area, RVOT VTI, and eccentricity index), and other clinical parameters (age, NT-proBNP, FC, and 6MWD) at baseline in all patients with PH or in the subgroup of CTEPH ($p > 0.05$ for all parameters, data not shown). However, in patients with PAH, RVSWI was related to the eccentricity index ($r = 0.48$, $p = 0.01$). Furthermore, RVSWI showed no difference in patients with coupling and uncoupling (coupling: 1386 ± 426 mmHg*mL/m^2, $N = 19$ vs. uncoupling: 1421 ± 389 mmHg*mL/m^2, $N = 35$, $p = 0.76$).

We examined the association between RVSWI and the presence of comorbidities that potentially modify cardiomyocyte function. Thirty-one patients (CTEPH $N = 14$, PAH = 17) had at least one comorbid condition at the time of PH diagnosis, all were well-controlled with adequate treatment (1 comorbidity: $N = 15$, 2–4 comorbidities $N = 16$, Table 3). Comorbidities included systemic hypertension ($N = 26$), diabetes mellitus ($N = 10$), coronary heart disease ($N = 7$), and obesity ($N = 8$). Patients with comorbidities were older and had less severe PH (characterized by lower values for mPAP, PVR and higher CI) than patients without comorbidities. However, RAP and PAWP were higher in the comorbid group than in patients without accompanying diseases. Of note, RVSWI was decreased in comorbid patients compared to patients with no comorbidities (1323 ± 384 vs. 1522 ± 400, mmHg*mL/m^2, $p = 0.04$). Furthermore, patients with PAH and a comorbidity ($N = 17$) had lower RVSWI than PAH patients without comorbidities ($N = 13$, $p = 0.001$), as shown in Figure 2, but no difference was noted between comorbid and non-comorbid patients with CTEPH ($p = 0.37$).

At diagnosis 10, 12, 19, and 13 patients were grouped into having a low, intermediate-low,

TABLE 2 Parameters of right heart catheterization at baseline.

Variables	Control	PAH + CTEPH	*p* Value	PAH	CTEPH	*p* Value
sPAP, mmHg	27.3 ± 6.9	69.7 ± 19.3	<0.001	68.2 ± 20.2	71.5 ± 17.3	0.13
dPAP, mmHg	9.4 ± 3.8	28.8 ± 9.4	<0.001	28.5 ± 9.6	29.2 ± 9.1	0.15
mPAP, mmHg	16.3 ± 2.6	43.9 ± 11.6	<0.001	43.1 ± 12.3	44.8 ± 10.4	0.12
RAP, mmHg	1.7 ± 3.8	7.8 ± 4.7	<0.001	7.2 ± 4.3	8.5 ± 4.9	0.16
PAWP, mmHg	5.6 ± 3.7	9.5 ± 3.7	<0.05	9.0 ± 3.8	10.1 ± 3.4	0.27
CI, L/min/m^2	2.8 ± 0.6	2.4 ± 0.6	<0.05	2.5 ± 0.5	2.4 ± 0.7	0.27
PVR, WU	2.2 ± 0.8	8.3 ± 4.1	<0.001	8.2 ± 4.2	8.4 ± 34	0.39
PAC, mL/mmHg	5.8 ± 4.8	1.7 ± 0.9	<0.001	1.7 ± 0.9	1.8 ± 1.2	0.43
RVSWI, mmHg*mL/m^2	704 ± 140	1408 ± 391	<0.001	1406 ± 342	1409 ± 470	0.98
SvO_2,%	75.5 ± 5.5	67 ± 10	<0.05	69.2 ± 10.1	64 ± 9.1	<0.05

Note: Data are presented as mean ± standard deviation. Control versus Total PH and PAH versus CTEPH groups were compared with *T*-test.

Abbreviations: CI, cardiac index; CTEPH, chronic thromboembolic PH; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; s/d/mPAP, systolic/mean/diastolic pulmonary artery pressure; SVO_2, mixed venous oxygen saturation.

TABLE 3 Subgroup analysis based on the presence of comorbidities at diagnosis.

Variables	PH with comorbidities*N* = 31	PH without comorbidities*N* = 23	*p* Value
Age, years	62 ± 11	55 ± 14	<0.05
6MWD, m	284 ± 196	367 ± 146	0.13
NT-proBNP, pg/mL	2418 ± 3613	2249 ± 1693	0.84
Hemodynamic parameters at diagnosis			
sPAP, mmHg	64.8 ± 18	76.2 ± 18.6	<0.05
dPAP, mmHg	27.5 ± 9.4	30.6 ± 9.1	0.23
mPAP, mmHg	41.1 ± 11.3	47.6 ± 10.7	<0.05
RAP, mmHg	8.9 ± 4.6	6.3 ± 4.3	<0.05
PAWP, mmHg	10.4 ± 3.2	8.3 ± 3.9	<0.05
CI, L/min/m^2	2.6 ± 0.6	2.2 ± 0.5	<0.05
PVR, Wood Unit	6.7 ± 3.5	10.3 ± 3.9	<0.05
PAC, mL/mmHg	2.0 ± 1.1	1.4 ± 0.7	0.13
SVO_2,%	68 ± 11	65 ± 8	0.26
RVSWI	1323 ± 378	1513 ± 391	<0.05
Echocardiographic parameters at diagnosis			
TAPSE, mm	19.4 ± 6.2	17.6 ± 4.6	0.24
RV diameter, mm	40.1 ± 8.5	41.2 ± 8.6	0.66
RA area, cm^2	25.8 ± 8.2	25.1 ± 7.5	0.76
RVOT VTI, cm	13.8 ± 5.8	11.0 ± 3.7	0.08

Note: Data are presented as mean ± standard deviation. PH with and without comorbidities groups were compared with *T*-Test.

Abbreviations: CI, cardiac index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAC, pulmonary arterial compliance; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RV, right ventricular; RVOT VTI, right ventricular velocity time integral; RVSWI, right ventricular stroke work index; s/d/mPAP, systolic/mean/diastolic pulmonary artery pressure; SVO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; 6MWD, 6-min walk distance.

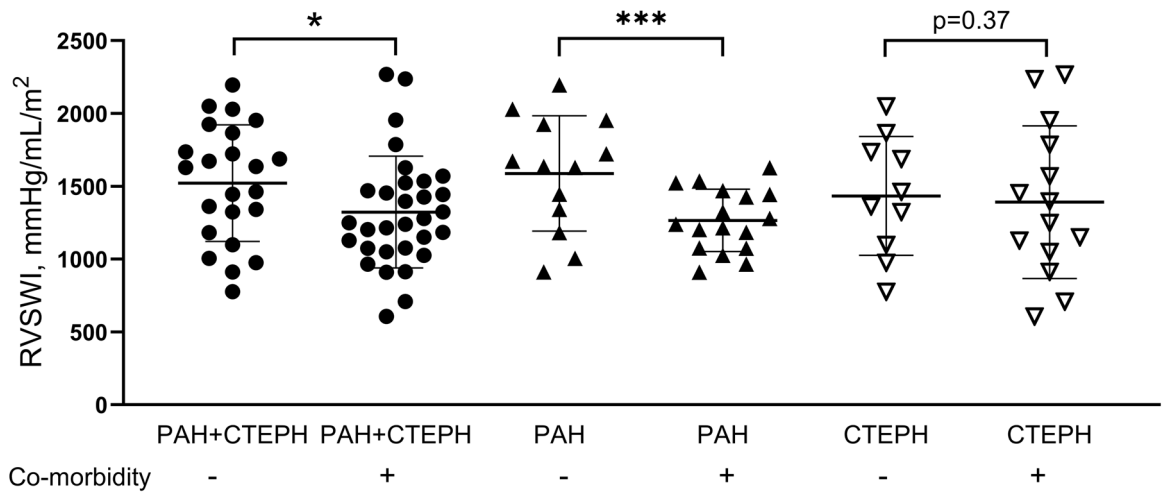

FIGURE 2 RVSWI at diagnosis between patients with and without comorbidities. Mean with standard deviation is shown, groups are compared with unpaired t-test. *$p < 0.05$, ***$p < 0.001$. CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; RVSWI, right ventricular stroke work index.

intermediate-high, and high mortality risk, respectively. RVSWI did not differ in groups with different mortality risk (low: 1368 ± 382 vs. intermediate-low: 1352 ± 408 vs. intermediate-high:1529 ± 416 vs. high:1311 ± 382 mmHg*mL/m^2; $p = 0.82$).

Baseline RVSWI and parameters at clinical follow-up

Out of the PAH and CTEPH groups, a total of 37 patients completed clinical visits with follow-up measurements within 12 months after the initiation of adequate therapies or following surgical interventions. Pharmacological therapies are shown in Table 4. Out of the CTEPH patients, one underwent balloon pulmonary angioplasty and one patient had pulmonary endarterectomy before the follow-up visit. The other 17 patients from the study population either did not receive pulmonary vasodilator therapy because of early disease stage ($N = 5$, mPAP: 21−24 mmHg), or they had inadequate compliance to treatment ($N = 5$) or have been receiving specific therapy for less than 6 months ($N = 7$), so their control examinations were still not available at the end of the observation period.

Patients were divided by the median RVSWI value (1450 mmHg*mL/m^2) at diagnosis (Table 4). More severe PH with increased PAP, but increased CI were found in the high-RVSWI (≥1450 mmHg*mL/m^2) than in the low-RVSWI subgroup (<1450 mmHg*mL/m^2). We analyzed the change in mortality risk score after short-term follow-up (median: 12; range 3−17 months). The improvement in the risk score was higher in the high-RVSWI group than in the low-RVSWI group, and we noted a trend for a higher improvement in NT-proBNP in the high-RVSWI patients (Table 4).

DISCUSSION

The assessment of global right ventricular function is via the construction of pressure-volume loops, a method cumbersome in clinical use. Here, we studied the clinical application of RVSWI, a calculated parameter of active work of the RV during contraction. RVSWI was increased in patients with PAH or CTEPH, but no difference was found between the PH groups. In PAH, a decreased RVSWI was associated with the presence of comorbidities impairing myocardial function. Interestingly, patients with RVSWI ≥ 1450 mmHg*mL/m^2 showed a greater reduction in mortality risk 1 year after specific treatment.

In recent years, advancement in the management of PH has resulted in improved overall outcomes. Upfront combined treatment regimens[15] and the use of a risk assessment tool[1] are effective, but currently, there are limited data on which baseline parameters can best predict therapeutic response. RVSWI is a calculated hemodynamic parameter that measures active RV work.[7,16] We used a formula which takes into account both the steady and pulsatile components of RVSW. It not only characterizes the active work of the RV myocardium but also provides additional information on RV adaptation superior to the volumetric and functional parameters of imaging studies. Because of its complex ability to reflect the dysfunction of the RV, the RVSWI

TABLE 4 Follow-up data of based in the subgroups based on baseline RVSWI values.

Variables	Low-RVSWI group $N = 18$	High-RVSWI group $N = 19$	p Value
Baseline mortality risk stratification parameters			
PAH/CTEPH, *N*	10/8	11/8	1.00
6MWD, m	304 ± 205	331 ± 150	0.83
FC	2.8 ± 0.7	2.8 ± 0.5	0.79
NT-proBNP, ng/mL	2882 ± 2806	2426 ± 3579	0.78
Mortality risk score	2.6 ± 0.9	2.8 ± 0.5	0.79
Baseline hemodynamic parameters			
sPAP, mmHg	69.6 ± 14.8	82.6 ± 14.5	<0.001
dPAP, mmHg	27.6 ± 7.0	35.2 ± 8.3	<0.001
mPAP, mmHg	43.2 ± 8.4	52.2 ± 8.9	<0.001
RAP, mmHg	7.2 ± 3.6	8.0 ± 5.3	0.68
PAWP, mmHg	7.8 ± 3.0	10.1 ± 3.6	0.06
CI, L/min/m^2	2.1 ± 0.4	2.5 ± 0.5	<0.05
PVR, Wood Unit	10.2 ± 3.8	9.3 ± 3.8	0.69
PAC, mL/mmHg	1.3 ± 0.8	1.6 ± 0.9	0.23
SvO_2,%	62.6 ± 9.5	66.2 ± 7.1	0.30
Baseline echocardiographic parameters			
SPAPe, mmHg	70.6 ± 16.7	74.1 ± 21.3	0.38
TAPSE, mm	17.2 ± 5.9	17.6 ± 4.9	0.82
RV diameter, mm	37.5 ± 8.7	43.1 ± 8.8	0.06
RA area, cm^2	23.2 ± 7.5	27.9 ± 8.5	0.08
RVOT VTI, cm	11.8 ± 6.2	12.7 ± 3.2	0.69
Short-term follow-up data using the COMPERA 2.0 stratification parameters			
Therapy at follow-up			
PDE5i, *N*	5	10	NA
ERA, *N*	2	0	NA
PDE5i + ERA, *N*	4	4	NA
sGC stimulator, *N*	3	3	NA
PGI_2, *N*	1	0	NA
PDE5i + PGI_2, *N*	1	0	NA
PDE5i + ERA + PGI_2, *N*	1	1	NA
Change in outcomes compared to baseline			
Δmortality risk score	0.0 ± 1.0	−0.7 ± 0.6	<0.05
Δ6MWD, m	32 ± 196	29 ± 132	0.94
ΔNT-proBNP, pg/mL	56 ± 2010	−1280 ± 2103	0.06
ΔFC	0.6 ± 0.6	−0.7 ± 0.5	0.84

Note: Data are presented as mean ± standard deviation. Groups were compared with unpaired *t*-test or Mann–Whitney test.

Abbreviations: CI, cardiac index; ERA, endothelin receptor antagonist; FC, WHO functional class; NA, not applicable; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAC, pulmonary arterial compliance; PDE5i, phophodiesterase-5 inhibitor; PGI^2, prostacyclin; PVR, pulmonary vascular resistance; RA, right atrium; RAP, right atrial pressure; RV, right ventricle; RVSWI, right ventricular stroke work index; RVOT VTI, right ventricular velocity time integral; s/d/mPAP, systolic/mean/diastolic pulmonary artery pressure; sGC, soluble guanylate cyclase; SPAPe, estimated pulmonary arterial systolic pressure; SvO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; 6MWD, 6-min walk distance.

has been proposed as a promising prognostic marker in PH patients, however, its ability to predict response to therapy has not been evaluated.

Previous studies have found that lower RVSWI was associated with decreased survival in patients with PH associated with connective tissue disease,[17] familial and idiopathic PAH.[18] These studies have examined homogenous groups and proposed that baseline RVSWI might both be associated with etiology and could predict outcome. In our study, RVSWI was higher in PAH and CTEPH patients compared to the control subjects, on par with previous findings.[6,19] However, we found no difference in RVSWI in PAH and CTEPH groups. This might be explained by the diverse composition of our study group. Further studies on homogenous PH groups might aid in better understanding the value of RVSWI at diagnosis.

Progression in PH is difficult to predict, and several factors can adversely affect RV function, such as advanced age and certain comorbidities. Comorbidities, particularly the ones that impair the physiological processes of the myocardium due to hypoxia or metabolic disorders, have mainly been investigated in regard to LV function.[20] In PAH, it has been reported that diabetes has a negative effect on RVSW.[21] In our cohort, the presence of co-morbidities (coronary heart disease, hypertension, diabetes, obesity)[5] is associated with older age and less severe PH based on mPAP, PVR and CI values. The decreased afterload can explain the low RVSWI values in comorbid patients. Interestingly, the difference in RV function confirmed by RVSWI is not reflected by routine echocardiographic parameters showing similarly reduced RV function in patients with and without comorbidities.

It is also noteworthy that the difference in the study population only appears in the PAH group, while not in CTEPH. It is assumed that the change in RV work results from complex mechanisms. In addition to the degree of afterload and co-morbidities affecting the functioning of the myocardium, differences in the extent of the obstruction in CTEPH and the propagation of the pulse wave also play a role in RVSW (Figure 2). Therefore, in mainly PAH, the RVSWI provides additional information about the state of the RV in addition to routine echocardiographic parameters, which may impact therapy management and the course of the disease.

Another important aspect of progression in PH is the biphasic nature of RV contractility and its systolic functional reserve. In the early stage of the disease, systolic functional reserve and contractility increase in parallel with the increasing pressure load. At a later stage, when the systolic reserve is exhausted, further progression and an increase in the afterload result in decreasing systolic function.[22] When examining baseline RVSWI, we found no correlation to other echocardiographic, hemodynamic, or clinical parameters, or the presence of coupling. This could be explained by the previously described biphasic change, where a peak in RVSWI may be assumed during the RV-PA uncoupling. This could explain the lack of correlation between RVSWI and other parameters that mainly change linearly during the progression of PH.

The prognostic value of RVSWI in PH is well known. According to a previous study of adult precapillary PH patients, higher RVSWI was associated with better outcomes, lower heart failure death rates, and hospitalization.[16] In another study of pediatric PAH patients, RVSW was related to functional capacity and mortality.[23] The short follow-up period in our study did not permit a detailed analysis of outcomes including transplant-free survival or death in our cohort; however, we did calculate mortality risk according to current recommendations.[1] Although the guideline primarily uses risk determination in the context of PAH, several publications have used the same strategy in CTEPH patients.[24–26] Based on our data, RVSWI did not correlate with the calculated mortality risk. This seemingly contradictory finding could also be explained by the previously mentioned probable biphasic course of RVSW progression.

As an interesting finding, our follow-up analysis revealed that patients with higher baseline RVSWI responded better to specific therapy and the decrease in mortality risk was greater. This was accompanied by a greater improvement in functional capacity, as noted by higher 6MWD values. This phenomenon points to the possible role of RVSWI in guiding the selection and timing of specific therapy in PH.

Our study has several limitations. The retrospective nature, the low patient number, and the short follow-up time of the study do not permit clear conclusions regarding the role of RVSWI in predicting therapy response in PH. However, the composition of our study group reflects the real-world practice in managing an orphan disease with complex etiology. Multi-center, prospective studies with large patient numbers are needed to verify the predictive value of RVSWI in PH.

In conclusion, RVSWI can provide additional information about the active work of the RV in patients with PAH and CTEPH. Our results show that RVSWI may predict response to short-term specific therapy in this patient group. Regular monitoring of RVSWI during the course of the disease may aid in optimizing therapy selection and timing.

AUTHOR CONTRIBUTIONS

Study conception and design: Györgyi Csósza, Zsófia Lázár, Kristóf Karlócai. *Data collection*: Györgyi Csósza, Kristóf Karlócai. *Analysis and interpretation of results*: Györgyi Csósza, Luca Valkó, Elek Dinya. *Draft manuscript preparation*: Györgyi Csósza, Veronika Müller, Zsófia Lázár. *Contribution to the final version of the manuscript*: György Losonczy, Veronika Müller, Kristóf Karlócai. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

This study was approved by the Research Ethics Committee of Semmelweis University, protocol number: 84/2023. All participants voluntarily agreed to participate and signed an informed consent form.

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REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S, Schwerzmann M, Dinh-Xuan AT, Bush A, Abdelhamid M, Aboyans V, Arbustini E, Asteggiano R, Barberà JA, Beghetti M, Čelutkienė J, Cikes M, Condliffe R, de Man F, Falk V, Fauchier L, Gaine S, Galié N, Gin-Sing W, Granton J, Grünig E, Hassoun PM, Hellemons M,

Jaarsma T, Kjellström B, Klok FA, Konradi A, Koskinas KC, Kotecha D, Lang I, Lewis BS, Linhart A, Lip GYH, Løchen ML, Mathioudakis AG, Mindham R, Moledina S, Naeije R, Nielsen JC, Olschewski H, Opitz I, Petersen SE, Prescott E, Rakisheva A, Reis A, Ristić AD, Roche N, Rodrigues R, Selton-Suty C, Souza R, Swift AJ, Touyz RM, Ulrich S, Wilkins MR, Wort SJ. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618–731.

2. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. J Am Coll Cardiol. 2017;69(2):236–43.
3. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, Naeije R, Newman J, Oudiz RJ, Provencher S, Torbicki A, Voelkel NF, Hassoun PM. Right heart adaptation to pulmonary arterial Hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D22–33.
4. Csósza G, Csoma B, Rozgonyi Z, Losonczy G, Müller V, Lázár Z, Karlócai K. Pulmonary vascular remodeling and right ventricular adaptation in precapillary pulmonary hypertension. Cardiologia Hungarica. 2022;52(2):105–11.
5. Rosenkranz S, Pausch C, Coghlan JG, Huscher D, Pittrow D, Grünig E, Staehler G, Vizza CD, Gall H, Distler O, Delcroix M, Ghofrani HA, Ewert R, Kabitz HJ, Skowasch D, Behr J, Milger K, Halank M, Wilkens H, Seyfarth HJ, Held M, Scelsi L, Neurohr C, Vonk-Noordegraaf A, Ulrich S, Klose H, Claussen M, Eisenmann S, Schmidt KH, Remppis BA, Skride A, Jureviciene E, Gumbiene L, Miliauskas S, Löffler-Ragg J, Lange TJ, Olsson KM, Hoeper MM, Opitz C. Risk stratification and response to therapy in patients with pulmonary arterial hypertension and comorbidities: A COMPERA analysis. J Heart Lung Transplant. 2023;42(1):102–14.
6. Chemla D, Castelain V, Zhu K, Papelier Y, Creuzé N, Hoette S, Parent F, Simonneau G, Humbert M, Herve P. Estimating right ventricular stroke work and the pulsatile work fraction in pulmonary hypertension. Chest. 2013;143(5):1343–50.
7. Schramm W. The units of measurement of the ventricular stroke work: a review study. J Clin Monit Comput. 2010;24(3):213–7.
8. Yang W, Marsden AL, Ogawa MT, Sakarovitch C, Hall KK, Rabinovitch M, Feinstein JA. Right ventricular stroke work correlates with outcomes in pediatric pulmonary arterial hypertension. Pulm Circ. 2018;8(3):1–9.
9. Austin C, Alassas K, Burger C, Safford R, Pagan R, Duello K, Kumar P, Zeiger T, Shapiro B. Echocardiographic assessment of estimated right atrial pressure and size predicts mortality in pulmonary arterial hypertension. Chest. 2015;147(1):198–208.
10. Augustine DX, Coates-Bradshaw LD, Willis J, Harkness A, Ring L, Grapsa J, Coghlan G, Kaye N, Oxborough D, Robinson S, Sandoval J, Rana BS, Siva A, Nihoyannopoulos P, Howard LS, Fox K, Bhattacharyya S, Sharma V, Steeds RP, Mathew T. Echocardiographic assessment of pulmonary hypertension: a guideline protocol from the British society of echocardiography. Echo Res Pract. 2018;5(3):G11–24.
11. Tello K, Wan J, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, Roller F, Mohajerani E, Seeger W, Herberg U, Sommer N, Gall H, Richter MJ. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. Circ Cardiovasc Imag. 2019;12(9):e009047.
12. Tello K, Axmann J, Ghofrani HA, Naeije R, Narcin N, Rieth A, Seeger W, Gall H, Richter MJ. Relevance of the TAPSE/PASP ratio in pulmonary arterial hypertension. Int J Cardiol. 2018;266:229–35.
13. Kammin EJ. The 6-minute walk test: indications and guidelines for use in outpatient practices. J Nurse Practiti. 2022;18(6):608–10.
14. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Controlled Clin Trials. 1996;17(4):343–6.
15. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, Oudiz RJ, Vonk-Noordegraaf A, White RJ, Blair C, Gillies H, Miller KL, Harris JHN, Langley J, Rubin LJ. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373(9):834–44.
16. Ibe T, Wada H, Sakakura K, Ito M, Ugata Y, Yamamoto K, Taniguchi Y, Momomura S, Fujita H. Right ventricular stroke work index. Int Heart J. 2018;59(5):1047–51.
17. Clapham KR, Highland KB, Rao Y, Fares WH. Reduced RVSWI is associated with increased mortality in connective tissue disease associated pulmonary arterial hypertension. Front Cardiovasc Med. 2020;7:77.
18. Brittain EL, Pugh ME, Wheeler LA, Robbins IM, Loyd JE, Newman JH, Larkin EK, Austin ED, Hemnes AR. Shorter survival in familial versus idiopathic pulmonary arterial hypertension is associated with hemodynamic markers of impaired right ventricular function. Pulm Circ. 2013;3(3):589–98.
19. Delcroix M, Vonk Noordegraaf A, Fadel E, Lang I, Simonneau G, Naeije R. Vascular and right ventricular remodelling in chronic thromboembolic pulmonary hypertension. Eur Respir J. 2013;41(1):224–32.
20. Lopaschuk GD, Karwi QG, Tian R, Wende AR, Abel ED. Cardiac energy metabolism in heart failure. Circ Res. 2021;128(10):1487–513.
21. Benson L, Brittain EL, Pugh ME, Austin ED, Fox K, Wheeler L, Robbins IM, Hemnes AR. Impact of diabetes on survival and right ventricular compensation in pulmonary arterial hypertension. Pulm Circ. 2014;4(2):311–8.
22. Di Maria MV, Campbell KR, Burkett DA, Younoszai AK, Landeck BF, Mertens L, Ivy DD, Hunter KS, Friedberg MK. Parameters of right ventricular function reveal ventricular-vascular mismatch as determined by right ventricular stroke work versus pulmonary vascular resistance in children with pulmonary hypertension. J Am Soc Echocardiogr. 2020;33(2):218–25.
23. Di Maria MV, Younoszai AK, Mertens L, Landeck BF, Ivy DD, Hunter KS, Friedberg MK. RV stroke work in children with pulmonary arterial hypertension: estimation based on invasive haemodynamic assessment and correlation with outcomes. Heart. 2014;100(17):1342–7.
24. Sandqvist A, Kylhammar D, Bartfay SE, Hesselstrand R, Hjalmarsson C, Kavianipour M, Nisell M, Rådegran G, Wikström G, Kjellström B, Söderberg S. Risk stratification in chronic thromboembolic pulmonary hypertension predicts survival. Scand Cardiovasc J. 2021;55(1):43–9.

25. Quan R, Yang Y, Yang Z, Tian H, Li S, Shen J, Ji Y, Zhang G, Zhang C, Wang G, Liu Y, Cheng Z, Yu Z, Song Z, Zheng Z, Cui W, Chen Y, Liu S, Chen X, Qian Y, Xiong C, Shan G, He J. Risk prediction in medically treated chronic thromboembolic pulmonary hypertension. BMC Pulm Med. 2021;21(1):128.
26. Humbert M, Farber HW, Ghofrani HA, Benza RL, Busse D, Meier C, Hoeper MM. Risk assessment in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(6):1802004.

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