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Sex difference in pulmonary hypertension in the evaluation by exercise echocardiography

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Abstract

Male patients with pulmonary hypertension have poor survival than their female counterparts. Poor right ventricular function in men may be one of the major determinants of poor prognosis. This study aimed to investigate the difference in hemodynamics during exercise between men and women by exercise echocardiography. Consecutive patients with pulmonary hypertension who underwent right heart catheterization were enrolled, and survival was analyzed. In patients who underwent exercise echocardiography, the change in tricuspid regurgitation pressure gradient during exercise was calculated at multiple stages (low-, moderate-, and high-load exercise), and the mortality was also recorded. In a total of 93 patients, although there were no differences in pulmonary artery pressure and vascular resistance between sexes, male patients showed poor survival. In patients with exercise echocardiography, change in tricuspid regurgitation pressure gradient at low-load (25 W) exercise was significantly lower in men, although that at maximum-load exercise was not different between men and women. In the Kaplan–Meier analysis, in a median follow-up duration of 1760 days, male patients and those with lower change in tricuspid regurgitation pressure gradient at low-load exercise showed poorer survival ($P = 0.002$ and 0.026, respectively). In the Cox proportional hazards analysis, the change in tricuspid regurgitation pressure gradient at low-load exercise was independently associated with poor survival after adjustment for age and sex. In conclusion, a lower change in tricuspid regurgitation pressure gradient at low-load exercise was observed in male patients and was a prognostic marker, which may be associated, at least in part, with poorer prognosis in male patients with pulmonary hypertension.

Keywords

pulmonary hypertension, sex difference, exercise echocardiography

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Introduction

Pulmonary hypertension (PH) is caused by increased pulmonary vascular resistance (PVR) due to remodeling of a pulmonary artery, ultimately leading to right ventricular (RV) dysfunction. Generally, the incidence of PH is higher in women, whereas prognosis is poorer in men.[1–4] Male patients with PH have worse pulmonary hemodynamics, as shown in a pooled analysis of subjects from several randomized trials.[5] Some previous data support the role of sex hormones in disease pathogenesis and outcomes.[6] It is considered that genetic variation in sex hormone pathways may be associated with prognosis in PH. Because of this, right heart function is expected to be poorer in men than in women.[7,8]

PH is assessed by resting hemodynamics using invasive examination. However, resting hemodynamics is insufficient to assess the severity of PH; therefore, some severity-stratification systems include not only resting hemodynamics data but also physical findings, laboratory findings, and exercise capacity.[9] Moreover, accurate stratification of RV dysfunction in patients with PH may be important in estimating the prognosis, regardless of the etiology of PH. Recently, exercise echocardiography has been used as an evaluation tool in assessing right heart function in patients with PH.[10,11] A previous study has shown that a smaller

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increase in pulmonary artery systolic pressure (PASP) induced by exercise was associated with poor prognosis in patients with severe PH.[12] Therefore, this study aimed to investigate the change in right heart hemodynamics during exercise by exercise echocardiography in patients with moderate PH, focusing on the difference between men and women, and clarify the prognostic implication that may be explained by sex difference in PH.

Methods

Study cohort and design

This is a retrospective analysis of consecutive patients with PH who were admitted in Kindai University Hospital between 2009 and 2019. The patients were assessed by right heart catheterization (RHC) and diagnosed with PH, which was defined as mean pulmonary artery pressure (mPAP) $\geq$25 mmHg. The etiology was assessed by physical examinations, laboratory findings, respiratory function test, enhanced computed tomography, and perfusion imaging.[13] Among these, exercise echocardiography was performed in patients after exclusion of those with PH due to left heart disease and lung disease. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments and approved by the Ethics Committee of Kindai University Faculty of Medicine (2020-027).

Exercise echocardiography

Echocardiography was performed using Aplio 400 (Canon Medical Systems Corporation, Japan) with 2.5 MHz transducer according to the recommendation described by the American Society of Echocardiography.[14] Left ventricular (LV) and RV dimension, volume, and wall thickness were assessed by two-dimensional imaging. PASP was estimated using RV systolic pressure, calculated from the tricuspid regurgitation peak gradient (TRPG), and added to the assessment of right atrial pressure using inferior vena cava size and collapsibility. A variable load supine bicycle ergometer was used for exercise echocardiography. Workload increased in three steps from low- to high-load exercise by 25 W every three minutes. TRPG, heart rate, blood pressure, and oxygen saturation were measured at each stage. The change in TRPG during exercise was defined as ΔTRPG according to the following equation: ΔTRPG = peak TRPG – rest TRPG.

Clinical follow-up

Patients were followed retrospectively from the time of diagnosis of PH for 3000 days. Follow-up information on vital status and clinical events was obtained using telephone contact or chart view. The primary endpoint was all-cause mortality, and the secondary endpoint was major adverse cardiac event (MACE), which was defined as composite of all-cause death and hospitalization due to worsening PH.

Statistical analysis

Comparison between the groups was assessed by χ^2 test for categorical variables, and unpaired Student's *t*-test or analysis of variance for continuous variables as appropriate. Cumulative incidences of clinical events were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable analysis of clinical outcomes was evaluated using the Cox proportional hazards model. *P*-values < 0.05 were regarded as statistically significant. Statistical analysis was performed using the JMP version 13.0 (SAS Institute, USA).

Results

Baseline clinical and functional characteristics

In a total of 93 patients with PH, mean age was 65.4 ± 14.9 years, and 43.0% of patients were male. Although male patients were older, there were no significant differences in body mass index, functional class, and RHC data between sexes (Fig. 1a and Table 1). The most frequent diagnosis was World Health Organization (WHO) Group 1 in both sexes; however, WHO Group 3 was frequently observed in male patients. In rest echocardiography, LV ejection fraction (EF) was lower in male patients.

In a subcohort of 49 patients where PH with left heart disease (WHO Group 2) and lung disease (WHO Group 3) was excluded, exercise echocardiography was performed. There were no significant differences in age, B-type natriuretic peptide level, WHO functional class, and six-minute walk distance between sexes (Table 2). However, in RHC and rest echocardiography, mPAP, PVR, and PASP were significantly higher in male patients than those in female patients.

Exercise echocardiography

All patients performed low-load exercise (25 W) for three minutes, and there were no significant differences in total maximum workload, systolic blood pressure, heart rate, oxygen saturation, and double product during exercise between men and women (Table 3). However, the ΔTRPG at 25 W was significantly lower in men than that in women (Fig. 2). The ΔTRPG at 50 W or maximum workload did not show a significant difference between sexes.

Clinical outcomes

In the total cohort, male sex was associated with poorer survival and MACE occurrence in a median follow-up duration of 991 days (interquartile range, 539–1958 days) (Fig. 1b and c). Although mPAP and PASP were not associated with mortality, the PVR and LV EF were significant prognostic markers of poor survival in this cohort ($P = 0.005$ and 0.027, respectively).

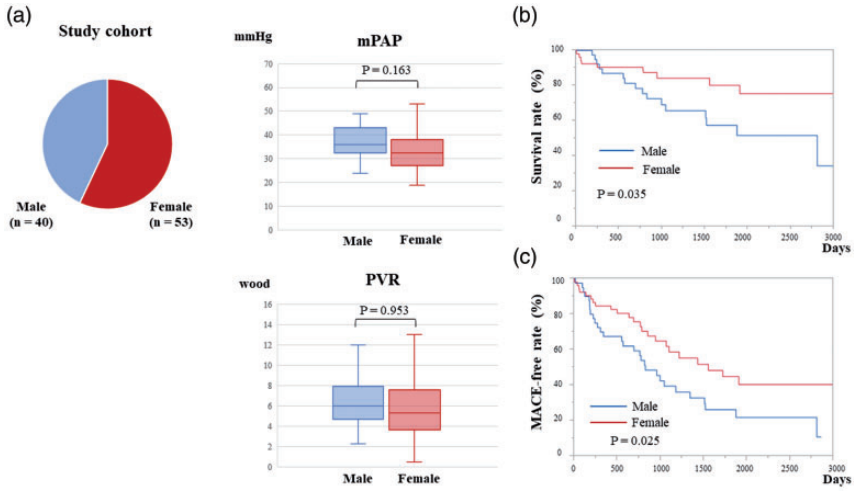

Fig. 1. Demographic and outcomes in patients with pulmonary hypertension. In a total of 93 patients with pulmonary hypertension, 43% were male and no difference was observed in mPAP and PVR by right heart catheterization between sex (a). However, male patients showed the worse prognosis; survival rate (b), and MACE-free rate (c).
MACE: major adverse cardiac event; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance.

Table 1. Baseline clinical characteristics in the total cohort.

	Male ($n = 40$)	Female ($n = 53$)	*P*-values
Age (years)	69.2 ± 14.4	62.5 ± 14.8	0.031
BMI (kg/m^2)	22.4 ± 4.2	22.5 ± 3.9	0.916
WHO functional class			0.134
Class I	1 (2.5)	4 (7.6)	
Class II	21 (52.5)	33 (62.3)	
Class III	17 (42.5)	12 (22.6)	
Class IV	1 (2.5)	4 (7.6)	
Six-minute walk distance (m)	285.3 ± 121.2	327.9 ± 61.9	0.170
Diagnosis (WHO)			0.003
Group 1	17 (42.5)	34 (64.2)	
Group 2	2 (5.0)	1 (1.9)	
Group 3	11 (27.6)	1 (1.9)	
Group 4	9 (22.5)	14 (26.5)	
Group 5	1 (2.5)	3 (5.7)	
Echocardiography			
LV EF (%)	66.4 ± 8.1	70.2 ± 6.6	0.015
E/e'	8.6 ± 2.3	8.4 ± 2.9	0.794
PASP (mmHg)	68.2 ± 14.3	62.1 ± 16.7	0.068
TAPSE (mm)	17.8 ± 3.3	17.4 ± 4.3	0.739
BNP (pg/dL)	121.5 ± 128.5	260.5 ± 427.9	0.053
Uric acid (mg/dL)	6.0 ± 1.6	5.4 ± 1.8	0.096
Vasodilators	11 (27.5)	18 (34.0)	0.504
Oxygen therapy	17 (42.5)	16 (30.2)	0.220

Note: Values are expressed as mean ± SD or number (%).
BNP: B-type natriuretic peptide; BMI: body mass index; E/e': ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EF: ejection fraction; LV, left ventricular; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; WHO: World Health Organization.

In the subcohort, in a median follow-up duration of 1760 days (interquartile range, 777–2237 days), the mPAP and PVR by RHC were not significant prognostic markers in mortality ($P = 0.288$ and 0.534, respectively). Moreover, the rest PASP and LV EF by echocardiography did not predict the mortality ($P = 0.618$ and 0.350, respectively). In contrast, both lower ΔTRPG at low-load exercise (ΔTRPG ≤13.3 mmHg) and male sex were associated with poor

Table 2. Baseline characteristics in a cohort with exercise echocardiography.

	Male ($n = 22$)	Female ($n = 27$)	*P*-values
Age (years)	67.2 ± 14.1	63.8 ± 12.3	0.365
BMI (kg/m^2)	23.1 ± 4.4	22.0 ± 3.8	0.326
WHO functional class			0.166
Class I	1 (4.6%)	3 (11.1%)	
Class II	14 (63.6%)	21 (77.8%)	
Class III	7 (31.8%)	3 (11.1%)	
Six-minute walk distance (m)	332.2 ± 91.5	336.9 ± 61.6	0.876
Diagnosis (WHO)			0.883
Group 1	14 (63.6%)	19 (70.4%)	
Group 4	7 (31.8%)	7 (25.9%)	
Group 5	1 (4.6%)	1 (3.7%)	
Right heart catheterization data			
Mean PAP (mmHg)	38.4 ± 8.8	30.2 ± 6.6	0.001
Right atrial pressure (mmHg)	6.4 ± 3.9	5.2 ± 2.8	0.223
PAWP (mmHg)	9.4 ± 4.3	8.8 ± 3.2	0.612
CO (L/min)	4.6 ± 1.7	4.7 ± 1.5	0.791
SvO2 (%)	66.3 ± 7.2	70.3 ± 6.9	0.063
PVR (WU)	7.1 ± 3.2	5.1 ± 2.8	0.031
Rest echocardiography			
LV EF (%)	68.3 ± 6.0	71.7 ± 6.1	0.057
E/e'	7.6 ± 1.0	9.4 ± 3.8	0.232
PASP (mmHg)	68.5 ± 15.3	56.8 ± 12.4	0.005
TAPSE (mm)	18.1 ± 5.5	19.1 ± 4.3	0.542
BNP (pg/dL)	119.4 ± 139.3	79.7 ± 72.4	0.206
Uric acid (mg/dL)	6.3 ± 1.8	5.3 ± 1.6	0.041
Vasodilators	5 (22.7%)	8 (29.6%)	0.585
Oxygen therapy	8 (36.4%)	10 (37.0%)	0.961

Note: Values are expressed as mean ± SD or number (%).
BNP: B-type natriuretic peptide; BMI: body mass index; CO: cardiac output; E/e': ratio between early mitral inflow velocity and mitral annular early diastolic velocity; EF: ejection fraction; LV, left ventricular; PAP: pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation; TAPSE: tricuspid annular plane systolic excursion; WHO: World Health Organization; WU: Wood units.

Table 3. Exercise echocardiographic findings.

	Male	Female	P-values
Exercise time (s)	291.8 ± 123.3	260.0 ± 82.2	0.288
Maximum load (W)	51.1 ± 18.1	43.5 ± 14.9	0.112
Rest			
Systolic pressure (mmHg)	133.0 ± 16.6	128.3 ± 26.5	0.479
Heart rate (bpm)	75.9 ± 15.8	72.6 ± 14.4	0.462
SpO_2 (%)	95.2 ± 2.9	94.7 ± 3.3	0.611
Peak			
Systolic pressure (mmHg)	166.3 ± 29.2	166.2 ± 35.1	0.999
Heart rate (bpm)	111.9 ± 17.2	114.5 ± 19.3	0.638
SpO_2 (%)	89.9 ± 4.7	89.1 ± 6.0	0.678
Double product	18,755 ± 5109	19,093 ± 5166	0.825
Echocardiography findings			
25 W TRPG (mmHg)	76.1 ± 19.8	74.0 ± 21.6	0.720
ΔTRPG (mmHg)	14.7 ± 9.1	24.5 ± 15.5	0.014
50 W TRPG (mmHg)	81.5 ± 19.1	83.9 ± 22.5	0.746
ΔTRPG (mmHg)	27.6 ± 14.1	36.7 ± 17.8	0.118
Maximum-load TRPG (mmHg)	90.8 ± 19.5	83.2 ± 22.4	0.220
ΔTRPG (mmHg)	28.7 ± 16.3	34.5 ± 18.9	0.263

Note: Values are expressed as mean ± SD.
SpO_2: saturation of percutaneous oxygen; TRPG: tricuspid regurgitation pressure gradient; ΔTRPG: change in tricuspid regurgitation pressure gradient.

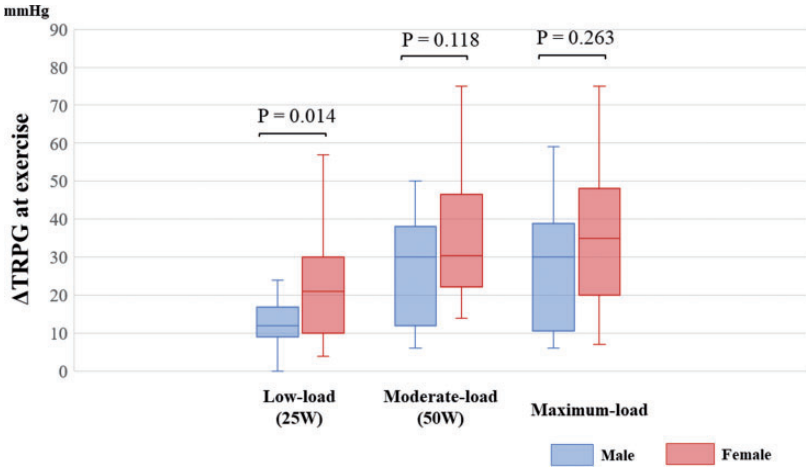

Fig. 2. Difference in TRPG change during exercise between male and female. Boxplots represent the changes in TRPG (ΔTRPG) at each workload. Only at low-load exercise (25 W), ΔTRPG in male (blue box) was significantly lower than that in female (red box).
ΔTRPG: change in tricuspid regurgitation pressure gradient.

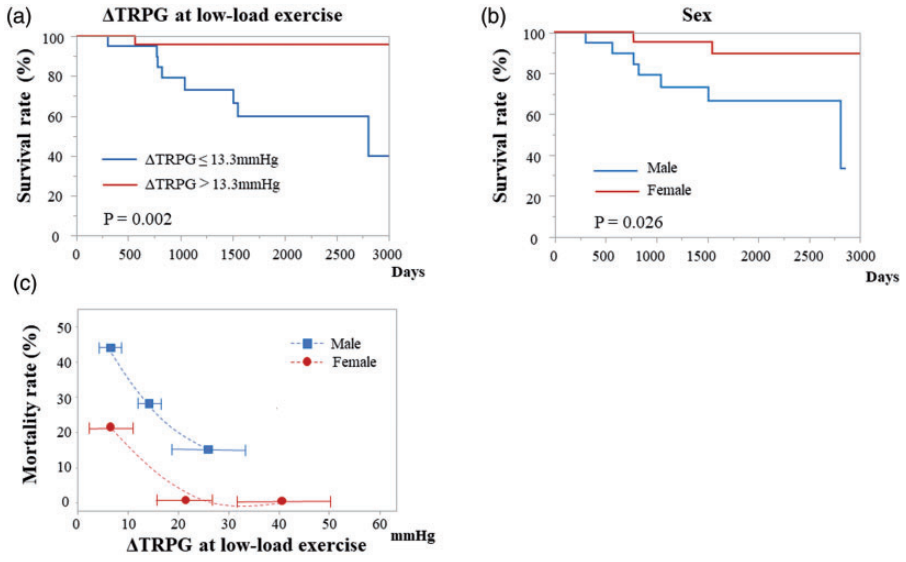

Fig. 3. Survival analysis stratified by TRPG change at low-load exercise and sex. In the Kaplan–Meier analysis, patients with lower ΔTRPG at low-load exercise (a) or male patients (b) showed the poorer survival. When the patients of each sex were divided into three groups based on the ΔTRPG at low-load exercise, the estimated mortality for male (blue square) and female (red circle) suggested that ΔTRPG at low-load exercise and sex were, at least in part, independent (c).
ΔTRPG: change in tricuspid regurgitation pressure gradient.

survival in Kaplan–Meier analysis (Fig. 3a and b, $P = 0.002$ and 0.026, respectively). WHO functional class was also associated with mortality. ΔTRPG at low-load exercise (25 W) was an independent prognostic marker after adjustment for age and sex by Cox proportional hazards analysis (Table 4). When the patients of each sex were divided into three groups based on the ΔTRPG value at low-load exercise, the estimated mortality for each sex suggested that ΔTRPG at low-load exercise and sex were, at least in part, independent (Fig. 3c).

Discussion

Although PH encompasses a heterogeneous group of diseases, it is marked by sexually dimorphic disease presentation wherein women are at increased risk for disease development but display increased survival compared with men.[15] Recent studies have shown that a number of factors have been suggested to contribute to the sex difference in PH, and the sex-specific association of PH with infections, autoimmune diseases, inflammation, and sex hormones are suggested.[16–19] Multiple sex hormones, receptors, and

Table 4. Cox proportional hazards analysis for mortality.

	Univariate model (unadjusted)			Multivariate Cox model (adjusted)[a]		
Variable (cutoff value)	HR	95% CI	*P*-values	HR	95% CI	*P*-values
Age (>68 years)	1.64	0.42–6.88	0.470			
Male	5.00	1.20–33.64	0.026	4.63	1.10–31.25	0.035
BMI (>22.1 kg/m^2)	0.29	0.04–1.20	0.089	0.31	0.04–1.38	0.129
WHO functional class (1, 2 vs 3, 4)	0.22	0.05–0.94	0.042	0.22	0.05–0.96	0.044
Diagnosis (WHO) (1 vs 4, 5)	1.76	0.43–11.8	0.459			
mPAP (>33 mmHg)	0.39	0.08–1.48	0.168			
SvO_2 (>68.4%)	0.77	0.19–2.94	0.698			
PVR (>5.5 WU)	1.61	0.42–7.64	0.495			
LV EF (>70%)	0.53	0.11–2.00	0.350			
PASP (>57 mmHg)	1.02	0.27–4.12	0.982			
TAPSE (>19 mm)	1.09	0.27–4.15	0.894			
BNP (>58 pg/dL)	0.91	0.22–3.48	0.893			
Uric acid (>5.7 mg/dL)	1.41	0.37–5.74	0.612			
Vasodilators	1.43	0.30–5.49	0.623			
Oxygen therapy	1.32	0.32–5.11	0.684			
Exercise echocardiography						
Maximum load (>25 W)	0.42	0.11–1.71	0.213			
Exercise time (>180 s)	0.46	0.12–1.87	0.263			
Peak SpO_2 (>89%)	1.41	0.26–7.62	0.678			
Δ maximum TRPG (>30 mmHg)	0.49	0.10–1.88	0.303			
Δ 25 W TRPG (>13.3 mmHg)	0.08	0.00–0.44	0.002	0.12	0.01–0.70	0.015

[a]HR was adjusted by incorporating the age and sex.

BMI: body mass index; BNP: B-type natriuretic peptide; CI: confidence interval; EF, ejection fraction; HR: hazard ratio; LV, left ventricular; mPAP: mean pulmonary artery pressure; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; TRPG: tricuspid regurgitation pressure gradient; TAPSE: tricuspid annular plane systolic excursion; SvO_2: mixed venous oxygen saturation; ΔTRPG: change in tricuspid regurgitation pressure gradient; WHO: World Health Organization; WU: Wood units.

metabolites may play a role in the disease pathogenesis and outcomes.[6,16] The key pathophysiological features of PH such as vasoconstriction/vasodilation, proliferation, vascular remodeling, and inflammation are affected by sex hormones. In particular, estrogen, which is considered to play a typical role among sex hormones, has various effects on pulmonary circulation. Umar et al. reported an improving effect of estrogen on preexisting PH rats by suppressing inflammatory cells in the lungs.[17] On the other hand, other gender-related factors of PH have also been suggested. High mobility group box 1 (HMGB1), as damage-associated molecular patterns, has been recognized in the development of PH, and male patients with PH show a higher level of HMGB1.[20] HMGB1 is reported to be released from either pulmonary artery endothelial cells or smooth muscle cells, and to play an important role in determining the severity of PH.[21] Moreover, the type of sex chromosome may contribute to sex difference in PH. Umar et al. revealed that the less severe PH in mice was due to the presence of Y chromosome, and they suggested the protective effect of the Y chromosome on PH.[22] Additionally, Yan et al. showed that the higher female incidence of PH was driven by specific factors to the Y chromosome that regulated the bone morphogenetic protein receptor type 2 through the transcription factor sex-determining region Y.[23]

Several pooled analyses showed that male patients with PH had poor hemodynamics and poor prognosis than their female counterparts.[5] In the present study, male patients showed poor survival in a total cohort of 93 patients and in a subcohort of 49 patients with exercise echocardiography. We did not find any clinical factors that were associated with mortality, except for age, sex, and ΔTRPG at low-dose exercise, in a subcohort with exercise echocardiography. Women had better RV systolic function in patients with PH and healthy subjects.[24,25] Ventetuolo et al. reported that the genetic variations in estrogen metabolism and androgen signaling had an association with RV morphology.[26] This sexual steroid metabolism may cause difference in RV function between sex, and survival bias conferred by female sex may be explained at least in part by sex hormone-mediated effects on the RV. Since we could not perform the analysis of RV function and morphology in detail, it is difficult to determine the sex difference in RV function and contribution to the prognosis in the present study. However, the exercise-induced increase in PASP is suggested as a possible measure of RV contractile reserve in patients with PH.[12] The present finding of lower ΔTRPG at low-load exercise in men may suggest poor RV contractile reserve in men, which was one of the prognostic determinants associated with sex.

Nagel et al. reported that, in patients with systemic sclerosis, exercise echocardiography improved sensitivity in detecting pulmonary artery hypertension than echocardiography at rest only.[10] PASP evaluation by exercise echocardiography may be useful especially in the diagnosis of early forms of PH. In contrast, Grünig et al. assessed the prognostic role of exercise echocardiography.[12] In 124 patients with severe PH who underwent exercise echocardiography, the lower increase in PASP at 50–75 W workload was an independent poor prognostic marker. It is concordant with the present result; however, the increase in PASP (i.e. ΔTRPG) at low-load exercise (25 W) was a stronger prognostic determinant than that at maximum workload (approximately 50 W) in the present study. Increase in PASP (ΔTRPG) at lower workload may be more sensitive because it may reflect RV contractile reserve accurately with less effects on pulmonary vasoconstriction, increased intrathoracic pressure, and transmission of increase in left atrial pressure.[27] There is also an issue regarding the accuracy of echocardiographic estimation of PASP during exercise. van Riel et al. evaluated the accuracy of exercise echocardiography by simultaneously using echocardiography and RHC during exercise.[28] They showed that agreement was good among the subset of patients with high-quality TR Doppler signal. Since high-quality TR Doppler signal is easy to obtain and evaluate in exercise echocardiography at low-dose workload, it may be useful in evaluating patients with moderate PH in the present study.

Korff et al. reported conflicting results; a higher TRPG increase during exercise may be a predictor of MACE in patients with any heart disease.[29] They analyzed 278 patients with PASP at rest > 35 mmHg who underwent exercise echocardiography and evaluated the increase in TRPG during exercise. They included patients mainly with ischemic heart disease (49.1%) and valvular disease (22.4%), and their PASPs were moderately increased (rest PASP, 45 mmHg). This result may be strongly influenced by the fact that most heart diseases were caused by left heart diseases and RV function was usually not impaired. Pre- and post-capillary PHs may show different responses by exercise echocardiography. Moreover, the extent of baseline PSAP may be associated with conflicting results. In the early stage of PAH, a more increase of TRPG during exercise may be a predictor of development of PH in the near future. In contrast, in advanced patients with PH, a smaller increase in TRPG may reflect poor RV function/reserve. A prospective validation study is necessary in confirming our findings and clinical relevance.

Study limitations

The current study has several limitations. First, it was a retrospective analysis in a single center and the sample number was small, which are susceptible to bias in data selection and analyses. The statistical analysis in Fig. 3c could not be performed due to the small number of the patients. Second, we could not perform exercise echocardiography in all patients with PH. Especially critical patients with PH were excluded for safety. It may explain the difference between our study and the study by Grünig et al. which was performed in patients with severe forms of PH.[12] Also, patients with PH due to left heart disease (Group 2) and lung disease (Group 3) were excluded in a subcohort with exercise echocardiography, which might cause the different results between the total cohort and subcohort. The patients with Groups 2 and 3 may have less or different impact on the sex difference of the right heart hemodynamics as compared with those with Groups 1 and 4[15] and the application of the present results to all patients with PH may be limited. Finally, there were limited data regarding RV function on exercise echocardiography. Only TRPG change was used as a parameter of RV function. Such a study as evaluating RV function in detail is necessary in clarifying the relationship between RV function and prognosis.

Conclusions

In the present study, we examined the usefulness of exercise echocardiography focusing on sex and prognosis in the patients with moderate PH. Lower ΔTRPG at low-load exercise (25 W) was observed in the male patients. It was found to be a prognostic marker, which may be associated, at least in part, with poorer prognosis in male patients.

Role of sponsors

The sponsor had no role in the design of the study, the collection, and analysis of the data, or the preparation of the manuscript.

Authors contributions

T.T., M.T., and Y. I. conceived the conception and design of the work. M.T. and Y.H. contributed to the data curation. T.T. and Y. I. performed the data analysis. G.N. and S.M. supervised the study. T.T. drafted and Y.I. reviewed and edited the manuscript.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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References

1. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary

Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122: 164–172.
2. Escribano-Subias P, Blanco I, López-Meseguer M, et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J* 2012; 40: 596–603.
3. Humbert M, Sitbon O, Yaïci A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J* 2010; 36: 549–555.
4. Jacobs W, Van De Veerdonk MC, Trip P, et al. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. *Chest* 2014; 145: 1230–1236.
5. Ventetuolo CE, Praestgaard A, Palevsky HI, et al. Sex and haemodynamics in pulmonary arterial hypertension. *Eur Respir J* 2014; 43: 523–530.
6. Docherty CK, Harvey KY, Mair KM, et al. The role of sex in the pathophysiology of pulmonary hypertension. *Adv Exp Med Biol* 2018; 1065: 511–528.
7. Lahm T, Tuder RM and Petrache I. Progress in solving the sex hormone paradox in pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2014; 307: L7–L26.
8. De Jesus Perez VA. Making sense of the estrogen paradox in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2011; 184: 629–630.
9. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018; 39: 4175–4181.
10. Nagel C, Henn P, Ehlken N, et al. Stress Doppler echocardiography for early detection of systemic sclerosis-associated pulmonary arterial hypertension. *Arthritis Res Ther* 2015; 17: 165.
11. Lancellotti P, Pellikka PA, Budts W, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2017; 30: 101–138.
12. Grünig E, Tiede H, Enyimayew EO, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation* 2013; 128: 2005–2015.
13. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493–2537.
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440–1463.
15. Hester J, Ventetuolo C and Lahm T. Sex, gender, and sex hormones in pulmonary hypertension and right ventricular failure. *Compr Physiol* 2019; 10: 125–170.
16. Mair KM, Johansen AK, Wright AF, et al. Pulmonary arterial hypertension: basis of sex differences in incidence and treatment response. *Br J Pharmacol* 2014; 171: 567–579.
17. Umar S, Iorga A, Matori H, et al. Estrogen rescues preexisting severe pulmonary hypertension in rats. *Am J Respir Crit Care Med* 2011; 184: 715–723.
18. Batton KA, Austin CO, Bruno KA, et al. Sex differences in pulmonary arterial hypertension: role of infection and autoimmunity in the pathogenesis of disease. *Biol Sex Differ* 2018; 9: 15.
19. Martin YN and Pabelick CM. Sex differences in the pulmonary circulation: implications for pulmonary hypertension. *Am J Physiol Heart Circ Physiol* 2014; 306: H1253–H1264.
20. Sauler M, Bazan IS and Lee PJ. Cell death in the lung: the apoptosis-necroptosis axis. *Annu Rev Physiol* 2019; 81: 375–402.
21. Zemskova M, McClain N, Niihori M, et al. Necrosis-released HMGB1 (high mobility group box 1) in the progressive pulmonary arterial hypertension associated with male sex. *Hypertension* 2020; 76: 1787–1799.
22. Umar S, Cunningham CM, Itoh Y, et al. The Y chromosome plays a protective role in experimental hypoxic pulmonary hypertension. *Am J Respir Crit Care Med* 2018; 197: 952–955.
23. Yan L, Cogan JD, Hedges LK, et al. The Y chromosome regulates BMPR2 expression via SRY: a possible reason "Why" fewer males develop pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2018; 198: 1581–1583.
24. Foppa M, Arora G, Gona P, et al. Right ventricular volumes and systolic function by cardiac magnetic resonance and the impact of sex, age, and obesity in a longitudinally followed cohort free of pulmonary and cardiovascular disease: the Framingham Heart Study. *Circ Cardiovasc Imaging*. 2016; 9: e003810.
25. Kawut SM, Al-Naamani N, Agerstrand C, et al. Determinants of right ventricular ejection fraction in pulmonary arterial hypertension. *Chest* 2009; 135: 752–759.
26. Ventetuolo CE, Mitra N, Wan F, et al. Oestradiol metabolism and androgen receptor genotypes are associated with right ventricular function. *Eur Respir J* 2016; 47: 553–563.
27. Naeije R, Vanderpool R, Dhakal BP, et al. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med* 2013; 187: 576–583.
28. Van Riel AC, Opotowsky AR, Santos M, et al. Accuracy of echocardiography to estimate pulmonary artery pressures with exercise: a simultaneous invasive-noninvasive comparison. *Circ Cardiovasc Imaging* 2017; 10: e005711.
29. Korff S, Enders-Gier P, Uhlmann L, et al. Systolic pulmonary artery pressure assessed during routine exercise Doppler echocardiography: insights of a real-world setting in patients with elevated pulmonary pressures. *Int J Cardiovasc Imaging* 2018; 34: 1215–1225.