Prolonged Elevation of Tricuspid Regurgitation Pressure Gradient After Exercise in Patients With Exercise-induced Pulmonary Hypertension

Michiyo Yamano, MD*, Tetsuhiro Yamano, MD, Kazuaki Takamatsu, MD, Chao Ma, MD, Noriyuku Wakana, MD, Kenji Yanishi, MD, Naohiko Nakanishi, MD, Kan Zen, MD, Takeshi Nakamura, MD, Hirokazu Shiraishi, MD, and Satoaki Matoba, MD

It is necessary to measure the peak tricuspid regurgitation pressure gradient (TRPG) that is recorded at maximum exercise intensity when diagnosing exercise-induced pulmonary hypertension (ePH) on exercise stress echocardiography (ESE). However, it is difficult to measure maximum TRPG during the treadmill exercise. If ePH induced TRPG elevation continues during recovery period after exercise termination, this elevation will serve as a practical diagnostic standard. We aimed to assess whether the elevation of postexercise peak TRPG prolong soon after finishing exercise in patients with ePH. Seventy-four patients underwent symptom-limited ESE by using a semirecumbent bicycle ergometer. ePH was defined as peak TRPG > 50 mm Hg at maximum exercise. We measured peak TRPG during exercise and until 5 minutes afterward. Thirty-five patients were diagnosed with ePH; their median TRPG was 57 mm Hg [interquartile range: 52−62 mm Hg] at maximum exercise. Peak TRPG in patients with ePH was > 40 mm Hg until 2 minutes after exercise. The cut-off values of peak TRPG to detect ePH were 43 mm Hg just after exercise and 41 mm Hg at 1 minute afterward (areas under the curve: 0.98, 0.92, respectively; both p < 0.001). In conclusion, elevated peak TRPG persisted for at least 2 minutes after finishing exercise, and this time frame will therefore provide a new window for diagnosing ePH by ESE. **(Am J Cardiol 2021;142:124−129)**

Exercise-induced pulmonary hypertension (ePH) is a crucial finding for diagnosing the etiology of exertional dyspnea on exercise stress echocardiography (ESE). When diagnosing ePH, it is necessary to measure maximum tricuspid regurgitation (TR) velocity, which is usually recorded at maximum exercise.[1,2] Treadmill exercise is one of the most widely used methods of stress testing, but measuring TR velocity during this exercise is impractical. On the other hand, use of a supine or semi-recumbent bicycle ergometer enables us to measure TR velocity during exercise as well as immediately afterward. If a high peak TR pressure gradient (TRPG) due to ePH persists after exercise, it may serve as a diagnostic clue. We aimed to assess whether the elevation of postexercise peak TRPG prolong soon after finishing exercise in patients with ePH.

Methods

A total of 82 patients underwent ESE at our institution to determine the existence of ePH or evaluation of heart disease associated with ePH. TR signals were observed at rest in all study subjects. Eight patients were excluded: 5 because their TR signals during exercise were incomplete, and 3 whose archived echocardiographic images were inadequate for diagnosing the existence of ePH. Finally, we enrolled 74 patients with sinus rhythm who could be diagnosed as having ePH or not. To determine whether functional mitral stenosis was present, ESE was performed in 28 patients with a normal transmitral pressure gradient at rest who had undergone mitral valve repair. Twenty-five patients with connective tissue disease and 6 patients who had been diagnosed with pulmonary arterial hypertension underwent ESE to determine the existence and/or degree of ePH. Other patients with significant valvular disease and those who complained of dyspnea underwent ESE to evaluate their exercise tolerance or the cause of their symptoms. All study subjects gave written informed consent.

Patients underwent conventional echocardiography at rest and symptom-limited ESE on a semi-recumbent bicycle ergometer (Lode B. V., Groningen, AN, Netherlands). The initial workload was 12 or 25 watts, and was increased by 12 to 13 or 25 watts every 3 minutes, respectively, until the workload could no longer be tolerated due to dyspnea or leg fatigue. We selected 12 watts as the initial workload and incremented this value by 12-13 watts when a patient's exercise tolerance was judged to be < 4 metabolic equivalents (METs) based on the interview before the ESE.[3,4] We also calculated the ratio of achieved METs to age- and gender-predicted METs.[5,6] We measured peak TR velocity during exercise and until 5 minutes after exercise using an E9 ultrasound system (GE Healthcare, Milwaukee, Wisconsin), and the

Department of Cardiovascular Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan. Manuscript received August 5, 2020; revised manuscript received and accepted November 30, 2020.

Disclosures: None.

*Corresponding author: Tel: +81-75-251-5511; fax: +81-75-251-5514.
E-mail address: m.yamano823@gmail.com (M. Yamano).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.11.037

velocity was averaged over at least 2 cardiac cycles. Pulmonary artery systolic pressure (PASP) was estimated from peak TR velocity using the modified Bernoulli equation, as follows: $4V^2$ + right atrial pressure.[7] All patients had an inferior vena cava that was < 20 millimeters, and respiratory variation was observed, so we added 3 mm Hg as the right atrial pressure.[8] Furthermore, the mean pulmonary artery pressure was estimated using the following previously reported formula: 0.61 x PASP + 2 mm Hg.[9] Cardiac output was determined based on the left ventricular (LV) stroke volume, which was calculated by multiplying the LV outflow tract area by the LV outflow tract velocity-time integral measured by pulsed Doppler. Patients were defined as having ePH if the peak TRPG at maximum exercise was > 50 mm Hg.[1,10]

All normally distributed values are expressed as mean ± standard deviation, and non-normally distributed values are expressed as median and interquartile range. The characteristics of patients with and without ePH were compared by the chi-square test for categorical variables. Differences in non-normally distributed values between the 2 groups were compared using the Mann-Whitney *U* test. The peak TRPG values during exercise and until 5 minutes afterward were analyzed using repeated measures analysis of variance. The cut-off values of peak TRPG to detect ePH at each time point were evaluated using receiver operating characteristic analysis. A 2-sided p value < 0.05 was considered statistically significant.

Results

Thirty-five patients (47%) were diagnosed with ePH, and their median TRPG at maximum exercise was 57 mm Hg [interquartile range: 52−62 mm Hg]. Fourteen patients out of 35 with ePH underwent cardiac catheterization to document the presence of pulmonary hypertension and decide the indication of medication for pulmonary hypertension. Table 1 shows the clinical comparisons between patients with and without ePH. Baseline echocardiographic parameters are shown in Table 2. There were 12 patients whose estimated mean PAP was higher than 25 mm Hg in patients with ePH. The exercise test values are shown in Table 3. Heart rate recovery after exercise was prolonged in patients with ePH, but the difference was not statistically significant compared with patients without ePH (Supplementary Figure 1).

Peak TRPG values calculated via echocardiography from baseline through 5 minutes after exercise completion are shown in Figure 1. The differences in peak TRPG between patients with and without ePH were statistically significant at all time points, and 95% confidence intervals at each stage did not overlap between the 2 groups (Supplementary Table 1). Although peak TRPG started to decrease immediately after exercise in both groups, it remained higher than 40 mm Hg at 2 minutes afterward in patients with ePH. Figure 2 shows representative patients with and without ePH. Peak TRPG was higher than 40 mm Hg at 2 minutes after exercise in the patient with ePH. The cut-off values of peak TRPG to detect ePH were 43 mm Hg just after finishing exercise (area under the curve = 0.98, p < 0.001; Figure 3) and 41 mm Hg at 1 minute after completing exercise (area under the curve = 0.92, p < 0.001).

Table 1
Baseline characteristics

Variable	ePH (+) n = 35	ePH (-) n = 39	p value
Age (years)	67 ± 14	65 ± 9	0.545
Male / female	8 / 27	14 / 25	0.220
Diagnosis			0.136
Post mitral valve repair	8 (23%)	20 (51%)	
Connective tissue disease	13 (37%)	12 (31%)	
Pulmonary arterial hypertension	5 (14%)	1 (3%)	
Aortic stenosis	2 (6%)	1 (3%)	
Severity (1/2/3/4)	0/0/2/0	0/0/0/1	
Mitral regurgitation	3 (9%)	3 (8%)	
Severity (1/2/3/4)	0/0/2/1	1/0/0/2	
Mitral stenosis	1 (3%)	0	
Severity (1/2/3/4)	0/0/0/1	-	
LV diastolic dysfunction	1 (3%)	1 (3%)	
LV systolic dysfunction	2 (6%)	1 (3%)	

ePH = exercise-induced pulmonary hypertension; LV = left ventricular.

Table 2
Baseline echocardiographic parameters

Variable	ePH (+)	ePH (-)	p value
LV diastolic diameter (mm)	42 ± 9	44 ± 7	0.399
LV ejection fraction (%)	62 ± 9	60 ± 11	0.398
Cardiac output (L/min)*	4.4 [3.3−5.4]	4.5 [3.6−5.4]	0.605
Left atrial volume index (mL/m^2)*	48 [33−57]	40 [34−49]	0.072
E (m/sec)	1.03 ± 0.60	0.89 ± 0.28	< 0.001
E/A	1.25 ± 0.92	1.15 ± 0.50	0.593
DT, ms	263 ± 182	225 ± 62	0.264
Septal e’ (cm/sec)	5.2 ± 1.4	6.5 ± 2.4	0.033
E/e’ septal	15.8 ± 6.6	12.0 ± 5.3	0.051
TR severity (1/2/3/4)	25/8/1/1	33/6/0/0	0.364
Peak TRPG (mm Hg)*	31 [22−35]	21 [18−25]	< 0.001

DT = deceleration time; ePH = exercise-induced pulmonary hypertension; E = early diastolic velocity; E/A = ratio of E to A (late diastolic velocity); e’ = early diastolic annular velocity; LV = left ventricular; TRPG = tricuspid regurgitation pressure gradient.
* Values are medians [interquartile range].

Discussion

Pulmonary hypertension occurs not only in patients with pulmonary arterial hypertension, but also in combination with left heart disease, systemic to pulmonary shunt, congenital heart disease, connective tissue disease, lung disease, and other systemic conditions.[7] The estimation of PASP based on peak TRPG in echocardiography is a standard method in clinical settings, and high-quality TR Doppler signals have been reported to correlate well with PASP calculated by cardiac catheterization.[11] Furthermore, the effectiveness of exercise testing, including ESE, in predicting the prognosis of patients with PH has often been reported.[10,12,13] The occurrence of ePH during ESE has been reported to be an important finding in patients with PH of various backgrounds.[14,15] Most studies have reported that patients with a pathologic PASP response during exercise demonstrate a normal PASP at rest.[1,16] In our study, the peak TRPG at baseline was higher in patients with ePH than in those without it. One of the reasons is that some

Table 3
Exercise test values in subjects with and without ePH

Variable	ePH (+)	ePH (-)	p value
Maximum load (watts)	50 [37−100]	75 [50−100]	< 0.001
Exercise time (min)	9 [6−12]	12 [9−12]	0.009
Target heart rate (bpm)	130 ± 12	132 ± 8	0.406
Heart rate at maximum exercise (bpm)	118 ± 19	115 ± 19	0.219
Heart rate at maximum exercise / target heart rate (%)	91 ± 13	87 ± 12	0.138
Achieved METs	3.8 ± 1.2	4.7 ± 1.3	0.003
Achieved METs / predicted METs (%)	62 ± 19	69 ± 19	0.117
Cause of exercise cessation			0.092
Dyspnea	14 (40%)	9 (23%)	
Leg fatigue	12 (34%)	14 (36%)	
Attainment of target heart rate	7 (20%)	6 (15%)	
Dyspnea and leg fatigue	2 (6%)	10 (26%)	
Cardiac output at maximum exercise (L/min)*	7.8 [6.4−11.3]	8.3 [6.2−10.1]	0.936
Peak TRPG at maximum exercise (mm Hg)*	57 [52−62]	38 [34−46]	< 0.001
Estimated PASP at maximum exercise (mm Hg)*	60 [55−65]	41 [37−49]	< 0.001
Estimated mean PAP at maximum exercise (mm Hg)*	38 [36−42]	27 [25−32]	< 0.001
Δmean PAP/Δcardiac output	6.5 [3.1−10.0]	3.2 [1.7−5.1]	0.012

ePH = exercise-induced pulmonary hypertension; METs = metabolic equivalents; PAP = pulmonary artery pressure; PASP = pulmonary artery systolic pressure; TRPG = tricuspid regurgitation pressure gradient.

* Values are medians [interquartile range].

patients underwent ESE to determine if their symptoms were correlated with ePH, irrespective of their high peak TRPG at rest;[17] that is, our study included a few patients whose peak TRPG at rest was higher than 36 mm Hg, which is considered to be significantly elevated based on the modified Bernoulli equation.[7,17]

The most important finding of the present study was that in patients with ePH, the elevated peak TRPG at the maximum exercise load persisted at least 2 minutes just after maximum exercise, though its value began returning to normal immediately after stopping exercise, and returned to the normal range by 5 minutes afterward. The appropriate cut-off values to detect ePH were considered to be 43 mm Hg just after exercise (area under the curve = 0.98, $p < 0.001$), and 41 mm Hg at 1 minute after exercise (area under the curve = 0.92, $p < 0.001$).

Acquiring echocardiographic images during the peak exercise state is useful during ESE with a supine or semi-recumbent bicycle ergometer, though it is impossible when using a treadmill.[18] Particularly in patients with ePH, determining a reliable peak TRPG value during maximum exercise should be just as important as provoking dyspnea during exercise. It may be worthwhile if we can diagnose ePH based on a reliable peak TRPG value during ESE using a treadmill which is physiological exercise and is more generally used. Therefore, when we conduct ESE using a treadmill, we must have a reliable criterion or cut-off value of peak TRPG obtained just after maximum exercise in patients with provoked ePH who are diagnosed during supine or semi-recumbent bicycle ergometer ESE.

Most authors have reported the significance of estimated PASP in patients with ePH only during or after completing

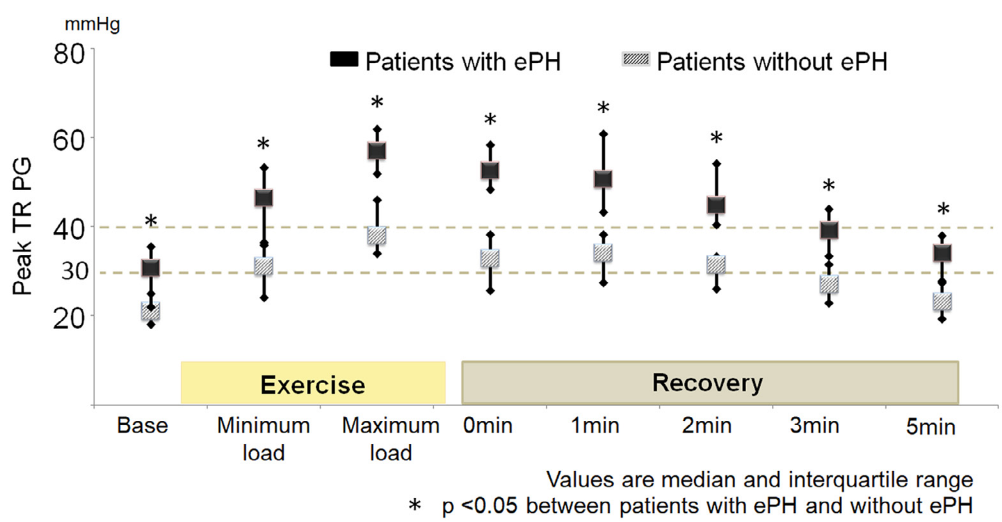

Figure 1. Changes of peak TRPG during and after finishing exercise. Base = baseline; ePH = exercise-induced pulmonary hypertension; TRPG = tricuspid regurgitation pressure gradient.

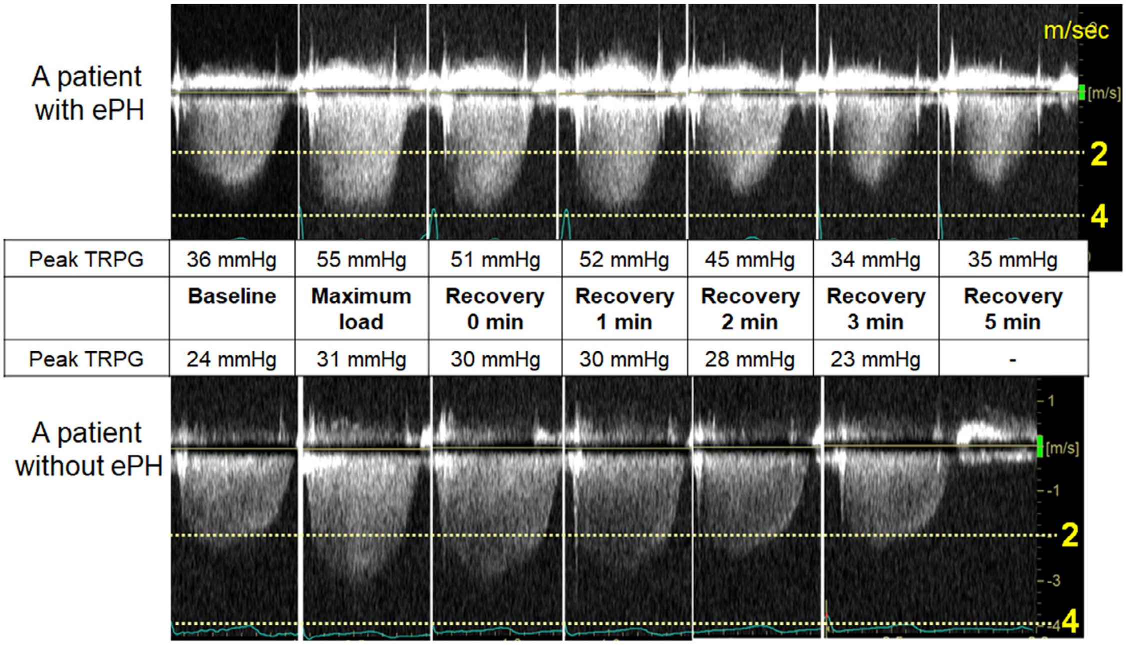

Figure 2. Representative patients with and without ePH. The peak TRPG values at each stage are shown in the table.

exercise.[19,20] Argiento et al[21] found that in healthy subjects, PASP levels that were elevated during exercise using a semi-recumbent cycle ergometer returned to normal immediately after exercise was stopped. Given that the right atrial pressure in their study was 5 mm Hg, which was different from that in our study, the mean PASP value at maximum exercise was 46 mm Hg. They calculated PASP at 5, 10, and 20 minutes after exercise, but not from exercise completion to 5 minutes afterward. The median peak TRPG value at 5 minutes after exercise in our patients with ePH was 33 mm Hg, which was about the same as baseline, but its value remained higher than 40 mm Hg through 2 minutes after exercise.

Previous studies used cut-off values of PASP that were considered to be the normal limits for healthy individuals or highly trained athletes.[1,21,22] All of these cut-off values were determined using data acquired during maximum exercise on a bicycle ergometer, and did not consider data obtained just after finishing exercise. Therefore, the estimation and diagnosis of ePH using PASP determined just after completing exercise, that is, in the setting of ESE using a treadmill, may differ from the cut-off values estimated

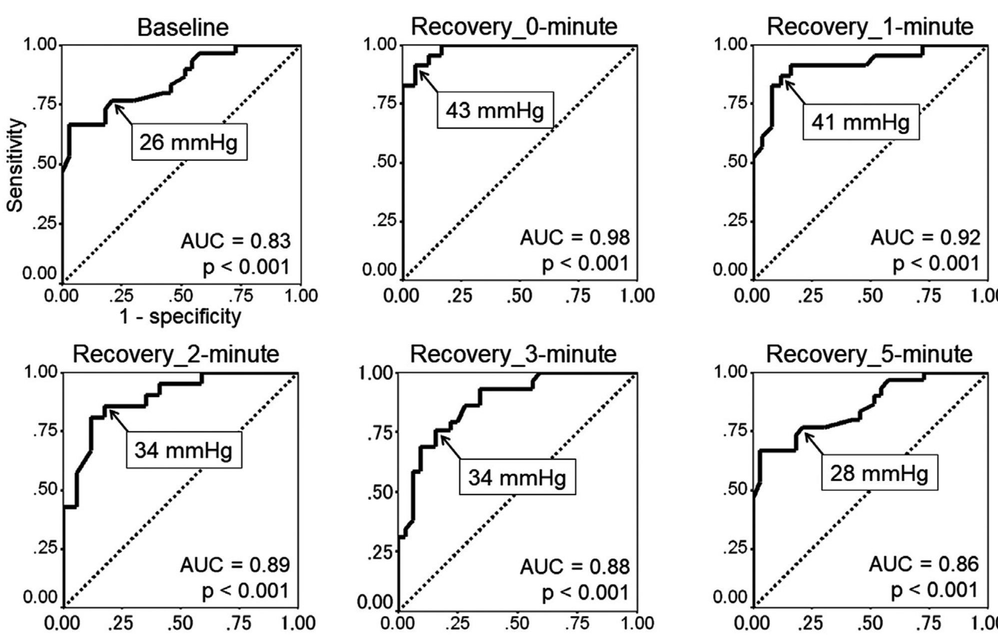

Figure 3. The cut-off points to detect ePH during and until soon after finishing exercise. AUC = area under the curve.

during maximum exercise in the setting of ESE using a bicycle ergometer. It may make sense to use different cut-off values depending on different types of exercise stress. The cut-off value obtained just after finishing exercise, that is, a lower peak TRPG than the widely used cut-off value to diagnose ePH based on maximum exercise, may be suitable in the setting of treadmill exercise.

Based on our study analyzing the cut-off values of peak TRPG to deduce the presence of ePH during and soon after exercise, a peak TRPG higher than 41 mm Hg at 1 minute after the completion of exercise may be the appropriate cut-off value for ePH. Although acquiring the targeted parameters or images in ESE often takes longer with a treadmill than with a bicycle ergometer, previous studies reported that the initial images could be acquired in the first 1 to 2 minutes of ESE using a treadmill.[18,23,24] Therefore, a peak TRPG value > 40 mm Hg obtained between the completion of exercise until 1 to 2 minutes afterward, as evaluated in the present study, may be a reliable and practicable standard.

This study had several limitations. First, this was a single-center, retrospective cohort analysis. Second, we used the same ePH criterion although pulmonary hypertension in our patients had a variety of etiologies. Although the values of Δmean PAP/Δcardiac output during ESE were reported to differ by disease groups,[17,25-27] no differences in the cut-off values of peak TRPG were previously reported. Furthermore, the estimation of ePH in the present study was based on echocardiographic parameters, not on catheterization data. However, we used a cut-off value of peak TRPG > 50 mm Hg, which has been widely reported.

The criterion for ePH during ESE using a treadmill, which is more widely employed than a bicycle ergometer in clinical settings, has not been evaluated, and the cut-off value of peak TRPG estimated during maximum exercise may differ from that obtained just after finishing exercise. Therefore, the cut-off value of peak TRPG could be helpful for diagnosing ePH during ESE using a treadmill when continuous measurements are obtained throughout exercise until soon after completing it.

In conclusion, prolonged TRPG elevation after exercise in patients with ePH after exercise will be a clue or new simple standard for the diagnosis of ePH in ESE.

Authors' contributions

Michiyo Yamano: Conceptualization, Methodology, Formal analysis, Investigation, Writing- Original draft preparation, Visualization. **Tetsuhiro Yamano:** Methodology, Writing- Review and Editing. **Kazuaki Takamatsu, Chao Ma, Noriyuki Wakana, Kenji Yanishi, Naohiko Naknishi, Kan Zen, Takeshi Nakamura, Hirokazu Shiraishi:** Writing- Review and Editing. **Satoaki Matoba:** Writing- Review and Editing, Supervision.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Acknowledgments

We would like to express our gratitude to Dr. Tsutomu Takagi at the Takagi Cardiology Clinic in Japan for his precious advice regarding the design of this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.037.

1. Grunig E, Weissmann S, Ehlken N, Fijalkowska A, Fischer C, Fourme T, Galie N, Ghofrani A, Harrison RE, Huez S, Humbert M, Janssen B, Kober J, Koehler R, Machado RD, Mereles D, Naeije R, Olschewski H, Provencher S, Reichenberger F, Retailleau K, Rocchi G, Simonneau G, Torbicki A, Trembath R, Seeger W. Stress Doppler echocardiography in relatives of patients with idiopathic and familial pulmonary arterial hypertension: results of a multicenter European analysis of pulmonary artery pressure response to exercise and hypoxia. *Circulation* 2009;119:1747–1757.
2. Argiento P, Vanderpool RR, Mule M, Russo MG, D'Alto M, Bossone E, Chesler NC, Naeije R. Exercise stress echocardiography of the pulmonary circulation: limits of normal and sex differences. *Chest* 2012;142:1158–1165.
3. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation* 1981;64:1227–1234.
4. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130:2215–2245.
5. Morris CK, Myers J, Froelicher VF, Kawaguchi T, Ueshima K, Hideg A. Nomogram based on metabolic equivalents and age for assessing aerobic exercise capacity in men. *J Am Coll Cardiol* 1993;22:175–182.
6. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CN, Lauer MS, Marwick TH, Pandey DK, Wicklund RH, Thisted RA. The prognostic value of a nomogram for exercise capacity in women. *N Engl J Med* 2005;353:468–475.
7. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, Cittadini A, Rubenfire M, Naeije R. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr* 2013;26:1–14.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39.
9. Chemla D, Castelain V, Humbert M, Hebert JL, Simonneau G, Lecarpentier Y, Herve P. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest* 2004;126:1313–1317.
10. Lancellotti P, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M, Pierard LA. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. *Circulation* 2012;126:851–859.
11. van Riel AC, Opotowsky AR, Santos M, Rivero JM, Dhimitri A, Mulder BJ, Bouma BJ, Landzberg MJ, Waxman AB, Systrom DM, Shah AM. Accuracy of Echocardiography to Estimate Pulmonary Artery Pressures With Exercise: A Simultaneous Invasive-Noninvasive Comparison. *Circ Cardiovasc Imaging* 2017;10:e005711.
12. Shim CY, Kim SA, Choi D, Yang WI, Kim JM, Moon SH, Lee HJ, Park S, Choi EY, Chung N, Ha JW. Clinical outcomes of exercise-induced pulmonary hypertension in subjects with preserved left

ventricular ejection fraction: implication of an increase in left ventricular filling pressure during exercise. *Heart* 2011;97:1417–1424.
13. Kusunose K, Yamada H, Hotchi J, Bando M, Nishio S, Hirata Y, Ise T, Yamaguchi K, Yagi S, Soeki T, Wakatsuki T, Kishi J, Sata M. Prediction of Future Overt Pulmonary Hypertension by 6-Min Walk Stress Echocardiography in Patients With Connective Tissue Disease. *J Am Coll Cardiol* 2015;66:376–384.
14. Tumminello G, Lancellotti P, Lempereur M, D'Orio V, Pierard LA. Determinants of pulmonary artery hypertension at rest and during exercise in patients with heart failure. *Eur Heart J* 2007;28:569–574.
15. Magne J, Lancellotti P, Pierard LA. Exercise pulmonary hypertension in asymptomatic degenerative mitral regurgitation. *Circulation* 2010;122:33–41.
16. Grunig E, Mereles D, Hildebrandt W, Swenson ER, Kubler W, Kuecherer H, Bartsch P. Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. *J Am Coll Cardiol* 2000;35:980–987.
17. Lau EM, Manes A, Celermajer DS, Galie N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. *Eur Heart J* 2011;32:2489–2498.
18. Armstrong WF. Treadmill exercise echocardiography: methodology and clinical role. *Eur Heart J* 1997;18(Suppl D):D2–D8.
19. Gargani L, Pignone A, Agoston G, Moreo A, Capati E, Badano LP, Doveri M, Bazzichi L, Costantino MF, Pavellini A, Pieri F, Musca F, Muraru D, Epis O, Bruschi E, De Chiara B, Perfetto F, Mori F, Parodi O, Sicari R, Bombardieri S, Varga A, Cerinic MM, Bossone E, Picano E. Clinical and echocardiographic correlations of exercise-induced pulmonary hypertension in systemic sclerosis: a multicenter study. *Am Heart J* 2013;165:200–207.
20. Misra D, Kendes A, Sulica R, Carabello B. Exercise-induced pulmonary hypertension by stress echocardiography: Prevalence and correlation with right heart hemodynamics. *Int J Cardiol* 2017;228:518–522.
21. Argiento P, Chesler N, Mule M, D'Alto M, Bossone E, Unger P, Naeije R. Exercise stress echocardiography for the study of the pulmonary circulation. *Eur Respir J* 2010;35:1273–1278.
22. Bossone E, Rubenfire M, Bach DS, Ricciardi M, Armstrong WF. Range of tricuspid regurgitation velocity at rest and during exercise in normal adult men: implications for the diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 1999;33:1662–1666.
23. Dagianti A, Penco M, Bandiera A, Sgorbini L, Fedele F. Clinical application of exercise stress echocardiography: supine bicycle or treadmill. *Am J Cardiol* 1998;81:62g–67g.
24. Shin JH, Kang KW, Kim JH, Chin JY, Kim NY, Park SH, Kim WH, Choi YJ, Jung KT. Treadmill exercise-induced E/e' elevation as a predictor of cardiovascular event in end-stage renal disease on peritoneal dialysis. *Korean J Intern Med* 2016. [Epub ahead of print].
25. Domingo E, Grignola JC, Aguilar R, Arredondo C, Bouteldja N, Messeguer ML, Roman A. Impairment of pulmonary vascular reserve and right ventricular systolic reserve in pulmonary arterial hypertension. *BMC Pulm Med* 2014;14:69–78.
26. Lewis GD, Murphy RM, Shah RV, Pappagianopoulos PP, Malhotra R, Bloch KD, Systrom DM, Semigran MJ. Pulmonary vascular response patterns during exercise in left ventricular systolic dysfunction predict exercise capacity and outcomes. *Circ Heart Fail* 2011;4:276–285.
27. Hilde JM, Skjorten I, Hansteen V, Melsom MN, Hisdal J, Humerfelt S, Steine K. Haemodynamic responses to exercise in patients with COPD. *Eur Respir J* 2013;41:1031–1041.