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REVIEW ARTICLE

Rest and exercise echocardiography for early detection of pulmonary hypertension

Kenya Kusunose[1] · **Hirotsugu Yamada**[1]

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Abstract Early detection of pulmonary hypertension (PH) is essential to ensure that patients receive timely and appropriate treatment for this progressive disease. Rest and exercise echocardiography has been used to screen patients in an attempt to identify early stage PH. However, current PH guidelines recommend against exercise tests because of the lack of evidence. We reviewed previous studies to discuss the current standpoint concerning rest and exercise echocardiography in PH. Around 20 exercise echocardiography studies were included to assess the cutoff value for exercise-induced pulmonary hypertension (EIPH). Approximately 40 exercise echocardiography studies were also included to evaluate the pulmonary artery pressure-flow relationship as assessed by the slope of the mean pulmonary artery pressure and cardiac output (ΔmPAP/ΔQ). There were several EIPH and ΔmPAP/ΔQ reference values in individuals with pulmonary vascular disease. We believed that assessing the ΔmPAP/ΔQ makes sense from a physiological standpoint, and the clinical value should be confirmed in future studies. Exercise echocardiography is an appealing alternative in PH. Further studies are needed to assess the prognostic value of the pulmonary artery pressure-flow relationship in high-risk subjects.

Keywords Connective tissue disease · Pulmonary hypertension · Echocardiography · Stress echocardiography

Introduction

Pulmonary hypertension (PH) is a crucial hemodynamic state defined by a resting mean pulmonary artery pressure (mPAP) ≥25 mmHg regardless of the etiology. Current guidelines provide a classification system that categorizes PH into five groups with specific pathogeneses and clinical characteristics [1, 2]. Group 1 comprises pulmonary arterial hypertension (PAH) associated with idiopathic disease, connective tissue disease (CTD), congenital heart disease, and genetic disease. Group 2 includes PH caused by left heart failure, such as valvular heart disease or myocardial disease. Group 3 PH is caused by sleep-disordered breathing or lung disease such as chronic obstructive pulmonary disease (COPD). Group 4 includes chronic thromboembolisms (CTEPH), and group 5 indicates PH with unclear multifactorial mechanisms. Whatever the PH etiology, severe PH is a critical hemodynamic state. In PAH patients, severe PH is a leading cause of death, and several new treatments have been developed and provide benefits. In patients with left heart failure, PH is found in 15–60 % and is associated with a higher risk of cardiac events [3].

Poor PH outcomes might be explained not only by the severity of comorbidities but also by the delay in diagnosis. Thus, early detection of PH is essential to ensure that patients receive timely and appropriate treatment for this progressive disease. Current screening recommendations are based on several guidelines by the American College of Cardiology Foundation/American Heart Association (ACC/AHA) and the European Society of Cardiology/European Respiratory Society (ESC/ERS) [1, 2]. In the guidelines, transthoracic

✉ Hirotsugu Yamada
yamadah@tokushima-u.ac.jp

Kenya Kusunose
kusunosek@tokushima-u.ac.jp

[1] Department of Cardiovascular Medicine, Tokushima University Hospital, 2-50-1 Kuramoto, Tokushima, Japan

echocardiography is used to assess the pulmonary artery pressure (PAP) by Doppler measurements and should always be performed when PH is suspected. In addition, N-terminal pro-brain natriuretic peptide, as a marker of myocardial stress and a disproportionately reduced pulmonary diffusing capacity for carbon monoxide, is widely used. When remarkable findings are detected, right heart catheterization (RHC) is recommended. The diagnosis of PH is confirmed at RHC by an mPAP of $\geq$25 mmHg. The diagnostic criteria of PAH include a pulmonary capillary wedge pressure $\leq$15 mmHg and pulmonary vascular resistance >3 Wood units in the absence of other causes of precapillary PH, such as lung diseases or human immunodeficiency infection.

Early detection of PH remains a clinical challenge despite the development of several diagnostic tools. Because elevated PAP during exercise can be a cause of dyspnea and fatigue, exercise-induced pulmonary hypertension (EIPH) has been described as a potential useful indication for the early identification of patients at the risk of developing resting PH [4]. RHC is the gold standard for defining PAP during exercise. However, RHC is an invasive procedure, and we need noninvasive tests to screen for PH in all cohorts. Exercise echocardiography has been used to screen patients in an attempt to identify early stage PH with no remarkable echocardiographic findings at rest [5]. The American Society of Echocardiography (ASE) consensus had recommended that exercise Doppler echocardiography is a safe screening tool for detecting a pulmonary hypertensive response to exercise in high-risk patients [6]. However, the current PH guidelines (ACC/AHA and ESC/ERS) recommend against exercise echocardiography because there are relatively few published data [1, 2]. In addition, even in normal individuals, pulmonary pressure elevations will develop during exercise with increasing cardiac output. Evaluation of PH during exercise in the absence of knowledge of the cardiac output may be problematic. Several investigators showed that the exercise-induced increases in mPAP relative to cardiac output (ΔmPAP/ΔQ) were more likely to be useful for assessing the prognosis of PH [5]. The goal of this review is to clarify the current standpoint and future directions concerning exercise echocardiography for pulmonary hemodynamics in PH.

Echocardiographic assessment of pulmonary hypertension at rest

The guidelines clearly describe echocardiographic assessments of right heart function in PH [7]. The most important measurement of PH assessment is the estimation of the systolic PAP (sPAP). The estimation of sPAP is based on the tricuspid regurgitation pressure gradient (TR-PG) according to the simplified Bernoulli equation, taking into account the estimated right atrial pressure in the absence of right ventricular outflow tract obstruction. The mPAP can be estimated by the following simple formula: mPAP = 0.61 × SPAP + 2 mmHg [7]. Figure 1a shows measurement of the TR-PG. Previous studies have shown modest to good correlations between the estimated PAP and invasively measured pressures. Concerning limitations, sPAP has a wide limit of agreement in Bland-Altman analysis (−19 to 18 mmHg) [8], and there are many formulas for calculating the mPAP. We should use this index to guide clinical decision-making, not to diagnose PH.

There are several parameters of echocardiographic right ventricular (RV) function for assessing the disease state in PH. Patients with PH have gradually reduced exercise capacity related to decreasing RV function. Thus, the progression of PH is determined by the severity of the increase in the resting PAP and RV function. An increased RV afterload may cause RV dysfunction, which leads to advanced RV failure and cardiac death. Although RV dysfunction is closely associated with elevated PAP, RV impairment can be observed in patients with relatively normal PAP because of other underlying factors. Therefore, detection of RV dysfunction in the development of PH might be useful in clinical follow-up.

Assessment of RV morphology is also often challenging, and the assessment of the RV by conventional echocardiography remains difficult because of the complex shape of the chamber. Tricuspid annular plane systolic excursion (TAPSE) has been previously reported to have good predictive value for RV failure, and it is simple and easy to measure (Fig. 1b). RV fractional area change (RVFAC) is also measured by two-dimensional echocardiograms in the RV focused view by the following formula: (RV end diastolic area − RV end systolic area)/RV end diastolic area (Fig. 1c). TAPSE <17 mm or RVFAC <35 % should be considered a marker of RV dysfunction from the reference values according to the guideline [7]. Doppler tissue imaging of the basal tricuspid annular motion has been applied to assess RV function in several cardiac diseases including PH. According to the guideline, the systolic annular motion velocity of the RV free wall (RVS') <10 cm/s is a reference value (Fig. 1d). The RV strain analysis by two-dimensional speckle-tracking echocardiogram has been proposed to allow the quantification of RV myocardial deformation (Fig. 1e). The speckle-tracking technique is angle independent, which enables an assessment of the RV myocardial strain from a two-dimensional speckle-tracking echocardiogram. Analysis of the RV strain may provide prognostic information and could help in the stratification of patients with PH. Recently, three-dimensional speckle-tracking echocardiography (3D-STE) was developed in the clinical setting.

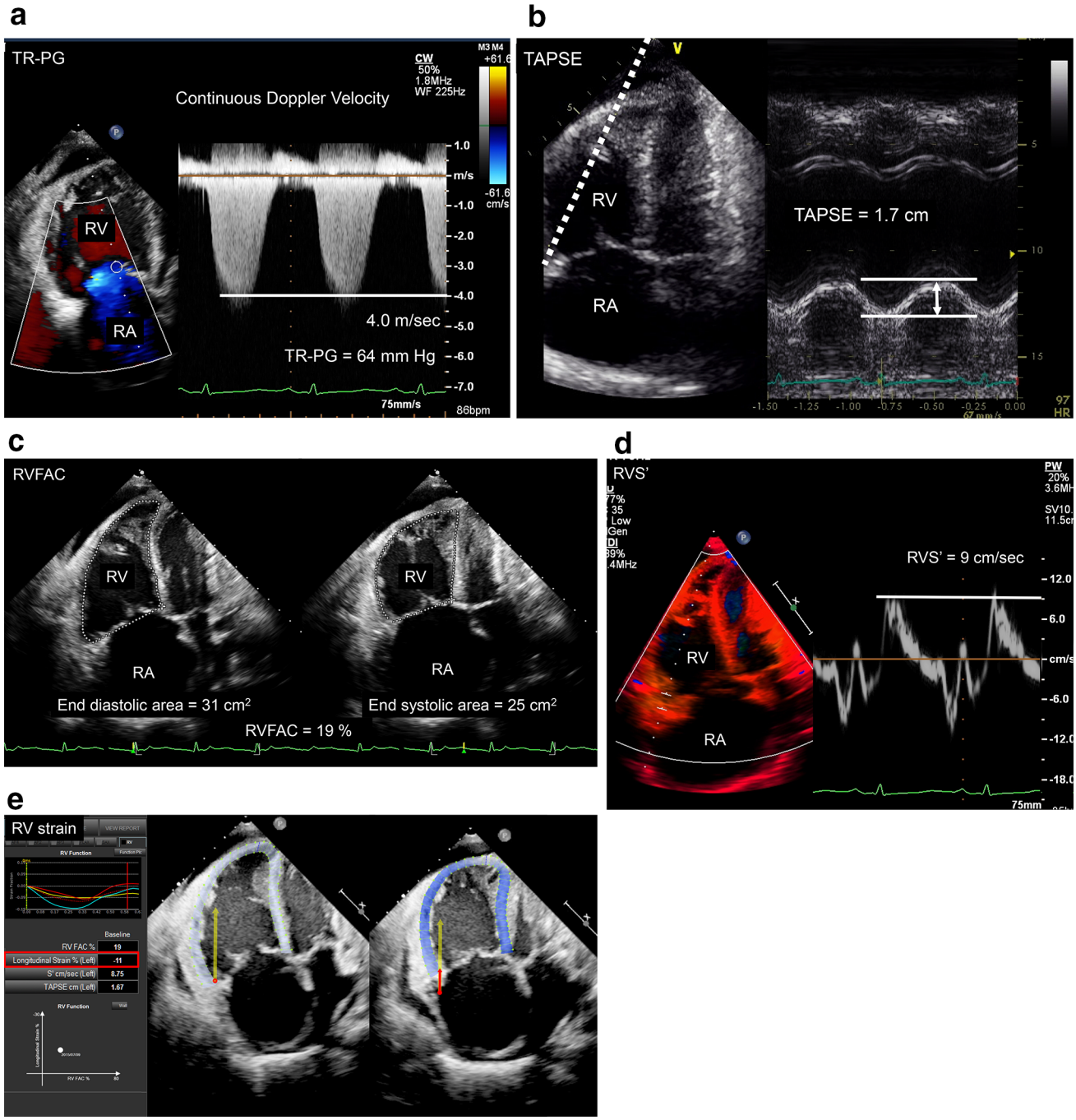

Fig. 1 Conventional and new echocardiographic parameters for the assessment of PH. **a** Elevated pulmonary artery pressure by the tricuspid regurgitant pressure gradient (TR-PG). **b** M-mode recording through the lateral tricuspid valve annulus to measure the tricuspid annular plane systolic excursion (TAPSE). **c** Two-dimensional image demonstrating dilated right ventricular size caused by elevated pulmonary artery pressure. Right ventricular fractional area change (RVFAC) is measured by the following formula: (RV end diastolic area − RV end systolic area)/RV end diastolic area. **d** Tissue Doppler image of the lateral tricuspid valve annulus. Peak systolic annular motion velocity of the RV free wall (RVS') impaired in PH. **e** Speckle-tracking analysis of a patient with severely reduced myocardial defamation of the right ventricular (RV strain). *RA* right atrium

Some investigators suggested that the strain and RV ejection fraction (EF) measured by 3D-STE may help risk stratify patients with PH and guide clinical management [9]. However, the limitations of 3D-STE are the low temporal and spatial resolution and limited acoustic windows. Thus, it has been recommended to combine various RV echocardiographic parameters to assess the RV function in PH.

Exercise-induced pulmonary hypertension (EIPH)

In pulmonary hemodynamics, the large reserve of the pulmonary circulation indicates that PH is usually diagnosed late in its course, with an asymptomatic stage preceding onset. Therefore, patients with early PH may present with almost normal resting PAP, but an abnormal exercise PAP, with an increase in pulmonary blood flow. Several investigators showed abnormal PAP elevation during exercise in patients with high-risk PH, including CTD. This is referred to as EIPH. Previous papers suggested that EIPH is a marker for the risk of developing resting PH [10]. However, there are several exercise protocols and many cutoff values to assess the EIPH. An overview of the studies of exercise echocardiography for detecting EIPH in a high-risk population is presented in Table 1. The PAP cutoff value affects the accuracy of the detection of PH by Doppler echocardiography. Low PAP leads to false-positive results, and high PAP leads to false-negative results. In patients with CTD including mainly systemic sclerosis (SSc), abnormal responses were defined by an sPAP greater than 30–35 mmHg during exercise or a post-exercise increase in sPAP by >20 mmHg. Recent studies generally showed that abnormal responses were defined by an sPAP >50 mmHg during exercise in order to exclude false-positive results in the screening tests [11–22]. In group 2 PH, the PAP cutoff value was variable and depended on the specific diseases [23–30]. The cutoff values should be taken into consideration in each patient. The other specific limitation is that several stress methods are widely used in the clinical setting (Fig. 2). Exercise data during ergometer exercise should not be applied to post-treadmill or other exercises because each protocol is characterized by different loading conditions.

Representative EIPH case

A 50-year-old female was referred to a clinic for SSc 5 years ago (Fig. 3). She was admitted to our hospital to check the PAP with dyspnea. Echocardiography showed a TR-PG of 22 mmHg at rest, indicating normal sPAP, and

Table 1 Pulmonary artery pressure response to exercise

Disease	*n*	Age	Stress protocol	Variables	Cutoff value (mmHg)	Years (Ref.)
CTD						
SSc	65	51 ± 12	Treadmill	sPAP	35	2006 [11]
SSc	51	54 ± 12	Treadmill	sPAP	35	2006 [12]
SSc	25	56 ± 12	Ergometer	TRPG	30	2007 [13]
SSc	54	53 ± 17	Treadmill	sPAP	31	2008 [14]
SSc	54	53 ± 17	Treadmill	sPAP	Increase of 20	2008 [12]
SSc	29	56 ± 11	Ergometer	mPAP	28	2009 [15]
SSc	52	54 ± 11	Ergometer	sPAP	40	2010 [16]
SSc	57	51 ± 13	Ergometer	mPAP	30	2010 [19]
SSc	172	52 ± 22	Ergometer	sPAP	46	2011 [17]
SSc	52	57 ± 13	W master	sPAP	70	2013 [18]
SSc	164	58 ± 13	Ergometer	sPAP	50	2013 [20]
SSc	63	54 ± 3	Ergometer	sPAP	50	2014 [21]
SSc	133	63 ± 12	W master	sPAP	50	2015 [22]
PAH						
PAH	52	58 ± 13	Ergometer	sPAP	40	2000 [23]
PAH	291	37 ± 16	Ergometer	sPAP	43	2009 [24]
PAH	124	54 ± 16	Ergometer	sPAP	Increase of 30	2013 [25]
Others						
Dyspnea/fatigue	78	59 ± 15	Ergometer	mPAP	30	2008 [29]
HAPE	9	45 ± 8	Ergometer	sPAP	45	2000 [26]
CHD	44	18 ± 3	Ergometer	sPAP	50	2010 [27]
VHD	196	56 ± 13	Treadmill	sPAP	54	2013 [28]
VHD	159	50 ± 15	Treadmill	sPAP	44	2014 [30]

CTD connective tissue disease, *SSc* scleroderma and systemic sclerosis, *sPAP* systolic pulmonary artery pressure, *TRPG* tricuspid regurgitation pressure gradient, *mPAP* mean pulmonary artery pressure, *PAH* pulmonary arterial hypertension, *HAPE* high-altitude pulmonary edema, *CHD* congenital heart disease, *VHD* valvular heart disease

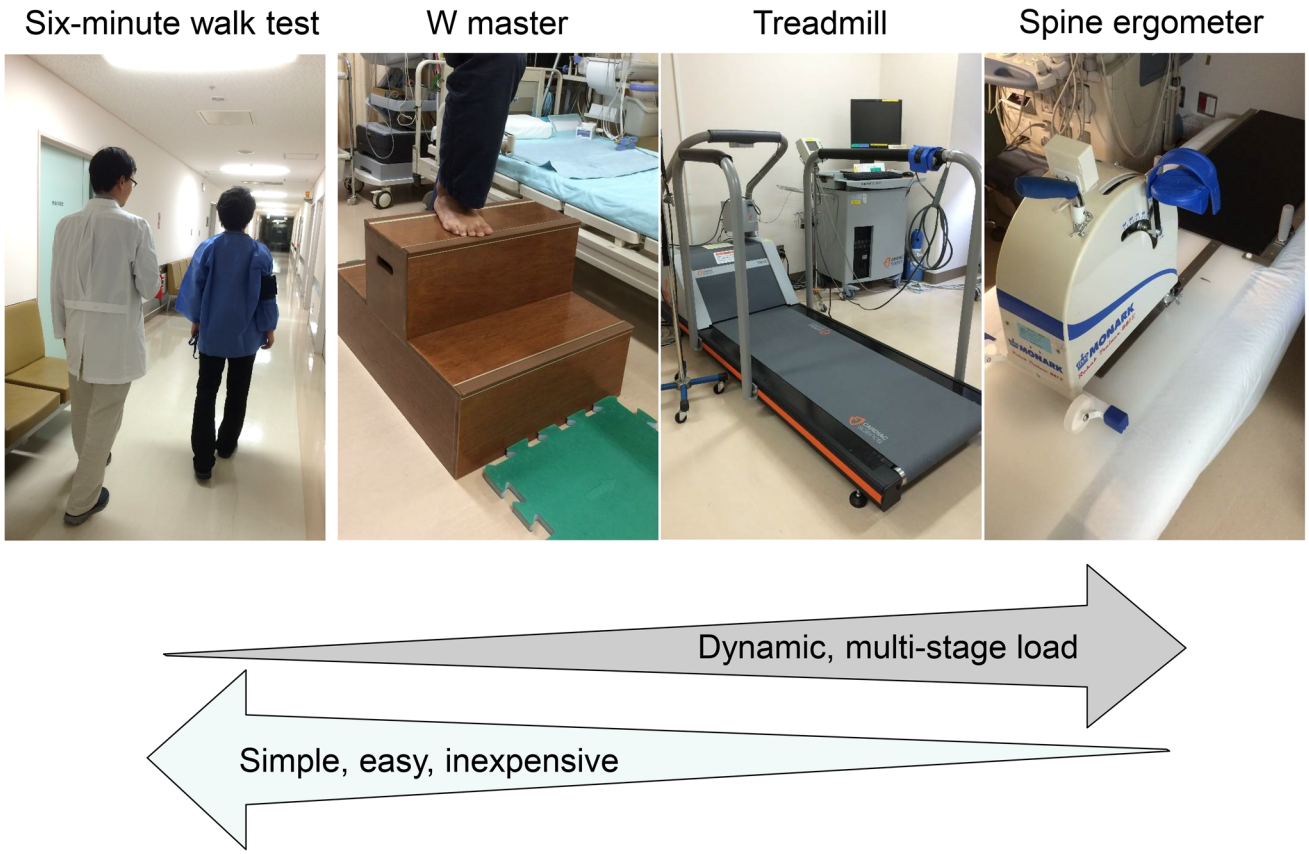

Fig. 2 Methods of exercise echocardiography. The 6-min walk test is a simple, easy, inexpensive method and widely used in the clinical setting

the 6-min walk distance was 510 m, indicating an almost normal exercise capacity (the 6-min walk test is equivalent to the ergometer test with 90 % workload) [31]. However, the TR-PG just after the 6-min walk test was elevated to 36 mmHg, indicating a poor pulmonary vascular response (Fig. 3a). Oxygen saturation was slightly decreased from 97 to 94 % by exercise. Supine ergometer exercise echocardiography was performed to assess the details of EIPH. TR-PG at baseline was 23 mmHg and increased in severity at 25 and 50 W of exercise (Fig. 3b). During exercise, the peak TR-PG was elevated to 58 mmHg. In our experience, the PAP increase with the 6-min walk test was similar to a 25-W workload with a supine ergometer. We suspected EIPH and transferred this patient to the catheter laboratory. RHC at rest showed an mPAP of 24 mmHg and PCWP of 11 mmHg, which did not meet the criteria of PH with normal left ventricular EF and no coronary artery stenosis. Then, during exercise using a supine ergometer, the mPAP was significantly elevated (25 W: mPAP = 41 mmHg; 50 W: mPAP = 55 mmHg) with remarkable dyspnea (Fig. 3c). PVR was also elevated during exercise (at baseline: PVR = 3.2 Wood units, 25 W: PVR = 4.2 Wood units; 50 W: PVR = 4.7 Wood units). This case clearly showed significant changes in PAP developed even with mild exercise with a spine ergometer.

Pulmonary artery pressure-flow relationship

One concern of previous EIPH criteria is the lack of cardiac output when considering the pulmonary circulation because PAP is a flow-dependent variable. Several investigators have reported the upper limits of sPAP in healthy individuals from exercise echocardiography are 40–45 mmHg. However, the upper limits are 55–60 mmHg with significantly increasing cardiac output in top athletes. In addition, some investigators showed that a PAP increase during exercise might be a marker of a good RV contractile reserve and prognosis in patients with moderate to severe impairment of PH [23]. They stated that a greater increase in pressure allows a higher stroke volume, and the contractile reserve can be defined by the increase in pressure. Therefore, in the evaluation of PH, cardiac output should be given, and the multipoint pressure-flow response of the pulmonary circulation may be a useful method.

Previous studies have described abnormal cardiac output responses for increments of mPAP as having the potential

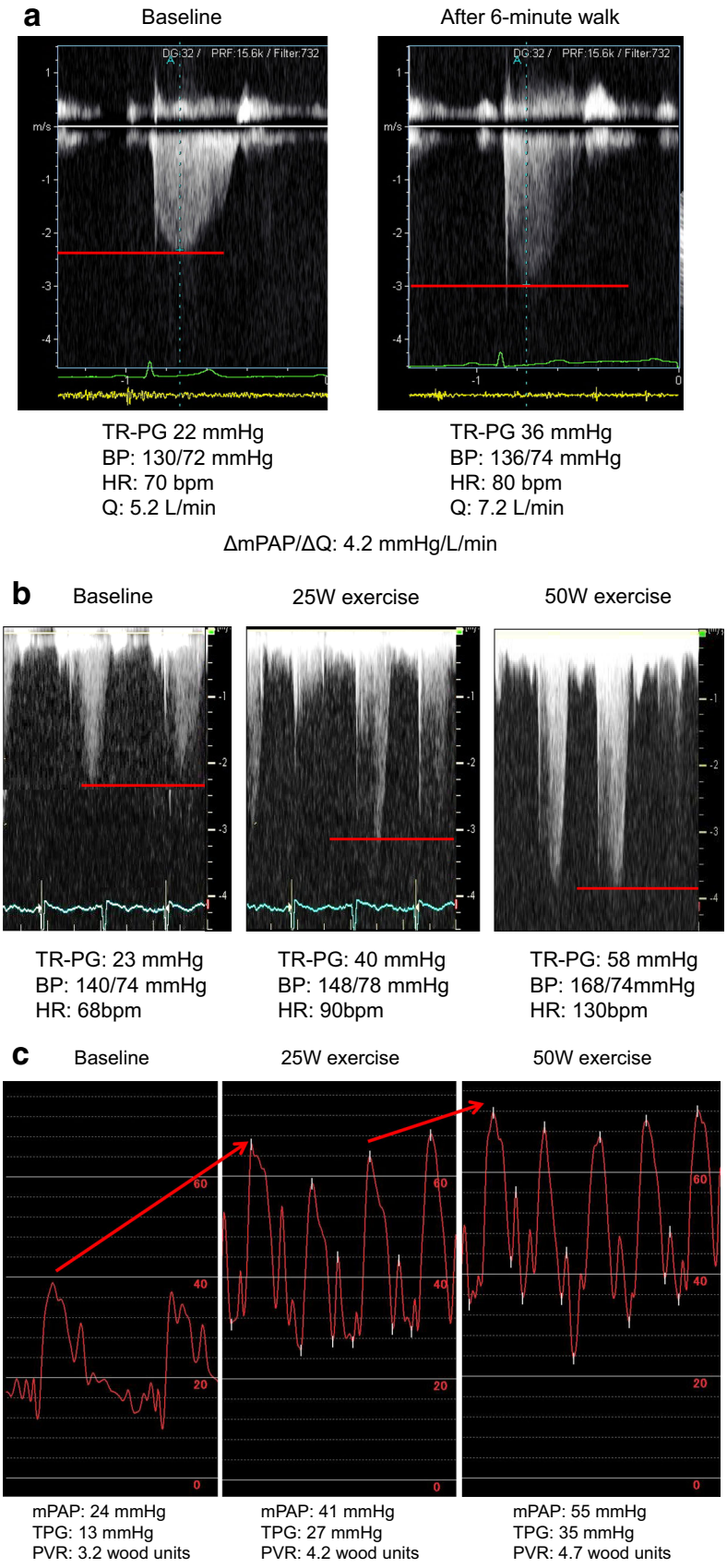

Fig. 3 Invasive and noninvasive parameters of the 6-min walk test and spine ergometer test: a representative case. *TR-PG* tricuspid regurgitant pressure gradient, *BP* blood pressure, *HR* heart rate, *Q* cardiac output, *mPAP* mean pulmonary artery pressure, *TPG* transpulmonary gradient, *PVR* pulmonary vascular resistance

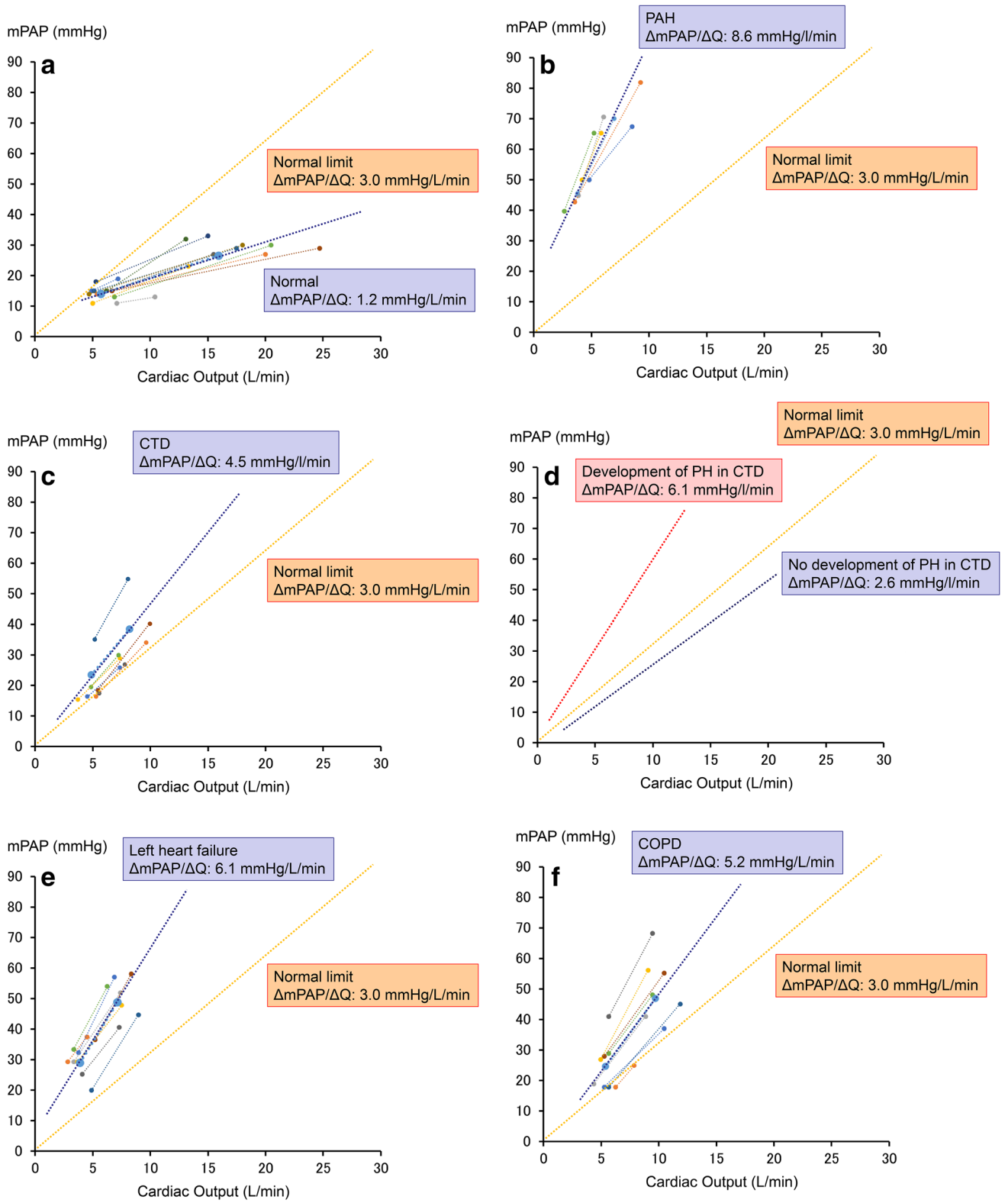

Fig. 4 Pulmonary artery pressure-flow relationships. **a** On 11 normal studies [27, 35–44]. **b** On 5 pulmonary arterial hypertension (PAH) studies [45–49]. **c** On 7 connective tissue disease (CTD) studies [4, 19, 20, 32, 50–52]. **d** Prediction for development of pulmonary hypertension (PH) in our study [33]. **e** On 8 left heart failure studies [26, 28, 30, 53–56]. **f** On 8 chronic obstructive pulmonary disease (COPD) studies [57–62]

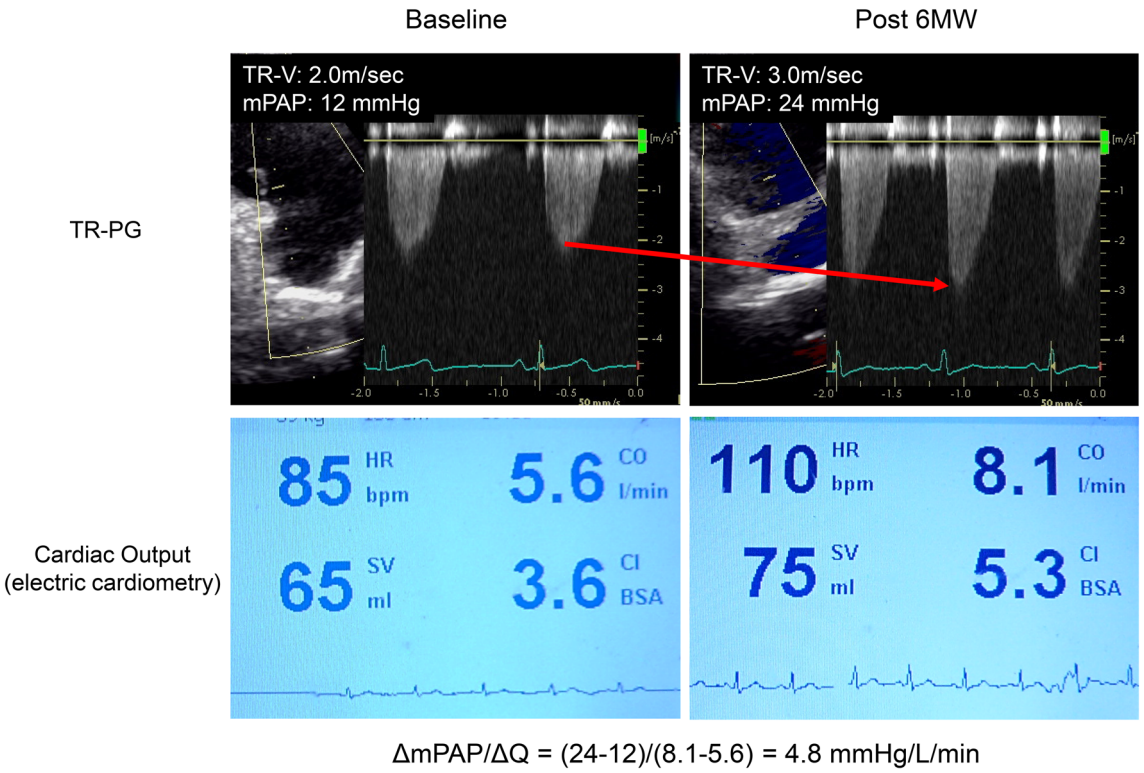

Fig. 5 Six-minute walk (6MW) stress echocardiography in a patient with connective tissue disease

to assess the disease state and functional class in PH. When we gathered a sufficient number of ΔmPAP/ΔQ data, we think it became possible to identify a reference value of this slope in each disease. In any type of PH, specific cutoff values of ΔmPAP/ΔQ can be presented. In normal individuals, invasive and noninvasive studies have clearly showed the slope of the linearized mPAP-Q relationship should not exceed 3 mmHg/l/min. The average of ΔmPAP/ΔQ is 1.2 mmHg/l/min as calculated from 11 previous studies in normal control studies (Fig. 4a).

PAH is associated with remodeling of the small pulmonary arteries and leads to an increase in pulmonary vascular resistance with right heart failure. The pulmonary vascular bed is severely damaged, and ΔmPAP/ΔQ is significantly increased. According to five previous studies, the average ΔmPAP/ΔQ is 8.6 mmHg/l/min in PAH patients (Fig. 4b). Patients with CTD are also considered a high-risk group for developing PH, and SSc is the highest risk group within CTD. Estimation of the lifetime risk of developing PAH is 10–15 %. PAH is associated with 30 % of all deaths in SSc [32]. In this type of disease, the pulmonary circulation depends mainly on the inability of the pulmonary vascular bed to dilate under stress and consequently reflects the abnormally stiff vascular system characteristics. In seven previous studies with subjects without PH at rest, the average ΔmPAP/ΔQ was 4.5 mmHg/l/min in CTD (Fig. 4c). This cutoff value is significantly higher than the upper limit of the reference value. Recently, our institute developed 6-min walk stress echocardiography to detect the early stage of PH in CTD [33]. We demonstrated that ΔmPAP/ΔQ obtained by 6-min walk stress echocardiography was a predictor of the future development of PH in patients with CTD and was independent of the 6-min walk distance. In the Fig. 4d, the ΔmPAP/ΔQ in patients with events (development of overt PH) was significantly higher than in patients without events (6.1 vs. 2.6 mmHg/l/min; $p < 0.001$). Using a receiver-operating characteristic curve, the best cutoff value of ΔmPAP/ΔQ for predicting the development of PH was >3.3 mmHg/l/min. CTD patients with greater increases in PAP relative to cardiac output are at increased risk of developing PH during long-term follow-up. Figure 5 shows the case of one representative patient with CTD who underwent 6-min walk stress echocardiography. TR-PG by echocardiography and cardiac output by electric cardiometry were increased post 6-min walk test. We can calculate the pulmonary artery pressure-cardiac output relationships as ΔmPAP divided by ΔQ (ΔmPAP/ΔQ). To our knowledge, this is the first report to combine measures of the change in the pressure-flow relationship and long-term outcomes for the development of PH in CTD. Exercise echocardiography has been

described as a safe and valuable screening tool for detecting an abnormal response of pulmonary artery pressure in high-risk patients such as those with CTD, but it remains technically difficult and requires experience.

PH at rest or during exercise is associated with an adverse outcome in patients with left heart failure (group 2 PH). The presence of PH at rest or during exercise has also been included in the risk assessment of valve surgery. Patients with normal or mildly elevated PAP at rest may develop severe PH during exercise in the left heart failure group. In eight previous studies with left heart failure, the average ΔmPAP/ΔQ was 6.1 mmHg/l/min (Fig. 4e). In COPD patients (group 3 PH), the prevalence of PH was from 30 to 70 %, and PH was significantly correlated with a decrease in the exercise capacity and mortality. A relationship between the pulmonary circulation and severity of hypoxemia suggested that hypoxia causes pulmonary vascular remodeling in COPD. In eight previous studies with COPD, the average ΔmPAP/ΔQ was 5.2 mmHg/l/min (Fig. 4f). Therefore, there were several reference values of EIPH and ΔmPAP/ΔQ in individuals with pulmonary vascular disease.

Future directions

In high-risk patients (e.g., those with SSc, left heart failure with valve disease, COPD, and CTEPH), the ΔmPAP/ΔQ according to exercise echocardiography as a marker of pulmonary circulation can be a useful measurement of the disease state of PH. However, the clinical utility of ΔmPAP/ΔQ has only been supported by small and cross-sectional studies. The clinical implication was also limited because of the absence of longitudinal data with medical treatment. Well-controlled multicenter studies in large cohorts of high-risk patients are needed to validate exercise echocardiographic data including ΔmPAP/ΔQ. Therapeutic strategies for EIPH have not been described in the recent guidelines. Patients with EIPH according to echocardiography need to have the actual pressure confirmed by RHC individually. In addition, a small study reported that endothelin receptor antagonists have been used for early stage PH [34].

Conclusions

From our comprehensive review, we suggest that multipoint assessment of mPAP relative to Q during exercise should be taken into consideration for the assessment of the pulmonary circulation. ΔmPAP/ΔQ >3 mmHg/l/min represents an abnormal pulmonary vascular response to exercise. We believe that this index makes sense from a physiological standpoint, and the clinical worth should be confirmed in the future studies. Exercise echocardiography is an appealing alternative in PH. Further studies are needed to assess the prognostic value of the pulmonary artery pressure-flow relationship in high-risk subjects.

Compliance with ethical standards

Conflicts of interest Kenya Kusunose and Hirotsugu Yamada declare that they have no conflict of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients for being included in the study.

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