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RAPID COMMUNICATION

Optimal Cut-Off of Tricuspid Regurgitation Velocity According to the New Definition of Pulmonary Hypertension

— Its Use in Predicting Pulmonary Hypertension —

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Background: The 6th World Symposium on Pulmonary Hypertension proposed that precapillary pulmonary hypertension (PH) be defined as mean pulmonary arterial pressure (mPAP) >20 mmHg instead of mPAP ≥25 mmHg. Peak tricuspid regurgitation velocity (TRV) >3.4 m/s is widely used to predict PH, but it is unclear whether this value remains reliable for the new definition of PH.

Methods and Results: We found that the optimal cut-off value of peak TRV for 511 PH patients was >2.8 m/s, with a sensitivity of 89.5%, specificity of 73.4%, and area under the curve of 0.89 (P<0.001).

Conclusions: Based on the new definition of PH, TRV >2.8 m/s can be considered to indicate a high probability of PH.

Key Words: Echocardiography; Guidelines; Pulmonary hypertension

Since the 1st World Symposium on Pulmonary Hypertension (WSPH), pulmonary hypertension (PH) has been defined as mean pulmonary artery pressure (mPAP) ≥25 mmHg measured by right heart catheterization (RHC) at rest. This definition remained unchanged for a long time,[1,2] although data from normal individuals revealed that mean (±SD) normal mPAP at rest was 14.0±3.3 mmHg, with mPAP >20 mmHg considered to be the upper limit of normal (97.5th percentile).[3] Moreover, recent studies have suggested that PH patients with mPAP >20 mmHg should be considered at high risk, with possibly poor outcomes if left unfollowed.[4,5] Therefore, the 6th WSPH held in 2018 in Nice, France, proposed that precapillary PH be defined as mPAP >20 mmHg as measured by RHC instead of ≥25 mmHg at rest.[2] To differentiate increases in pulmonary artery (PA) pressure due to pulmonary vascular disease from those resulting from an elevation of PA wedge pressure or high cardiac output, the 6th WSPH included pulmonary vascular resistance (PVR) ≥3 Wood units in the definition of PH.[6,7]

In the clinical setting, transthoracic echocardiography is a well established tool for the identification of suspected PH. If PH is suspected on the basis of echocardiography, RHC is required to confirm the diagnosis of PH. The guidelines for the diagnosis and treatment of PH established in 2015 by the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) recommended using continuous wave Doppler measurement of peak tricuspid regurgitation velocity (TRV) as the main variable for assigning the echocardiographic probability of PH.[1]

In view the changes in the definition of PH from the ESC/ERS 2015 guidelines to the 2018 6th WSPH definition, it is unclear whether the cut-off value of peak TRV for strong suspicion of PH should remain >3.4 m/s. Thus, the aim of the present study was to evaluate the optimal cut-off value of peak TRV to predict a high probability of PH according to the new definition of PH from the 6th WSPH.

Methods

Study Population

In all, 511 PH patients who were admitted to the PH Clinic of Kobe University Hospital between July 2011 and May 2020 for initial evaluation of PH or follow-up evaluation after PH-specific therapy were retrospectively recruited for this study. PH patients with left-sided heart disease, defined as pulmonary capillary wedge pressure ≥15 mmHg as measured with RHC (Group II), were excluded from the

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Table 1. Characteristics of Patients With Pulmonary Hypertension (n=511)	
Age (years)	68.0 [52.0–75.0]
Female sex	377 (74)
BNP (pg/mL)	38.6 [17.1–95.3]
Etiology of PH	
Group I	133 (26)
Group III	41 (8)
Group IV	322 (63)
Group V	15 (3)
Hemodynamic parameters	
mPAP (mmHg)	26.0 [19.0–36.0]
PVR (Wood units)	4.4 [2.7–6.8]
Cardiac output (L/min)	3.8 [3.1–4.7]
Cardiac index (L/min/m^2)	2.4 [2.0–3.0]
Mean RA pressure (mmHg)	4.0 [2.0–6.0]
Echocardiographic parameters	
LVEDV (mL)	58.7 [47.2–74.8]
LVESV (mL)	19.6 [14.1–27.2]
LVEF (%)	66.7 [61.4–72.0]
LA volume index (mL/m^2)	30.2 [23.5–39.3]
Peak TRV (m/s)	3.0±0.9
RV/LV diameter ratio	1.1 [0.9–1.2]
LV eccentricity index	1.1 [1.0–1.2]
RVOT AT (ms)	90.7 [77.9–102]
Early diastolic PR velocity (m/s)	2.0 [1.7–2.4]
PA diameter (mm)	24.9 [22.2–27.8]
RA area at end-systole (cm^2)	15.0 [12.0–19.0]
IVC diameter (mm)	11.2 [8.6–14.4]
Severity of TR	
None or trace	234 (46)
Mild	196 (38)
Moderate	68 (13)
Severe	13 (3)

Continuous variables are given as the mean±SD for normally distributed data or median [interquartile range] for non-normally distributed data. Categorical variables are given as n (%). AT, acceleration time; BNP, B-type natriuretic peptide; IVC, inferior vena cava; LA, left atrial; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; mPAP, mean pulmonary artery pressure; PA, pulmonary artery; PH, pulmonary hypertension; PR, pulmonary regurgitation; PVR, pulmonary vascular resistance; RA, right atrial; RV, right ventricle; RVOT, right ventricular outflow; TR, tricuspid regurgitation; TRV, tricuspid regurgitation velocity.

study. All patients underwent echocardiography and RHC within 48 h.

This study complied with the principles of the Declaration of Helsinki regarding investigations in humans, and was approved by the local ethics committee of Kobe University Hospital Clinical & Translational Research Center (No. B200136).

Hemodynamic Measurements

All patients underwent RHC for hemodynamic measurements. mPAP, PVR, right atrial (RA) pressure, and cardiac output were calculated using the Fick principle for estimation. Pressure was measured by an investigator who was blinded to the echocardiographic data.

Echocardiographic Examination

All echocardiographic studies were performed using commercially available echocardiography systems equipped with a 3.5-MHz transducer (Vivid E9; GE Vingmed Ultrasound AS, Horten, Norway). Routine digital grayscale 2D cine loops and tissue Doppler cine loops were obtained from three consecutive beats with end-expiratory apnea and from standard apical and parasternal views. Sector width was optimized to allow for complete myocardial visualization, whereas frame rate was maximized regardless of heart rate.

Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACI).[8] Specifically, parasternal and apical four-chamber views with color flow imaging were used to obtain the highest tricuspid regurgitation (TR) Doppler velocity aligned with continuous-wave Doppler, followed by adjustment of gain and contrast to display the complete spectral envelope without signal spikes or feathering. Peak TRV was defined as the peak modal velocity during systole at the leading edge of the spectral waveform. The following additional echocardiographic parameters for predicting PH based on ESC/ERS 2015 guidelines[1] were also measured: right ventricular (RV)/left ventricular (LV) basal diameter ratio, LV eccentricity index, RV outflow tract (RVOT) acceleration time, early diastolic pulmonary regurgitation (PR) velocity, PA diameter, and RA area. RA pressure was estimated as 3, 8, or 15 mmHg based on the diameter of the inferior vena cava and the percentage decrease in its diameter during inspiration based on the current guidelines of the ASE and EACI.[8]

Definition of PH

PH was defined as resting mPAP ≥25 mmHg measured by RHC (ESC/ERS 2015 Guidelines),[1] and as resting mPAP >20 mmHg with PVR ≥3 Wood Units measured by RHC (6th WSPH definition).[2]

Statistical Analysis

Continuous variables are expressed as the mean±SD for normally distributed data and as the median and interquartile range (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. Parameters between groups were compared using Student's t-test or the Mann-Whitney U-test as appropriate. Univariate correlation analysis was used for comparison of mPAP and TRV. Multiple regression analysis was used to identify independent determinants to predict PH according to the 6th WSPH definition. Optimal cut-off values for echocardiographic variables to predict PH according to the 6th WSPH definition were determined on the basis of receiver operator characteristics (ROC) curve analysis. For all tests, $P<0.05$ was considered significant. All analyses were performed using MedCalc Software version 18.1.1 (MedCalc Software, Mariakerke, Belgium).

Results

Patient Characteristics

The clinical and echocardiographic characteristics of the 511 PH patients are summarized in **Table 1**. The median age of patients was 68 years (IQR 52.0–75.0 years) and 377 patients (74%) were female. Median mPAP was 26.0 mmHg (IQR 19.0–36.0 mmHg) and median PVR was 4.4 Wood

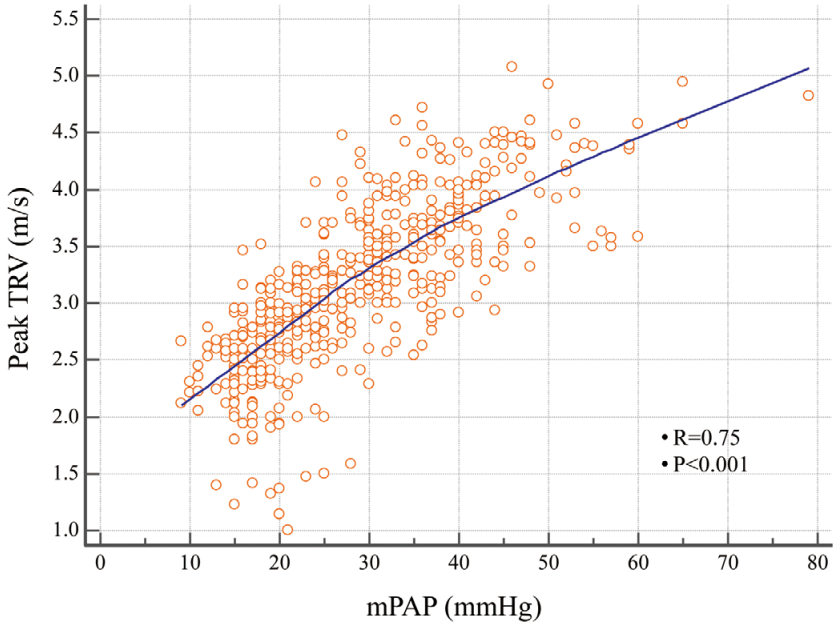

Figure 1. Dot plots of mean pulmonary arterial pressure (mPAP) and peak tricuspid regurgitation velocity (TRV), demonstrating a good correlation between the 2.

units (IQR 2.7–6.8 Wood units). A diagnosis of PH according to the 2015 ESC/ERS guidelines was established in 285 patients (55%), whereas 305 patients (59%) were diagnosed with PH based on the 6th WSPH definition. Peak TRV was measured in 488 (80%) patients, but could not be measured in the remaining patients because of no or negligible TR. Moreover, multivariate logistic regression analysis showed that among the echocardiographic parameters examined in this study, peak TRV was strongly associated with a prediction of PH (odds ratio 13.3; 95% confidential interval 3.9–45.1; P<0.001). RA pressure estimated by echocardiography was 3 mmHg in 470 patients (92%), 8 mmHg in 33 patients (6.5%), and 15 mmHg in 8 patients (1.5%).

Optimal Cut-Off Value of Peak TRV for Predicting PH Based on the 6th WSPH Definition

Peak TRV had a good correlation with mPAP (r=0.75, P<0.001; **Figure 1**). The optimal cut-off value determined by ROC analysis for predicting PH according to the 6th WSPH definition is shown in **Figure 2**. Peak TRV >2.8 m/s predicted PH with a sensitivity of 89.5%, a specificity of 73.4%, and an area under the curve (AUC) of 0.89 (P<0.001). However, when the cut-off value was set at peak TRV >3.4 m/s, the sensitivity for predicting PH according to the 6th WSPH definition was low (53.3%).

Optimal cut-off values of additional echocardiographic parameters for predicting PH according to the ESC/ERS 2015 guidelines and 6th WSPH definition were compared. These parameters included RV/LV basal diameter ratio, LV eccentricity index, RVOT acceleration time, early diastolic PR velocity, PA diameter, and RA area (**Table 2**). Of 183 patients with TRV <2.8 m/s, some had positive echocardiographic parameters for predicting PH according to the 6th WSPH definition: 20% of patients had an RV/LV basal diameter ratio >1.1, 48% of patients had an LV eccentricity index >1.0, 25% of patients had an RVOT acceleration time ≤89 ms, 15% of patients had an early diastolic PR velocity >1.9 m/s, 9% of patients had a PA diameter >25 mm, and 22% of patients had an RA area >16 cm^2.

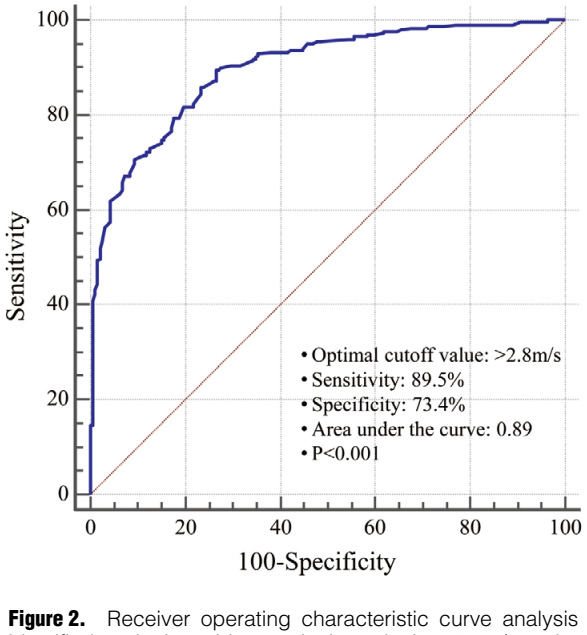

Figure 2. Receiver operating characteristic curve analysis identified peak tricuspid regurgitation velocity >2.8 m/s as the best predictor for pulmonary hypertension according to the 6th World Symposium on Pulmonary Hypertension definition.

Discussion

The key findings of this study are: (1) peak TRV >2.8 m/s, not >3.4 m/s, should be the optimal cut-off value for predicting a high probability of PH based on the 6th WSPH

Table 2. Comparison of Optimal Cut-Off Values for Echocardiographic Parameters for Predicting PH Between the 2015 ESC and ERS Guidelines[1] and the 6th World Symposium on Pulmonary Hypertension Definition[2]

	ESC/ERS 2015 guidelines	6th WSPH definition
Peak TRV (m/s)	>3.4	>2.8
RV/LV basal diameter ratio	>1.0	>1.1
LV eccentricity index	>1.1	>1.0
RVOT acceleration time (ms)	<105 and/or notching	≤89
Early diastolic PR velocity (m/s)	>2.2	>1.9
PA diameter (mm)	>25	>25
RA area (cm^2)	>18	>16

ERS, European Respiratory Society; ESC, European Society of Cardiology. Other abbreviations as in Table 1.

definition; and (2) the optimal cut-off values of most additional prespecified echocardiographic variables also differ from those established previously using the 6th WSPH definition of PH.

Peak TRV for Predicting PH

Echocardiography is widely used as an easy-to-use, non-invasive examination to identify suspected PH in the clinical setting. If PH is suspected on the basis of echocardiography, RHC should be considered for a definitive diagnosis of PH. The estimation of systolic PA pressure is based on peak TRV taking into account RA pressure. Of several established echocardiographic parameters used for suspected PH, peak TRV is considered the most reliable parameter for predicting PH. In fact, of the various echocardiographic parameters examined in the present study, multivariate logistic regression analysis showed that peak TRV was the most strongly associated with the prediction of PH.

Although the prediction of PH is relatively simple, assessment of peak TRV is associated with several limitations. Errors may occur in when measuring the peak TRV signal, which can result in both over- and underestimation of the signal if the quality of the Doppler signals is poor or inaccurate as a result of suboptimal Doppler alignment because of eccentric jets. When patients have no negligible or even mild TR, peak TRV is technically difficult to measure. Berger et al reported that the prevalence of TR in patients with PA systolic pressure ≥35 mmHg is only 80%, but increases to >95% in those with PA systolic pressure >50 mmHg.[9] In the present study, peak TRV could not be assessed in 20% of PH patients. Moreover, TRV may be significantly underestimated, and thus cannot be used to exclude the presence of PH in patients with severe TR.

Because TRV cannot be determined in all patients, other echocardiographic variables may raise or reinforce suspicion of PH regardless of the presence or absence of TRV. The use of several additional echocardiographic signs in addition to criteria based on peak TRV according to the ESC/ERS 2015 guidelines has been proposed. These signs include the RV/LV basal diameter ratio, the LV eccentricity index, RVOT acceleration time, early diastolic PR velocity, PA diameter, and RA area; the measurement of these parameters enables assessment of RV size and pressure overload, the pattern of blood flow velocity out of the RV, the diameter of the PA and an estimate of RA pressure.

Since the 1st WSPH, PH has been defined as resting mPAP ≥25 mmHg measured by RHC. This definition remained unchanged for a long time, and is reflected in the ESC/ERS 2015 Guidelines.[1,2] However, data from normal subjects show that mean (±SD) normal mPAP at rest is approximately 14.0±3.3 mmHg, and two standard deviations above this mean value would indicate that mPAP >20 mmHg would be the threshold for abnormal PA pressure.[3] Moreover, recent studies have suggested that mPAP >20 mmHg in PH patients is strongly associated with the likelihood of poor outcomes.[4,5] Therefore, the task forces of the 6th WSPH proposed that precapillary PH, regardless of etiology, should be defined as mPAP >20 mmHg with PVR ≥3 Wood units measured by RHC at rest.[2] The 6th WSPH comprised 124 experts, divided into 13 task forces, that started their work in January 2017 and presented their consensus opinions in 2018 at the meeting held in Nice, France. As noted above, peak TRV is widely used to identify suspected PH, and peak TRV >3.4 m/s is considered to indicate a high probability of PH according to ESC/ERS 2015 guidelines.[1] With the change in the definition of PH to mPAP >20 mmHg, it seems doubtful whether the cut-off value of peak TRV >3.4 m/s will remain reliable for highly suspected PH.

In the present study, we found that the optimal cut-off value of peak TRV for predicting PH based on the 6th WSPH definition should be 2.8 m/s, not 3.4 m/s, and that TRV >2.8 m/s with an AUC of 0.89 was a good parameter for predicting PH. In addition, we compared the optimal cut-off values of other echocardiographic parameters for predicting PH as determined according to the ESC/ERS 2015 guidelines and the 6th WSPH definition, and found that the optimal cut-off values of most parameters differed from those established previously. However, because the present study comprised a relatively small number of patients, did not include any patients without PH, and was a single-center retrospective study, future studies with larger patient populations including non-PH patients will be needed to validate our findings. Another limitation of this study is that all the patients underwent echocardiography and RHC within 48 h, but only 167 patients underwent echocardiography and RHC on the same day.

Conclusions

Peak TRV >2.8 m/s may be considered to indicate a high probability of PH based on the 6th WSPH definition. Therefore, the findings of this study may have clinical implications for screening and diagnosing PH patients in the not too distant future.

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Disclosures

None declared.

IRB Information

This study was approved by Kobe University Hospital Clinical & Translational Research Center (Reference no. No. B200136).

References

1. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2015; **37:** 67–119.
2. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J* 2019; **53:** 1802148.
3. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: A systematic review. *Eur Respir J* 2009; **34:** 888–894.
4. Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension is associated with increased mortality: A systematic review and meta-analysis. *J Am Heart Assoc* 2018; **7:** e009729.
5. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: Insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *Circulation* 2016; **133:** 1240–1248.
6. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019; **53:** 1801913.
7. Yaghi S, Novikov A, Trandafirescu T. Clinical update on pulmonary hypertension. *J Investig Med* 2020; **68:** 821–827.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. 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.e14.
9. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *Am J Coll Cardiol* 1985; **6:** 359–365.