

# **Improving echocardiographic subclassification of pulmonary hypertension: Relating the tricuspid regurgitation velocity to estimated pulmonary artery wedge pressure**

Josefine Kron-Thörnqvist, ST-läkare, Klinisk fysiologienheten Centrallasarettet  
Växjö, josefine.kron@kronoberg.se

# 1. Background

Pulmonary hypertension (PH) is a severe condition with a wide range of etiologies (1), in which elevated pulmonary arterial pressure (PAP) results from increased pulmonary vascular resistance (PVR) and decreased pulmonary vascular compliance (PVC) (2). A fundamental distinction is made between pre-capillary pulmonary hypertension, where elevated PAP results from pulmonary vascular disease and isolated post-capillary pulmonary hypertension (IpcPH), where elevated PAP is caused by elevated left ventricular filling pressures. Additionally, these two entities can co-exist in combined pre- and post-capillary pulmonary hypertension (CpcPH) (3). It is essential to correctly identify the PH subtype, as treatment strategies differ. Delayed diagnosis of pre-capillary PH is not uncommon and can potentially lead to a worsened prognosis and patient distress (4, 5).

The reference method for diagnosing PH is right heart catheterization (RHC), in which a catheter is introduced through a vein into the right heart chambers and the pulmonary circulation, allowing for haemodynamic measurements. These include right atrial pressure (RAP), PAP and pulmonary artery wedge pressure (PAWP), which closely reflects mean LAP. It also enables the calculation of cardiac output (CO) and PVR (6). RHC is an invasive procedure, albeit with a low rate of severe complications and mortality, and its limited availability highlights the need for more accessible and reliable diagnostic methods (7).

According to the 2022 update of the ESC/ERS Guidelines on the diagnosis and treatment of pulmonary hypertension, PH is defined as a mean PAP (mPAP) exceeding 20 mmHg at rest – a reduction from the previous threshold of 25 mmHg (8). PH is further subclassified into pre-capillary PH, IpcPH and CpcPH according to PAWP and PVR (Table 1). Transthoracic echocardiography is recommended as the primary screening modality, while RHC remains necessary for the definitive diagnosis (1).

**Table 1.** Subclassification of pulmonary hypertension according to the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension.

	<b>mPAP (mmHg)</b>	<b>PVR (WU)</b>	<b>PAWP (mmHg)</b>
<b>Pre-capillary PH</b>	>20	>2	≤15
<b>CpcPH</b>	>20	>2	>15
<b>lpcPH</b>	>20	≤2	>15

**Abbreviations:** mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary artery wedge pressure; Pre-capillary PH: pre-capillary pulmonary hypertension; CpcPH: combined post- and pre-capillary pulmonary hypertension; lpcPH: isolated post-capillary pulmonary hypertension.

Echocardiography can be used to estimate PAP, including systolic pulmonary artery pressure (sPAP) (9). Echocardiographically estimated sPAP correlates with invasive measurements and has shown good performance in identifying PH (10, 11), although its precision has been questioned (12, 13). The estimation of sPAP requires the presence of tricuspid regurgitation (TR) and is based on Doppler assessment of its peak velocity ( $TRV_{max}$ ). By applying the modified Bernoulli equation ( $\Delta P = 4 \times TRV_{max}^2$  in m/s), the systolic pressure gradient between the right ventricle and the right atrium can be estimated. sPAP can then be derived by adding  $\Delta P$  to estimated RAP (14). However, echocardiographic estimation of RAP – based on inferior vena cava (IVC) dimensions – has been shown to overestimate invasively measured RAP, and its role in improving  $TRV_{max}$ -based sPAWP estimations remains uncertain due to conflicting results (10, 13).

Subclassification of PH using echocardiography remains challenging. Several approaches have been evaluated, demonstrating varying diagnostic performance (15-19). Among these, Scalia et al. introduced an echocardiographic parameter (ePLAR) to differentiate pre-capillary PH from lpcPH in patients with invasively confirmed PH. ePLAR was derived by dividing  $TRV_{max}$  by the ratio of mitral peak early velocity to early diastolic myocardial velocity ( $E/e'$ ) as a surrogate for left ventricular filling pressure (LVFP). ePLAR was demonstrated to identify isolated pre-capillary PH with good accuracy (20). However,  $E/e'$  alone has been shown to have a limited correlation with LVFP (21, 22), and the currently recommended ASE/EACVI algorithm for the evaluation of LVFP has also shown insufficient diagnostic accuracy (22).

Consequently, Venkateshvaran et al. employed left global atrial strain (LA-GS), an echocardiographic parameter shown to be superior to  $E/e'$ , as a surrogate for LVFP (23). As a result, the  $TRV_{max}$  to LA-GS ratio (ePLAGS) demonstrated higher diagnostic accuracy than ePLAR in distinguishing precapillary from postcapillary PH in patients with invasively confirmed PH (24).

Recently, an equation for quantitative echocardiographic estimation of PAWP (ePAWP) have been described. The estimation is based on indexed left atrial volume (LAVi), early mitral inflow (E) and pulmonary vein systolic velocity (PVs) (*Equation 1*). ePAWP demonstrated good agreement with invasive PAWP and a superior diagnostic performance in identifying elevated filling pressures than the ASE/EACVI algorithm (14, 25). We hypothesize that the diagnostic accuracy in discriminating precapillary from postcapillary PH could be further improved by relating  $TRV_{max}$  to ePAWP ( $TRV_{max}/ePAWP$ ).

*Equation 1*

$$ePAWP = 0.179 \times LAVi (mL/m^2) + 2.672 \times \frac{\text{mitral } E (m/s)}{PVs (m/s)} + 2.7$$

## 2. Aim

The aim of this study is to describe the diagnostic accuracy of  $TRV_{max}/ePAWP$  in the identification of precapillary PH and to compare its diagnostic performance with that of ePLAGS.

## 3. Materials and methods

### 3.1 Design

The study will be conducted as a retrospective analysis of data from the Karolinska-Umeå hemodynamic database (KARUM).

### 3.2 Study population

The KARUM hemodynamic database includes 480 patients consecutively referred to PH-centres at Karolinska University Hospital (2014-2018) or Norrlands University Hospital (2010-2015) for

RHC due to dyspnoea, advanced heart failure, suspected pulmonary arterial hypertension (PAH) or follow-up for verified PAH. The inclusion criterion for the present study is echocardiographic signs of PH defined as  $TRV_{max} > 2.8$  m/s. Exclusion criteria are (1) severe tricuspid regurgitation, (2) non-sinus rhythm, (3) at least moderate mitral regurgitation or stenosis and (4) insufficient echocardiographic data for the calculation of ePAWP or LA-GS.

### 3.3 Methods

#### *Echocardiographic examination*

Echocardiographic examinations were performed in all patients by experienced sonographers in accordance with a standardized protocol (26). The echocardiographic examinations were conducted within three hours of the RHC using the Vivid E9 ultrasound system (GE Ultrasound, Horten, Norway). All acquired images were subsequently analysed by experienced personnel blinded to the results from the RHC using the EchoPAC PC software (version 11.0.0.0, GE Ultrasound, Waukesha, Wisconsin).

#### *Right heart catheterization*

All patients underwent RHC within 3 hours from the echocardiographic examination. The procedure was performed by experienced personnel who were blinded to the echocardiographic results. The femoral or jugular vein was used to introduce a 6F Swan-Ganz catheter. After calibrating the transducer to zero, pressure measurements were recorded during end-expiration during five to ten heart cycles from right atria, right ventricle and pulmonary artery. All measurements were analysed using a hemodynamic software package (WITT Series III, Witt Biomedical Corp., Melbourne, FL).

### 3.4 Statistical analysis

Baseline patient characteristics will be described as mean with standard deviation, if normally distributed, or otherwise as median with interquartile range for continuous variables.

Comparison of group means will be performed using the student t-test. Comparison of median between groups will be performed using Wilcoxon's rank sum test. Proportional differences between groups will be assessed using chi-square test. Receiver operating characteristic (ROC) analysis will be used to evaluate the diagnostic performance of  $TRV_{max}/ePAWP$  and  $TRV_{max}/ePLAGS$  respectively in detecting precapillary PH, defined as  $mPAP > 20$  mmHg,  $PAWP \leq 15$  mmHg and  $PVR > 2$ . The results will be reported as the area under the curve (AUC) with 95%

confidence interval (CI). Comparison between AUCs will be performed using DeLong's test for correlated ROC curves. The correlation between  $TRV_{max}/ePAWP$  and PVR will be assessed using the Spearman rank correlation coefficient and visualized in a scatter plot. A p-value  $<0,05$  will be considered statistically significant. Statistical analysis will be performed using R version 4.2.1 (R Core 239 Team, Vienna, Austria).

### **3.5 Ethical considerations**

The original study and inclusion of patients in the KARUM database was approved by the local ethics committees (Karolinska 2024-02861-01 and Umeå 007-092M). All patients provided written informed consent.

The patients included in the KARUM database underwent only clinically justified examinations based on their symptomatology. The present study solely includes pre-existing, pseudonymized data and will therefore have no negative implications for the study participants. The participants cannot, however, be expected to benefit from the study either. For future patients the study has the potential to contribute to earlier diagnosis of precapillary PH, which may lead to improved prognosis and reduced suffering.

### **3.6 Time plan**

2025: Data analysis

2025/2026: Writing of study manuscript

## 4. References

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-731.
2. Vonk Noordegraaf A, Westerhof BE, Westerhof N. The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension. *J Am Coll Cardiol*. 2017;69(2):236-43.
3. 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(1).
4. Armstrong I, Billings C, Kiely DG, Yorke J, Harries C, Clayton S, et al. The patient experience of pulmonary hypertension: a large cross-sectional study of UK patients. *BMC Pulm Med*. 2019;19(1):67.
5. Strange G, Gabbay E, Kermeen F, Williams T, Carrington M, Stewart S, et al. Time from symptoms to definitive diagnosis of idiopathic pulmonary arterial hypertension: The delay study. *Pulm Circ*. 2013;3(1):89-94.
6. Kubiak GM, Ciarka A, Binięcka M, Ceranowicz P. Right Heart Catheterization-Background, Physiological Basics, and Clinical Implications. *J Clin Med*. 2019;8(9).
7. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *J Am Coll Cardiol*. 2006;48(12):2546-52.
8. "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)." Nazzareno Galiè, Marc Humbert, Jean-Luc Vachiery, Simon Gibbs, Irene Lang, Adam Torbicki, Gérald Simonneau, Andrew Peacock, Anton Vonk Noordegraaf, Maurice Beghetti, Ardeschir Ghofrani, Miguel Angel Gomez Sanchez, Georg Hansmann, Walter Klepetko, Patrizio Lancellotti, Marco Matucci, Theresa McDonagh, Luc A. Pierard, Pedro T. Trindade, Maurizio Zompatori and Marius Hoeper. *Eur Respir J* 2015; 46: 903-975. *Eur Respir J*. 2015;46(6):1855-6.
9. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713; quiz 86-8.
10. Bech-Hanssen O, Smith JG, Astengo M, Bollano E, Bobbio E, Polte CL, et al. Pulmonary Hypertension Phenotype Can Be Identified in Heart Failure With Reduced Ejection Fraction Using Echocardiographic Assessment of Pulmonary Artery Pressure With Supportive Use of Pressure Reflection Variables. *J Am Soc Echocardiogr*. 2023;36(6):604-14.
11. D'Alto M, Di Maio M, Romeo E, Argiento P, Blasi E, Di Vilio A, et al. Echocardiographic probability of pulmonary hypertension: a validation study. *Eur Respir J*. 2022;60(2).
12. D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, et al. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. *Int J Cardiol*. 2013;168(4):4058-62.
13. Venkateshvaran A, Seidova N, Tureli HO, Kjellström B, Lund LH, Tossavainen E, et al. Accuracy of echocardiographic estimates of pulmonary artery pressures in pulmonary hypertension: insights from the KARUM hemodynamic database. *Int J Cardiovasc Imaging*. 2021;37(9):2637-45.

14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29(4):277-314.
15. Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, et al. Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. *J Am Soc Echocardiogr.* 2013;26(10):1170-7.
16. Albani S, Stolfo D, Venkateshvaran A, Chubuchny V, Biondi F, De Luca A, et al. Echocardiographic Biventricular Coupling Index to Predict Precapillary Pulmonary Hypertension. *J Am Soc Echocardiogr.* 2022;35(7):715-26.
17. Bech-Hanssen O, Karason K, Rundqvist B, Bollano E, Lindgren F, Selimovic N. Can pulmonary hypertension and increased pulmonary vascular resistance be ruled in and ruled out by echocardiography? *J Am Soc Echocardiogr.* 2013;26(5):469-78.
18. Chubuchny V, Pugliese NR, Taddei C, Poggianti E, Spini V, Barison A, et al. A novel echocardiographic method for estimation of pulmonary artery wedge pressure and pulmonary vascular resistance. *ESC Heart Fail.* 2021;8(2):1216-29.
19. Saito N, Kato S, Nakachi T, Fukui K, Kosuge M, Kimura K. Distinction Between Precapillary and Postcapillary Pulmonary Hypertension by the Atrial Volume Ratio on Transthoracic Echocardiography. *J Ultrasound Med.* 2018;37(4):891-6.
20. Scalia GM, Scalia IG, Kierle R, Beaumont R, Cross DB, Feenstra J, et al. ePLAR - The echocardiographic Pulmonary to Left Atrial Ratio - A novel non-invasive parameter to differentiate pre-capillary and post-capillary pulmonary hypertension. *Int J Cardiol.* 2016;212:379-86.
21. Lancellotti P, Galderisi M, Edvardsen T, Donal E, Goliash G, Cardim N, et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging.* 2017;18(9):961-8.
22. van de Bovenkamp AA, Enait V, de Man FS, Oosterveer FTP, Bogaard HJ, Vonk Noordegraaf A, et al. Validation of the 2016 ASE/EACVI Guideline for Diastolic Dysfunction in Patients With Unexplained Dyspnea and a Preserved Left Ventricular Ejection Fraction. *J Am Heart Assoc.* 2021;10(18):e021165.
23. Cameli M, Sparla S, Losito M, Righini FM, Menci D, Lisi M, et al. Correlation of Left Atrial Strain and Doppler Measurements with Invasive Measurement of Left Ventricular End-Diastolic Pressure in Patients Stratified for Different Values of Ejection Fraction. *Echocardiography.* 2016;33(3):398-405.
24. Venkateshvaran A, Manouras A, Kjellström B, Lund LH. The additive value of echocardiographic pulmonary to left atrial global strain ratio in the diagnosis of pulmonary hypertension. *Int J Cardiol.* 2019;292:205-10.
25. Lindow T, Manouras A, Lindqvist P, Manna D, Wieslander B, Kozor R, et al. Echocardiographic estimation of pulmonary artery wedge pressure: invasive derivation, validation, and prognostic association beyond diastolic dysfunction grading. *Eur Heart J Cardiovasc Imaging.* 2024;25(4):498-509.
26. Mitchell C, Rahko PS, Blauwet LA, Canaday B, Finstuen JA, Foster MC, et al. Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2019;32(1):1-64.