Unbowed, unbent, unbroken: predicting pulmonary hypertension using echocardiography

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The probability of pulmonary hypertension can accurately be estimated by current echocardiographic criteria https://bit.ly/3KMCWQ2

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During the first meeting of the World Health Organization (WHO) in 1973, pulmonary hypertension (PH) was defined as mean pulmonary artery pressure (mPAP) ⩾25 mmHg measured by right heart catheterisation [1]. This criterion was chosen arbitrarily and was founded on the premise that mPAP at rest in a supine position does not exceed 15 mmHg [2]. In 2009, the landmark paper of Kovacs *et al.* [3] provided scientific evidence for this statement and showed that normal mPAP at rest was 14 mmHg, with an upper limit of normal of 20 mmHg. In addition, accumulating data has indicated that patients with mPAP ⩾19 mmHg but below the haemodynamic threshold of 25 mmHg are at increased mortality risk [4–6]. Therefore, a revised definition of PH was proposed during the 6th World Symposium on Pulmonary Hypertension (WSPH), which suggested lowering the diagnostic threshold from 25 to 20 mmHg. Because mPAP does not separate pulmonary vascular disease from increased cardiac output or pulmonary capillary wedge pressures, a pulmonary vascular resistance (PVR) >3 Wood Units (WU) was added to the definition [7]. An even lower PVR cut-off was considered, because a PVR of 2 WU is the upper limit of normal and higher values are associated with reduced life expectancy [6, 8]. However, it is not yet clear whether a lower cut-off value for PVR is to be used for PH diagnosis in the future.

How does that fit with the current diagnostic pathway for PH? Current guidelines recommend assigning a level of probability of PH, from a non-invasive estimate of systolic pulmonary artery pressure (sPAP) by Doppler echocardiography [9]. Based on the maximum velocity of the tricuspid regurgitation jet (TRV), the pressure gradient between the right ventricle and right atrium (ΔP) can be calculated using the modified Bernoulli equation (4 × maximum velocity^2). By adding the estimated right atrial pressure (RAP) from the diameter and collapse of the inferior vena cava, the estimated systolic pulmonary artery pressure (eSPAP) can be obtained [10]. According to the current guidelines, the probability of PH is primarily assigned to the echocardiographic estimation of pulmonary pressures by TRV, thereby neglecting estimated RAP because of its inaccuracy. In case of TRV ⩽2.8 m·s^{-1}, *i.e.* eSPAP ⩽31 mmHg with or without the presence of other echocardiographic PH signs, diagnosis of PH is unlikely. TRV between 2.9 m·s^{-1} and 3.4 m·s^{-1} (*i.e.* eSPAP of 34–46 mmHg) is associated with intermediate PH probability, and TRV >3.4 m·s^{-1} is associated with high probability of PH [9]. In addition to TRV measurements, echocardiographic signs are used to assess the probability of PH. These "indirect PH signs" include assessment of right ventricular (RV) and right atrial dimensions, flattening of the interventricular septum, flow pattern over the RV outflow tract (*i.e.* shortening of the pulmonary acceleration time and/or notching of the pulmonary artery Doppler signal) and the estimated RAP (figure 1) [9, 11].

The current TRV thresholds are based on the limits of normal and safety margins [9, 11]. A lower threshold of TRV ⩽2.8 m·s^{-1} has been validated in a large cohort of ∼1700 patients, with 72% PH prevalence [12]. An eSPAP of 36 mmHg (*i.e.* TRV of 2.8 m·s^{-1} (31 mmHg) with estimated RAP of

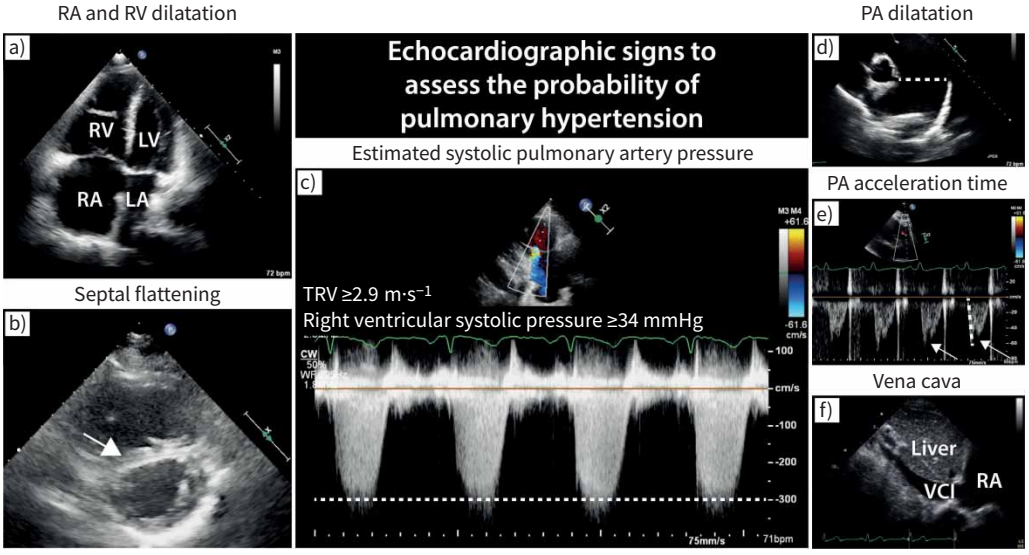

FIGURE 1 Echocardiographic signs to assess the probability of pulmonary hypertension (PH). a) Right atrial (RA) and right ventricular (RV) dilatation. In addition, the left atrium (LA) and left ventricle (LV) exhibit smaller dimensions due to under filling. b) Flattening of the interventricular septum (white arrow). c) The maximum velocity of the tricuspid regurgitation jet (TRV) assessed by continuous wave Doppler to estimate systolic pulmonary artery pressure. d) Dilatation of the pulmonary artery (PA). e) Shortening of the Doppler PA acceleration time and a mid-systolic PA notch (arrows). f) Dimensions of the vena cava inferior (VCI) to estimate right atrial pressure. D'Alto *et al.* [13] showed that a TRV $\geqslant$2.9 m·s^{-1} has the strongest diagnostic value to predict the presence of PH according to the new haemodynamic definition of mean pulmonary artery pressure >20 mmHg (sensitivity 83%, specificity 91%, positive predictive value of 99% and accuracy 83%).

5 mmHg) was able to predict PH defined by invasively measured mPAP $\geqslant$25 mmHg, with good sensitivity (87%), specificity (79%) and accuracy (85%). Higher TRV values yielded lower sensitivity, higher specificity and lower accuracy to estimate the likelihood of PH [12].

In the current issue of the *European Respiratory Journal*, D'Alto *et al.* [13] assessed the echocardiographic prediction of PH and/or pulmonary vascular disease based on the old and new PH diagnostic definitions. In a study population from a tertiary referral centre consisting of 146 pre-capillary PH, 94 post-capillary PH and 23 non-PH patients, a TRV $\geqslant$2.9 m·s^{-1} and $\leqslant$3.4 m·s^{-1} predicted PH defined by mPAP >20 mmHg. The cut-off value of TRV $\geqslant$2.9 m·s^{-1} showed the strongest probability of PH (sensitivity 83%, specificity 91%, positive predictive value of 99% and accuracy 83%). When considering PVR >2 WU, the TRV cut-off of 2.9 m·s^{-1} remained predictive of PH, the latter being slightly improved when combined with two or more indirect PH signs. For the first time, D'Alto *et al.* [13] demonstrate the validity of the current echocardiographic prediction strategy for PH (defined in the 2015 European Respiratory Society (ERS)/European Society of Cardiology (ESC) guidelines) for the new definition of PH based on mPAP >20 mmHg with or without PVR >2 WU.

The study by D'Alto *et al.* [13] comes timely to answer a critical question: do we have to adjust our TRV threshold for the probability of PH if the revised definition proposed at the 6th WSPH is adopted? The answer is clearly no: a TRV $\geqslant$2.9 m·s^{-1} remains appropriate even when invasive mPAP is lowered at 20 mmHg. Based on the study of D'Alto *et al.* [13], the added value of indirect PH signs appears limited. Is this disappointing? Well, not really and for several reasons. One should acknowledge that the retrospective design of the analysis, primarily focusing on the value of TRV, may underplay the role of subtle changes on the right ventricle induced by PH. In addition, the inclusion of low numbers of a non-PH population (a population with heart failure, tricuspid valve regurgitation and lung disease) might have contributed to diminishing the importance of these additional signs. In fact, both left ventricular–RV interactions and increased RV pre-load may have had an influence on its discriminative value for PH diagnosis in this population. Another explanation may be the moderate precision of TRV (in contrast with a good accuracy and reproducibility) in comparison to invasive pressure measurements [13–16]. Finally, a relatively low number of patients from the study with insufficient TRV signal quality were excluded,

reflecting the high level of expertise in echocardiographic imaging of the investigators [13]. This is in contrast with other studies showing that an accurate TRV signal cannot be obtained in about one-third of patients, and the absence of a measurable TRV does not rule out the presence of PH [17, 18]. Therefore, complete echocardiographic examination with assessment of indirect PH signs (*i.e.* characteristics of the right ventricle, right atrium, pulmonary artery flow and inferior vena cava) remains necessary (figure 1).

Let's turn the question the other way round: should we lower the threshold for TRV even below 2.9 $m \cdot s^{-1}$? This may be tempting, as evidence from recent studies suggests that a TRV up to 2.7 $m \cdot s^{-1}$ is associated with an increased risk of all-cause mortality risk [4, 19, 20]. Importantly, whether this lower prognostic TRV threshold represents a true PH diagnosis or simply more advanced underlying cardiopulmonary disease remains to be demonstrated. The study of D'Alto *et al*. [13] does not support such significant change in the context of PH probability assessment. Actually, this excellent work is in keeping with a recent analysis by Gall *et al*. [21], showing that lowering the TRV cut-off to below 31 mmHg was associated with lower specificity and positive predictive value in the prediction of PH defined by mPAP >20 mmHg. That said, this analysis also showed a poor correlation between TRV and invasively measured sPAP, especially at low pulmonary pressures, contrasting with previous studies [14–16]. The authors also found that higher TRV cut-offs (but below 46 mmHg) in combination with indirect PH-signs provided more accurate assessment of the PH risk according to the new haemodynamic criteria. The analysis performed by D'Alto *et al*. [13] confirms that a higher TRV threshold of 3.1 $m \cdot s^{-1}$ had the highest diagnostic accuracy to predict mPAP >20 mmHg.

Concomitant with the upper normal limit of mPAP of 20 mmHg, Kovacs *et al*. [3] showed that the upper limit of normal for invasively measured sPAP is 30 mmHg. This value corresponds to the non-invasive echocardiographic TRV of 2.8 $m \cdot s^{-1}$ and reinforces the evidence provided by D'Alto *et al*. [13] that a TRV cut-off at $\geqslant$2.9 $m \cdot s^{-1}$ is valid for the new diagnostic PH criteria.

Taken together, the data of D'Alto *et al*. [13] show that the contemporary echocardiographic TRV threshold $\geqslant$2.9 $m \cdot s^{-1}$ as stated in the 2015 ERS/ESC Guidelines remains a strong predictor of PH probability according to the new diagnostic definition based on mPAP $\geqslant$20 mmHg.

Unbowed, unbent, unbroken: the work by D'Alto *et al*. [13] confirms that the current echocardiographic standards for the assessment of a probability of PH do not have to change until further notice.

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