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Two-dimensional transthoracic echocardiography at rest for the diagnosis, screening and management of pulmonary hypertension

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Summary

Doppler echocardiography is widely used in everyday clinical practice for the detection of pulmonary hypertension (PH) in symptomatic patients and in populations particularly at risk of pulmonary arterial hypertension (PAH). It allows accurate estimation of systolic pulmonary arterial pressure but may lack precision in particular situations. In addition, echocardiography can help to distinguish between pre- and post-capillary PH and is a very good tool to evaluate right ventricular systolic function, which is of great prognostic interest in PAH. This article reviews the current knowledge about methodologic aspects of assessing pulmonary pressure and PH origin by echo, including a discussion about abnormal thresholds. It also details advanced techniques like right ventricular strain imaging and new concepts like right ventricle – pulmonary artery coupling evaluation that have become “matured” enough to be definitely brought to routine evaluation.

Introduction

Despite advances in other techniques, resting two-dimensional transthoracic echocardiography (TTE) remains key in the diagnosis, screening and follow-up of pulmonary hypertension (PH) [1]. Whereas TTE was used at first to estimate PH probability, it can also be used to determine the possible cause of PH and to evaluate right ventricular (RV) morphology and function. Nevertheless, in recent years, the reliability of TTE to estimate pulmonary pressure has been challenged [2–4] and recent algorithms proposing serial noninvasive risk assessment in pulmonary arterial hypertension (PAH) dismissed TTE [5, 6]. On the other hand, advanced techniques such as right ventricular strain assessment by speckle tracking imaging and new concepts like indirect right ventricle – pulmonary artery (PA) coupling evaluation improved the ability of TTE to predict outcome and to further understand the intimate relationship between the heart and pulmonary circulation.

With this review, the goal of the Swiss Society of Pulmonary Hypertension is to provide an update on current strengths and limitations of 2-D TTE in PH for sonographers and to encourage the implementation of convincing new findings in everyday practice. This review is also an attempt to gather sonographers from different PH expert centres of the country in order to define a consensus on TTE realisation. The authors hope that enhanced TTE standardisation will help PH physicians to get all the information they need to manage their patients at the highest quality level.

Echocardiography to assess pulmonary hypertension probability

TTE should be performed in all patients with suspected PH or unexplained dyspnoea, and in those at high risk of PAH with the aim of assessing PH probability [1]. Systolic pulmonary artery pressure (sPAP) can be assessed in 80–90% of cases and PH (sPAP >36 mm Hg) can be detected with 80–85% sensitivity-specificity by experienced sonographers [7]. In practice, sPAP is usually measured by applying the simplified Bernoulli equation to peak tricuspid regurgitation velocity (TRV) measured with continuous wave Doppler (CW), where sPAP = 4·(TRV)² + right atrial pressure (RAP) (fig. 1). Importantly, RAP is not measured but estimated from inferior vena cava diameter and inspiratory collapse [8]. TRV must be obtained from multiple views (parasternal long and short axis, apical four-chambers view), finally taking into account the maximum value obtained from the best quality TR jet envelope [9]. If peak TRV is hard to define, agitated saline can be injected to improve definition, but with the risk of overestimation due to contrast artefacts. Of note, TRV is not the only technique to estimate PAP by echo and alternatives based on...
pulmonary acceleration time and pulmonary regurgitation have been described; however, all have limitations [10].

Because of worries about overdiagnosis of PH, European guidelines conservatively set the maximum upper limit of normal peak TRV at 2.8 m/s, corresponding to an RV/RA pressure gradient of 31.3 mm Hg and to sPAP of 36.3 mm Hg if 5 mm Hg RAP is assumed [1]. On the other hand, the “classification” task force of the 2018 World Symposium on PH considered that the definition of PH should be strictly set according to epidemiological evidence and hence that the threshold for invasively measured abnormal mPAP should be reduced from 25 mm Hg (current guideline definition) to 21 mm Hg [11]. On the basis of epidemiological data for TTE, the upper limit of normal TRV can be considered to be 2.55 m/s, according to a recent meta-analysis pooling authors’ original data with 16 published studies [12]. According to the Bernoulli formula and assuming 5 mm Hg for RAP, a normal sPAP value would then not exceed 31 mm Hg, which is very near to the 29.6 mm Hg found by right heart catheterisation in healthy people [13]. Harmonising TTE thresholds for PH detection with the new invasive PH definition will be a task for the next European guidelines.

Despite adequate predictive values for PH detection, TTE may still lack precision for sPAP estimation [2–4, 7, 14], suggesting that it is reliable for disease screening, but that sPAP estimates can be falsely high or low under particular conditions. Importantly, TTE is accurate, meaning that there is no systematic bias for under- or overestimation [3, 4], although underestimation is probably more frequent [2, 3]. In everyday practice, imprecision should lessen if echocardiographers are aware of the pitfalls linked to sPAP evaluation [14]. Furthermore, obvious imprecision should be adequately recorded on TTE reports. The commonest causes of sPAP underestimation are incomplete spectral wave envelopes (fig. 1) and substantial angulation between CW and TR jet direction (maximum acceptable angle = 30°) [7]. Both pitfalls can often be resolved by a multiplane approach to TRV, including atypical views [9]. A less frequent reason for underestimation is severe TR, which rapidly abolishes the RV/RA pressure gradient and is typically recognisable by a dense triangular early peaking jet [7]. Furthermore, severe TR implies a non-stenotic orifice, where the simplified Bernoulli equation does not apply. Common causes of sPAP overestimation are mistakes of a TV closure artefact for the TR jet and incorrect assignment of a peak TRV out of the modal frequency (the frequency at which most red blood cells are moving, represented by the dense part of CW signal) in the case of maximum velocity boundary artefacts (“fringes”; fig. 1). This pitfall is avoided by carefully decreasing Doppler gain to improve the signal-to-noise ratio [7, 14]. Finally, RAP estimation according to inferior vena cava size and collapsibility is a major source of imprecision and very weakly correlates with invasive measurement [2, 3]. Very elevated RAPs are systematically underestimated with a TTE algorithm considering 15 mm Hg as the maximum achievable value, and up to 50% of overestimated sPAP can be attributed to RAP overestimation [2]. Consequently, current European PH guidelines removed RAP from their algorithm of PH probability estimation and concentrated only on TRV [1].

In order to improve the positive predictive value of TTE and given the possibility of missing PH if TVR-based sPAP is underestimated, guidelines recommend looking for indirect signs of PH in the case of normal or moderately elevated TRV [1]. Indirect signs are detailed and illustrated in figure 2 and must be looked for at the levels of the ventricles, PA, inferior vena cava and RA. In all situations except low PH probability, patients should be referred to PH expert centres for further investigations including right heart catheterisation unless they present evident heart or lung

**Figure 1:** A. Incomplete continuous wave (CW) Doppler spectral wave envelope leading to peak tricuspid regurgitation velocity (TRV) underestimation (3.89 m/s). B. Same patient after correct adjustment of CW Doppler in TR jet with correct TRV estimation (4.15 m/s). C. Inadequate CW gain with “fringes” and peak TRV overestimation (pink cross: 5.62 m/s); correct peak TRV estimation in modal frequency (4.69 m/s). D and E. Inferior vena cava (IVC) size during expiration and “sniff” in the same patient. SPAP = systolic pulmonary arterial pressure

| IVC size | Collapse during “sniff” | RAP |
|----------|-------------------------|-----|
| < 21 mm  | ≥50%                    | 3 mmHg |
| ≥21 mm   | ≤50%                    | 15 mmHg |
| < 21 mm  | ≤50%                    | 8 mmHg |
| ≥21 mm   | >50%                    | 8 mmHg |
disease (suggesting group 2 or 3 PH) compatible with TTE findings (fig. 3) [1, 15].

Echocardiography to evaluate the cause of pulmonary hypertension

Although right heart catheterisation is required to definitely differentiate precapillary (pulmonary artery wedge pressure [PAWP] ≤15 mm Hg) from postcapillary (PAWP >15 mm Hg) PH, TTE can fairly well predict the likelihood of both conditions [16–19]. This task can be challenging or sometimes impossible, particularly in patients with combined pre- and postcapillary PH, which shares features of both disorders [20, 21]. The general approach is to systematically look at parameters favouring either pre- or postcapillary PH and to develop a working diagnosis based on the predominant echo findings and the global clinical context. Referring patients to PH expert centres for right heart catheterisation and further investigations will finally be required only in unclear situations, when PAH or chronic thromboembolic pulmonary hypertension (CTEPH) is suspected or in the case of severe PH or RV dysfunction (fig. 3) [1, 15].

Table 1 gives an overview of clinical and TTE arguments favouring each condition. If left ventricular ejection fraction (LVEF) is clearly impaired or if there is severe aortic or mitral valve disease, postcapillary PH is very likely. Of note, heart failure and severe left-sided valvular heart disease can sometimes present without PH or alternatively with combined pre- and postcapillary PH. If LVEF is pre-

**Figure 2:** Indirect signs of pulmonary hypertension at the levels of the ventricles, pulmonary valve / pulmonary artery and inferior vena cava / right atrium. Adapted from Galiè 2016 [1].

**Figure 3:** Evaluation of the echocardiographic probability of pulmonary hypertension and further management in a 4 steps approach. For management, consider if the patient has risk factors (RF) or associated conditions for pulmonary artery hypertension (PAH), or chronic thromboembolic pulmonary hypertension (CTEPH). Adapted from Galiè 2016 [1]. Other TTE signs are considered if ≥2 indices from ≥2 classes are present. *Low peak TRV = ≤2.8 m/s according to guidelines and ≤2.55 m/s according to epidemiological data (cf text). **Intermediate peak TRV = 2.8–3.4 m/s according to guidelines; lower limit >2.55 m/s according to epidemiological data (cf text). ***High peak TRV >3.4 m/s according to guidelines.
served or mildly reduced with no significant valve disease, attention must be paid to markers of elevated left-sided filling pressures. In this context, the ratio of the peak early mitral inflow velocity to peak early mitral annular velocity (E/e′) is important. Even though E/e′ was found to be only mildly correlated to LV end-diastolic pressure and PAWP in patients with preserved LVEF [22], elevated E/e′ turned out to be a useful marker of a postcapillary disorder in PH [17, 18]. Given that e′ at the septal annulus may be influenced by right ventricular dysfunction, only e′ measured at the lateral annulus should be used to calculate E/e′. The measurement of left atrial (LA) size (LA anteroposterior diameter in parasternal long axis view, LA area in apical four-chamber view or preferably biplane LA volume index) is also important as it mirrors PAWP and LV filling pressure. LA dilatation is therefore a strong argument in favour of postcapillary PH. In addition, comparing the size of the left and right atria (RA) can give a feeling of the predominant problem, i.e., postcapillary PH if LA > RA and vice versa.

Given that no single parameter can differentiate pre- from postcapillary PH, several echo scores combining the most important parameters have been developed [17–19]. Table 1 shows the components of the three most important scores. Overall, the best predictors of precapillary PH include a small LA [17, 19], a dilated RV [18, 19], a clear septal D-shape [18], a notch in the pulsed wave Doppler (PW) signal of the pulmonary artery or a short acceleration time (<80 ms) [17]. The areas under the curves for these scores to predict precapillary PH range from 0.76 [18] to 0.93 [19]. Although these scores are not perfect and cannot replace right heart catheterisation in general, they can identify patients with clear postcapillary PH who will not require invasive assessment. For example, a patient with E/e′ >10, LA diameter >4.2 cm and no notch in the PA PW signal is very unlikely to have precapillary PH [17]. Finally, TTE is also useful in identifying congenital heart disease. Shunts must be suspected in cases of high pulmonary blood flow (PW Doppler), but may remain anatomically hidden as in the case of sinus venosus atrial septal defects or anomalous pulmonary venous return. Transoesophageal echo or cardiac magnetic resonance imaging (CMR) is warranted to define anatomical structures in such situations [1, 15].

### Echocardiography to assess right ventricular remodelling

With its thin wall and relatively nonmuscular structure, the RV is branched to the low resistance pulmonary vascular tree and faces low afterload in physiological conditions. With PH, hydraulic load increases and forces the RV to adapt itself in order to maintain stroke volume and cardiac output, or, in other words, to remain “coupled” to the pulmonary circulation. At first, RV contractility increases by a factor of 4 to 5 by the mean of increased sympathetic tone, hypertrophy and changes in muscle properties. This process is usually insufficient in severe PH and further stroke volume preservation can only be attempted through the Frank-Starling mechanism with an increase in RV end-diastolic volume [23–25]. To some extent, this adjustment is unavoidable in idiopathic PAH [26] and is considered maladaptive because RV dilation inevitably increases wall tension, which results in turn in increased oxygen demand, increased wall stiffness and increased ventricular interaction leading to further decreased cardiac output and eventually death [23]. As a clinical correlate, RV end-diastolic volume assessed by CMR is a very strong predictor of mortality in idiopathic PAH [27]. Unfortunately, RV 3-D geometry is too complex to allow volume modelling by simple geometrical assumptions on 2-D echo, but surrogates overcome this issue.

| Table 1: Clinical features and non-invasive findings favouring precapillary or postcapillary pulmonary hypertension (PH). |
|---------------------------------------------------------------|
| **Clinical features** |
| PRE-CAPILLARY PH | POST-CAPILLARY PH |
| Atrial fibrillation | No | Yes |
| Obesity/diabetes | No | Yes |
| Coronary artery disease | No | Yes |
| Chest X-ray | No pulmonary congestion | Pulmonary congestion |
| ECG | RV hypertrophy/strain | RV hypertrophy/strain |
| **Echocardiography** |
| LV+LA area <RV+RA area | Yes | No |
| Apex-forming RV | Yes | No |
| RV end-diastolic area | ↓ | ↓ |
| LV mass | ↓ | ↓ |
| LV eccentricity index (degree of LV “D-shape”) | ↑ ~1.0 | ↓ |
| E/e′ | ↓ | ↓ |
| LA area (apical for chamber view) | ↑ | ↓ |
| LA anteroposterior diameter (parasternal long axis view) | <3.2 cm | >4.2 cm |
| Mitral regurgitation | No/little | Little to severe |
| Peak TRV / VTI RV OT | ↑ | Normal† |
| Mid-systolic notch in pulmonary artery PW Doppler signal or acceleration time <60 ms² | Yes | No |
| IVC diameter >20 mm without inspiratory collapse (≤50%) | Yes | No |

E/e′ = ratio of the peak early transmural velocity to the peak early mitral annular velocity (ideally assessed at the lateral annulus); IVC = inferior vena cava; LA = left atrium; LV = left ventricle; PW = pulsed wave; RA = right atrium; RV = right ventricle; TRV = tricuspid regurgitation velocity; VTI RV OT = velocity time integral in the right ventricular outflow tract. * Parameters included in the score by Berthelot et al. [18], † by D’Alto et al. [18] and ‡ by Opopowsky et al. [17].
Assessment of right ventricular dimensions

On TTE, the RV appears to be wrapped around the left ventricle (LV) like a crescent in parasternal short axis view and appears with a triangular cavity from apical four-chamber view (A4C). RV cavity area can be measured from this view at end-diasotole and serve as a substitute for RV volume (table 2). On the other hand, well-defined RVEDA prognostic values are lacking in PH and RVEDA is mildly reproducible [31, 32]. Indeed, RV pronounced trabeculations and retrosternal location challenge echocardiographic evaluation and RV size may significantly fluctuate according to small plane variations in A4C [8]. Nevertheless, interobserver variability seemed to refine with time [33], possibly thanks to improved echocardiographic guidelines regarding RV imaging [8]. Typically, the RV-focused A4C (RVF-A4C) used to assess RVEDA differs from standard A4C view. It is obtained by moving the transducer more laterally in order to visualise the maximum basal RV width as well as the RV apex, which avoids RV foreshortening and usually brings the LV apex at the top of the scanning sector [8]. Of importance, the issue of RVEDA variability according to scanning plane can be attenuated by expressing RV dimensions in relation to LV metrics. Goda et al. recently showed that RV to LV end-diasotolic area ratio ≥0.93 predicted lower survival in PAH and added incremental value to age, gender and functional class in risk prediction [33]. Although imperfect, RVEDA and RV to LV EDA ratio remain the proper ways to assess RV remodelling by 2-D TTE, the option of measuring RV diameter or RV to LV diameter ratio being poorly validated (table 2).

Alternatively, Amsallem et al. proposed an index of RV end-systolic dimension seemingly less influenced by image acquisition with low intra-/interobserver variability. Their RV end-systolic remodelling index (RVESRI) is derived by dividing RV free wall longitudinal length by septal height taken in RVF-A4C, which partially corrects for apical foreshortening and integrates both dimensional and functional aspects of RV adaptation to PH. In a collective of 228 PAH patients, baseline RVESRI was strongly and independently associated with death, transplantation or hospitalisation and was incremental to the REVEAL score to predict outcome (table 2) [34].

Echocardiography to assess right ventricular systolic function: direct indices

After size and volume, RV dysfunction is the most powerful predictor of death in PH [35], making RV systolic function assessment another essential aspect of TTE in PH. Systolic function can be regarded as the interplay between intrinsic factors such as contractility and heart rate, extrinsic factors such as preload and afterload, and inter-ventricular interaction [36]. Mechanistically, it results in RV emptying by three mechanisms: radial displacement of the free wall towards the interventricular septum (IVS), IVS bulging into the cavity, and shortening of the long axis with descent of the tricuspid annulus (TA) towards the apex. Practically, RV function is often first assessed qualitatively by visual evaluation, but quantitative measurements should always be preferred when possible.

Two-dimensional surrogates of right ventricular ejection fraction

Right ventricular ejection fraction (RVEF) assessed with CMR is an aggregate of longitudinal and radial components of RV emptying and is a strong outcome predictor in PAH [37]. However, it again refers to volume variations not assessable by 2-D echo. Instead, TTE can measure the percent change in RV area between end-diastole and end-systole RV fractional area change (FAC), which is also an integration of longitudinal and radial shortenings (table 2, fig. 4). It is important to consider indices accounting for both RV radial and longitudinal shortening in PH because both components appear to be differently affected by afterload [38]. Indeed, CMR-based RVFAC is closely linked to RVEF whatever the PVR, whereas longitudinal function variables such as tricuspid annular plane systolic excursion (TAPSE) become weakly correlated to RVEF at high PVR [38, 39]. This finding may reflect a plateauing (“floor effect”) of longitudinal shortening after an initial parallel decline in both planes, further loss of systolic function being essentially generated by further leftward IVS bow-
Table 2: Echocardiographic assessment of right ventricular size and systolic function (see text for references).

| Parameter | Assessment / technique | Advantages | Limitations | Abnormality thresholds | Prognostic value in PH |
|-----------|------------------------|------------|-------------|------------------------|-----------------------|

**RV diameters**

| Parameter | RV focused 4-ch view at end-diastole | Easy and fast | Not indexed to BSA and gender | >41 mm | Unknown |
|-----------|--------------------------------------|--------------|--------------------------------|--------|---------|
|           | Distance from lateral endocardial border to IVS right border parallel to TA plane | Assessed from univoqual anatomical reference (unlike mid-diameter) | Not validated as a prognostic factor in PH |        |         |
|           | Max transversal dimension of the basal one third | | Dependent on probe rotation. May be underestimated. | | |

| Parameter | RV end-diastolic area | Relatively easy and fast | Mildly reproducible | Men >24 cm² | RVEDA prognostic values poorly defined |
|-----------|-----------------------|-------------------------|-------------------|-------------|--------------------------------------|
|           | RV focused 4-ch view | No geometrical assumptions needed | Incomplete visualisation of RV cavity with severe enlargement | Women >20 cm² | RVEDA/LVEDA >0.93 |
|           | Manual tracing of RV endocardial border from lateral TA to apex back to medi-al TA along IVS at end-diastole and end-systole. | Normal values well established | Suboptimal endocardial definition | RV indexed for BSA | |
|           | (RVEDA – RVESA) / RVE- | Correlated to RV pump function | (trabeculations to be included in the cavity) | Men >12.5 cm²/m² | |
|           | astole and end-systole. | Sensitive marker to reverse remodelling on therapy | Sensitive to minor plane variations (attenuated if RV indexed for LVEDA) | Women >+11.5 cm²/m² | |
|           | | | May under- or overestimate RV size | Normal right/left ventricle ratio <0.66 | | |

| Parameter | RV end-systolic remodelling index | Less dependent on image acquisition | Derived from a single centre observation, not validated by others | RVESRI <1.35; adapted RVESRI 1.35–1.7; adverse remodelling | |
|-----------|----------------------------------|----------------------------------|------------------------------------------------|----------------------------|-------|
|           | RV focused 4-ch view | Corrects for apical fore-shortening | Incomplete visualisation of RV free wall in the case of severe enlargement | RVESRI >1.7; severe re-modelling | |
|           | ratio of end-systolic RV free wall length to end-systolic septal height | Improved Intra-/interobserver variability | No need for endocardial border definition | | |
|           | free wall length from lateral TA RV insertion of IVS. | | | | |
|           | Septal height as a straight line from septal TA to RV insertion on IVS | | | | |
|           | RV basal diameter | Incudes longitudinal and radial systolic function (global RV systolic function) | Well correlated to RVEF | | |
|           | RV focused 4-ch view at end-diastole | Same limitations as RVEDA | Not indexed to RV-EF | | |
|           | Distance from lateral endocardial border to IVS right border parallel to TA plane | Does not consider outflow | Not angle-dependent | | |
|           | Max transversal dimension of the basal one third | | | | |

**Direct indices of RV systolic function**

| Parameter | RV FAC | Quick and easy | Highly reproducible | Not indexed to BSA and gender | Threshold values for prognosis poorly defined |
|-----------|--------|---------------|-------------------|----------------------------|----------------------------------|
|           | Manual tracing of RV endocardial border from lateral TA to apex back to medi-al TA along IVS at end-diastole and end-systole. (RVEDA – RVESA) / RVE- | Includes longitudinal and radial systolic function (global RV systolic function) | Angle dependent | | |
|           | DA | Well correlated to RVEF | Load dependent | | |
|           | RVESRI >1.35 | Sensitive to passive trans-lational motions | | | |
|           | | Transversal shortening and outflow tract not accounted | | | |

| Parameter | TAPSE | Quick and easy | Highly reproducible | Similar to TAPSE | No specific data in PH |
|-----------|--------|---------------|-------------------|----------------|-----------------------|
|           | RV-modified 4-ch view. Cursor aligned on TA displacement axis | In time acquisition | Less dependent on image quality | <9.5–10 cm/s | |
|           | M-mode | | | | |

| Parameter | PW-TDI | Quick and easy | Highly reproducible | Similar to TAPSE | No specific data in PH |
|-----------|--------|---------------|-------------------|----------------|-----------------------|
|           | RV-modified 4-ch view. Cursor aligned on TA displacement axis | In time acquisition | Less dependent on image quality | | |
|           | S’ wave | | | | |
|           | | | | | |

| Parameter | RV-MPI by PW-TDI | Single beat acquisition | Not a “pure” systolic function index | Normal: <0.38 | 0.64 |
|-----------|-----------------|------------------------|-------------------------------------|------------------|--------|
|           | Tissue Doppler on TA in RV-focused 4-ch view | | | Upper reference limit: <0.43 | >0.83 |
|           | End of a’ to onset of e’ = S’ wave = (S’/S) MPI = ([a’–e’] – S’) / S’ | | | | |
|           | Normal: >21 mm | Mild/moderate/severe dys-function: 18–20/16–17/≤15 mm | Highly load dependent | | |
|           | Angle dependent | Load dependent | | | |
|           | Requires 2 different heartbeats with possibly different cycle lengths | Unreliable in atrial fibril-la-tion | | | |
|           | Other limitations similar to RV-MPI by PW-TDI | | | | |
|           | Normal: <0.28 | Upper reference limit: <0.43 | | | |
|           | Conventional RV inflow and outflow Doppler | Required 2 different heartbeats with possibly different cycle lengths | Unreliable in atrial fibrillation | | |
|           | End of A to onset of E waves interval on inflow (=A–E); onset to end of S wave on outflow (=S) MPI = ([A–E] – S) / S | | | | |
|           | Normal: <0.28 | Upper reference limit: <0.43 | | | |
|           | RV MPI by PW Doppler | Requires 2 different heartbeats with possibly different cycle lengths | Unreliable in atrial fibrillation | | |
|           | | | | | |

| Parameter | RV longitudinal free wall strain | Angle independent | Radial function not considered | Normal <~25% | 0.83 |
|-----------|-------------------------------|------------------|-------------------------------|------------------|--------|
|           | RV-focused 4-ch view | Translational motion independent | Outflow tract not considered | Associated with low RVEF | >0.83 |
|           | Sector depth and size adjusted to visualise RV apex and obtain frame rate >50–60 Hz | Reproducible | Load dependent | from <+20% | |
|           | Region of interest defined from lateral TA to RV apex (exclude RA and pericardi-um) | | Software originally created for left ventricle | | |
|           | Angle independent | Radial function not considered | Load dependent | Software originally created for left ventricle | |
|           | Translational motion independent | Reproducible | Load dependent | Inter-vendor variability | |
|           | Reproducible | | Load dependent | | |

| Parameter | RV dyssynchrony | Similar to RVLS | Similar to RVLS | Dysynchrony = RV-SD4 | RV-SD4 >23 ms |
|-----------|----------------|---------------|---------------|------------------|--------|
|           | Same technique as for RVLS | | | | |
|           | Standard deviation of time to peak strain across 4 | | | | |
Pericardial effusion
Measurement in diastole where PEF appears the biggest
Easy and fast
Not sensitive for RV dysfunction
No effusion normally visualised
<1 cm intermediate outcome
>1 cm poor outcome

Right atrial area
RV-focused 4-ch view
Planimetry by endocardial border tracing at end-systole; exclude area between leaflets and annulus; exclude right appendage
Relatively easy and fast
No geometrical assumptions needed
Indirect measure of RV function
Accounts for dimension change in a single plane
Interobserver variability not well reported
Men: 15.8–16.6 cm²
Women: 14.7–15.7 cm²
Worse prognosis: >18 cm²

Eccentricity index
Parasternal short axis view
Papillary muscle level
End of systole (es) and/or end of diastole (ed)
LV diameter 1 parallel to IVS (LVD1) and LV diameter 2 perpendicular to LVD1 (LVD2)
EI = LVD1/LVD2
Reproducible
Relatively cumbersome
Inaccurate if measured in oblique sections
Not independently associated with outcome in most studies
Normal value ~1
EIes >1.56 and EIed >1.81 whatever RV function
Worse outcome with EIes >1.7 if TAPSE <15 mm

Tricuspid regurgitation
Multiple views
Severe TR: vena contracta >7 mm, PISA radius >9 mm (Nyquist limit 28 cm/s) and systolic hepatic vein flow reversal
Reproducible
Moderate to severe TR associated with later stages of RV dilatation/dysfunction
Mild TR usual with PH; does not affect prognosis
Moderate to severe TR

4-ch = four-chamber; BSA = body surface area; FAC = fractional area change; IVS = intraventricular septum; LV = left ventricular; LVEDA = left ventricular end-diastolic area; RVEDA = right ventricular end-diastolic area; RVESRI = right ventricular end-systolic remodelling index; RVFAC = right ventricular fractional area change; RV-SD4 = standard deviation of the times to peak systolic strain for the four mid-basal right ventricular; segment; TA = tricuspid annulus; TAPSE = tricuspid annulus plane systolic excursion; TR = tricuspid regurgitation

In precapillary PH, TAPSE <18 mm was associated with lower stroke volume, dilated right atrium and reduced survival [32], whereas TAPSE ≤15 mm was associated with a nearly 3-fold rise of mortality or emergent lung transplantation in PAH [45]. However, TAPSE seems to lose predictive power in populations with severe PH and a dilated RV, where a “floor effect” can appear in addition to paradoxical improvement due to afterload decrease on worsening tricuspid regurgitation (TR), like for any other load-dependent variable [46, 50].

Another means to quantify longitudinal function is to measure lateral TA systolic excursion velocity (S’) by pulsed wave tissue Doppler imaging (PW-TDI). As opposed to TAPSE, S’ can still be acquired on images of suboptimal quality. As both indices highly correlate (R >0.9), they basically convey similar information (table 2, fig. 4) [36].

Analysis of time intervals
RV myocardial performance index (MPI), or Tei index, globally reflects RV systolic and diastolic performance. It is defined as the sum of isovolumic contraction and relaxation times divided by ejection time [51], higher values indicating poorer function. RV-MPI can be assessed by conventional PW-Doppler from two different views (ejection time at the pulmonary valve from the short axis view and isovolumic intervals derived from tricuspid flow in any view), and hence from two heartbeats with possibly different cycle lengths. Alternatively, RV-MPI can be acquired by PW-TDI on the lateral TA during a single beat to circumvent this issue (table 2, fig. 4). Correlation between both techniques is surprisingly modest and normal values differ from one method to the other [8]. Although several factors such as pseudo-normalisation with increasing RAP (reduction of isovolumic relaxation time) [52] and dependence
on loading conditions [53] significantly limit RV-MPI, this variable was consistently associated with outcome in PAH and mixed PAH/CTEPH populations, including after adjustment for numerous other TTE and haemodynamic variables [46, 51, 54].

Right ventricular deformation imaging (strain)

Strain refers to the magnitude of myocardial deformation occurring in a given segment during systole and is calculated as the percent change of length separating two points during movement \[(\text{end-systole} - \text{end-diastole}) / \text{end-diastole lengths} \times 100\]. Global strain is the average of all segments and negative values represent shortening. Strain is nowadays assessed by speckle tracking imaging, using an algorithm tracking constant pattern of black and white spots, i.e., speckles produced by ultrasound in the acoustically inhomogeneous myocardium within a user-defined region of interest. Speckles are tracked in any direction, making strain an angle-independent variable, with the additional strength of being mainly dependent on local shortening and less influenced by external traction due to displacement of neighbouring segments [55].

At the RV level, global longitudinal strain is assessed on RVF-A4C with 85–95% feasibility [50, 56] and low intra/interobserver variability [57], and can include (RVGLS$_{\text{Total}}$) or exclude the IVS (RVGLS$_{\text{Freewall}}$). Image acquisition must be optimised in order to obtain a frame rate ≥50–60 Hz, avoid reverberation and visualise the RV apex throughout the complete cardiac cycle [8]. Reference points and regions of interest should be defined with care, the inclusion of atrial wall or pericardium in the region of interest producing falsely low strain (table 2, fig. 4).

Unfortunately, consensus about the best algorithm for strain analysis is lacking, and software show a low intervendor agreement [55]. Consequently, longitudinal patient follow-up should be performed with similar equipment and software for comparison. Nevertheless, both RVGLS$_{\text{Total}}$ and RVGLS$_{\text{Freewall}}$ correlate better with CMR-derived RVEF than conventional indices \(R = -0.77 \text{ to } -0.86\) [43, 58, 59]. A recent meta-analysis proposed \(-27\% \pm 2\%\) as normal range for RVGLS$_{\text{Freewall}}$ [60] with detection thresholds for abnormal RVEF at \(-20\%\) [61]. Focardi et al. reported sensitivity and specificity of 96% and 93% for RVGLS$_{\text{Freewall}} \geq -17\%$ to predict RVEF <45% [43].

In the largest prospective study conducted so far (406 pre-capillary PH and 169 non-PH subjects), RVGLS$_{\text{Freewall}}$ was the only direct RV function index to predict mortality after adjustment for functional class, N-terminal pro-B-type natriuretic peptide (NTproBNP) and 6-minute walking distance [56]. Others found similar results and two recent meta-analyses reported a pooled unadjusted hazard ratio (HR) of 3.67 (95% confidence interval [CI] 2.88–4.77) for mortality using binary RVGLS$_{\text{Freewall}}$ cut-off values in pre-capillary PH (76% PAH) [62], and a HR of 2.96 (95% CI 2.0–4.38) for all-cause mortality with a 22% relative reduction of RVGLS$_{\text{Freewall}}$ [63].

Beside global strain, speckle tracking imaging can assess RV dyssynchrony. In PH, electrophysiological remodelling creates zones of slow conduction and prolonged action po-

Figure 4: 76-year-old male with pulmonary arterial hypertension. Normal TAPSE, S’ velocity and FAC with abnormal MPI and right ventricular free-wall strain. FAC = fractional area change; TAPSE = tricuspid annular plane systolic excursion; S’ = TA tissue Doppler velocity; MPI = Tei index; TCO = tricuspid valve closure to opening time; ET = ejection time.
tential in the RV with delayed peak myocardial shortening resulting in regional contraction inhomogeneity and finally in intraventricular dysynchrony [64]. With speckle tracking imaging, dysynchrony is assessed by measuring standard deviations (SDs) of time to peak strain across a chosen number of segments (models with four and six segments including the IVS). In PAH, RV dyssynchrony (RV-SD4 >18–19 ms) is frequent and affects haemodynamics, RVEF, functional class and functional capacity [65, 66]. With a 23-ms cut-off, RV-SD4 predicts 1-year event-free survival with negative and positive predictive values of 95% and 57% (table 2) [67].

**Echocardiography to assess right ventricular systolic function: indirect indices**

**Right atrial size**

RA size and pericardial effusion (PEF) are the only two TTE variables recommended for risk stratification in the current European Respiratory Society (ERS) / European Society of Cardiology (ESC) guidelines on PH [1]. Although international guidelines on TTE advocate volume assessment for RA size quantification [8], orthogonal views of the RA cannot be obtained for biplane calculation and minor axes of the RA may not be equal, particularly in the event of RA dilatation. As far as PH is concerned, RA size should be alternatively quantified by single plane assessment of its area (RAA) on A4C (table 2, fig. 2). Indeed, RAA correlates with RV function in PH patients and larger RAA has been associated with lower cardiac index reserve at exercise in PAH patients [29]. Of note, normal RAA values differ between men and women, and rise with high endurance training [68]. In addition, RA may also dilate because of TR and atrial fibrillation, and the reproducibility of RAA measurement is not well defined.

In PAH, RAA has been consistently reported as a strong prognostic factor, also after adjustment for relevant clinical, biological, haemodynamic and usual TTE variables [69–72]. However, it has not been adjusted for modern robust direct RV function variables such as RVGLS	extsubscript{Freewall}.

**Tricuspid regurgitation**

In PH, tricuspid regurgitation occurs as a consequence of RV remodelling, with tricuspid annular dilation, valve tenting and normal leaflets. Whereas virtually all newly diagnosed PAH patients display TR, severe regurgitation is rare (<20%) and reflects late-stage RV maladaptation [73] with poor outcome in PAH [46, 73].

**Pericardial effusion**

Pericardial effusion is common (20–50%) on initial imaging in PAH [26] and its volume correlates with RA pressure and size, RV size and function, and TR severity [74, 75]. Physiologically, it is caused by increased central venous pressure, which impairs both venous and lymphatic drainage of the heart, with swollen lymphatic subepicardial pre-collectors suffusing in the pericardial space [76]. Of note, pericardial effusion is not specific to RV dysfunction and may also reflect serositis in connective tissue disease-associated PAH [36, 74]. The presence and severity of pericardial effusion nevertheless remain correlated with poor outcome in PAH after adjustment for PAH aetiology and right atrial pressure [74, 77].

**Left ventricular eccentricity index**

As the IVS and the pericardium are shared by both ventricles, events occurring on one side influence the contratral one, a phenomenon called right-left ventricular interaction [78, 79].

With a flat configuration in the unloaded human heart [80], the IVS displays a concave shape during systole in physiological conditions because of a positive left to right transseptal pressure gradient. With PH, systolic interventricular gradient decreases, increasing in turn the IVS curvature (flattening) in a linear relationship [81]. During early diastole, interference occurs in PH through persisting RV free wall shortening, while IVS and LV free wall already relax. This results in a transient inverted trans-septal pressure gradient and in a rapid leftward septal motion (“early diastolic bounce”), with possible short reverse septal curvature in severe PH [82–84]. RV and LV pressures may finally equalise at end-diastole if RV dilatation is significant enough to induce pericardial constraint [78, 82]. Importantly, IVS mediated ventricular interactions reduce LV size, impair LV filling and may deeply reduce stroke volume in PAH [83, 85].

IVS flattening can be qualitatively assessed or quantified by measuring LV eccentricity index (EI) in parasternal short axis view (table 2, fig. 2). Systolic EI correlates with PVR and with RV function indices, and both end-systolic and end-diastolic EI predict outcome in PAH in univariate analysis. However, the association of EI with outcome may disappear after adjustment for clinical, haemodynamic and TTE variables such RV dyssynchrony [45, 46, 67, 69]. Overall, standard TTE assessment of the right heart should include several complementary indices of RV remodelling and systolic function, providing a cluster of direct and indirect evidence of RV adaptation or maladaptation to PH. Key variables exploring longitudinal function (TAPSE, S’, RVGLS	extsubscript{Freewall}, and RV dyssynchrony), global motion (RV-FAC, MPI), ventricular interaction, right atrium, pericardium and tricuspid valve should be assessed, highlighting the strengths and limitation of each of them according to the particular clinical situation.

**Evaluation of right ventricle-pulmonary arterial coupling**

Right ventricle-pulmonary arterial (RV-PA) coupling refers to the concept of RV contractility adaptation to the afterload conditions provided by pulmonary arteries. The only validated way to assess RV-PA coupling is the invasive generation of pressure-volume loops with conductance catheters at different preloads in order to determine RV end-systolic elastance (Ees = slope of the line joining the end-systolic pressure values acquired at different preloads) as a load-free determinant of contractility, and arterial elastance (Ea = end-systolic pressure / stroke volume), as an index aggregating both resistive and pulsatile components of afterload. RV-PA coupling can then be determined as the Ees/Ea ratio, with normal values between 1.5 and 2.0 [86].

In PH, RV volume increases when Ees/Ea is ≤20.8 [87] and RV-PA coupling was shown to be a main determinant of outcome [88]. As pressure-volume curves cannot be constructed with TTE, surrogates have been explored, such
TAPSE for Ees and sPAP for Ea. Although the assumptions that both terms hold for contractility and afterload, respectively, are far from perfect, TAPSE/sPAP was shown to correlate independently with Ees/Ea, and values <0.31 mm/mm Hg identified Ees/Ea <0.805 with good sensitivity and specificity [89]. Furthermore, trials showed a strong association between TAPSE/sPAP and outcomes in PH on left heart disease and PAH populations [89–91]. Of importance, TAPSE/sPAP appeared to be a stronger event predictor than RV systolic function variables such as TAPSE, RAA, S’ and MPI taken per se. Also, TAPSE/sPAP showed a clear pattern of distribution across the total PA compliance versus PVR curve, meaning that populations with a high TAPSE/sPAP value have high TAC and low PVR, and conversely. Of course, the above-described limitations of TAPSE taken in isolation remain true when associated with sPAP. Consequently, authors attempted to replace it by RVLS_global and RVLS_freeval and found RVLS/sPAP to be superior than TAPSE/sPAP to predict 1-year mortality in PH associated with chronic stable heart failure [92]. Like that of other experts in the field, the authors’ opinion is that TTE-evaluated RV-PA coupling allows a better understanding of RV adaptation to afterload and that TAPSE/sPAP is a “ready to use surrogate of RV to afterload coupling at the bedside” and should be routinely reported by sonographers [93].

Echocardiography for the follow-up of pulmonary hypertension

As PAH and other forms of precapillary PH such as CTEPH are progressive diseases and because response to therapies and interventions are not predictable on an individual basis, periodic risk stratification is of utmost importance in patients’ care [94]. For this purpose, current ESC/ERS guidelines recommend the use of multidimensional variables including TTE parameters (RAA and pericardial effusion) besides other modifiable factors [1]. This approach has been retrospectively validated in the Swedish PH registry [95], but further analyses of the German and French registries did not consider TTE for risk assessment, mainly because echo variables were not captured in these databases [5, 6]. Nevertheless, PAH and CTEPH outcomes remain closely related to changes in RV size and function on therapy [27, 37], which can be typically assessed by TTE.

Once medical therapy for PAH is established, sPAP does not change significantly enough to be reliably detected by TTE, but RV systolic function variables and size of the right cavities usually improve [37, 44]. As most RV-related TTE indices are afterload dependent, their changes reflect both treatment-induced afterload decrease and systolic function improvement. However, the proportion of RV function variation attributed to PVR change is quite small and RV function may still deteriorate in spite of decreased PVR in some patients, reflecting progressive RV failure and eventually poor outcome [37, 96].

Reverse remodelling of the right cavities (size reduction) on PH therapy affects both RA and RV. Because RA size is related to RV function [29], RA reverse remodelling is thought to reflect decreased RV filling pressure and volume overload, and hence improved RV systolic function. In patients on riociguat for PAH or CTEPH for 12 months, Marra et al. found that 31% of patients could recover normal RA size and Sano et al. showed that mid-term RA reverse remodelling (RAA decrease ≥15%) predicted long-term survival in PAH [30, 97]. At RV level, treatment-induced remodelling can be monitored by following RVEDA and RVESA. In their study, Sano et al. reported larger mid-term RVEDA and RVESA increases in patients with eventual events and excellent outcome in patients with reverse remodelling (RVEDA or RVESA decrease ≥15%) [97]. More recently, Badagliaca et al. showed that a score including RVEDA, LVEI and RAA reduction after 1 year of treatment independently predicted outcome in idiopathic PAH and improved prognostic models based on clinical and haemodynamic factors [96].

Following RVESRI change at 1 year also appeared to reflect RV adaptation vs maladaptation in PAH. Although a minority of patients (24%) had significantly changed RVESRI (>10%) on therapy, those with improvement had a good outcome and those with deterioration a poor prognosis. Of importance, RVESRI change seemed incremental to the REVEAL score for risk prediction [34].

Follow up of TTE indices of RV function on therapy is also of interest in PAH. For example, complete recovery of TAPSE (≥2 cm) at 1 year is an independent predictor of 3-year survival [98], and improvement of RVLS_freeval by ≥5% after 6 months independently predicts 4-year survival after adjustment for age, PAH cause and functional class [99].

Finally, following up pericardial effusion is also important in PAH because the emergence of a new pericardial effusion was recently found to be predictive of bad prognosis in two single centre studies [100, 101], whereas resolution pericardial effusion conferred a prognosis similar to no pericardial effusion at all and pericardial effusion persistence an even worse one than new pericardial effusion [101].

Echocardiographic screening for populations at high risk for PH

Several populations are at high risk of developing PH, including patients with connective tissue disease (scleroderma and scleroderma spectrum), congenital heart disease, human immunodeficiency virus (HIV), porto-pulmonary hypertension and relatives of patients with heritable PAH. Recommendations for screening modalities were reported at the 6th World Symposium for PH [15] and are endorsed by the Swiss Society for Pulmonary Hypertension. Most of them include TTE and are summarised hereafter.

Most data regarding screening for PAH in connective tissue diseases are based on patients with scleroderma [102], where the prevalence of PAH is ~10–12% (19% in patients with DLCO <60%). Screening is meaningful in scleroderma because PAH is one of the leading causes of death and outcome may improve with early PAH-specific therapy [103]. Multiple algorithms can be proposed: annual TTE [1], conditional TTE (DETECT algorithm [104]), and pulmonary function tests (FVC/DLCO ratio) associated with NTproBNP. If any of the tests is positive, right heart catheterisation should be undertaken. In congenital heart disease, PH is present by definition in patients with Eisenmenger Syndrome. In other cases, such
as persistent open systemic-to-pulmonary shunt or after defect correction, PH screening should be part of the regular follow-up TTE. Postoperative PAH screening is recommended after 3–6 months and then annually in patients with increased PVR at baseline [15].

In HIV, PH screening is recommended only in patients with risk factors such as female sex, intravenous drug or cocaine use, chronic hepatitis C infection, origin from high-prevalence countries, known Nef (negative regulatory factor) or Tat (transactivator of transcription) proteins and in US African-American patients [15].

PH screening with TTE is recommended for all patients with portal hypertension (0.5–5% prevalence) and in all patients before liver transplantation (prevalence ~10%). However, given the high incidence of hyperkinetic PH with liver disease, right heart catheterisation should be performed only if TRV is >3.4 m/s or if RA or RV enlargement is found [15].

Genetic screening in the French registry found PAH-associated mutations in 16.9% patients with sporadic PAH and in 89% of patients with a family history (heritable PAH) [105]. The risk of developing PAH being 14% for male and 42% for female mutation carriers [106], annual TTE and genetic counselling are recommended for all asymptomatic mutation carriers [15].

Finally, patients with hereditary haemorrhagic telangiectasia (HHT) have an increased risk of developing PH (TTE prevalence 4.23%). In most cases, PH is related to high-output heart failure, but PAH is possible and associated with poor survival [107]. TTE screening is recommended in all patients with HHT or family history of HHT with symptoms, heart failure or hepatic arteriovenous malformations [15].

**Conclusion**

Although right heart catheterisation remains unconditionally mandatory for a definite PH diagnosis, TTE can reliably detect abnormal haemodynamics and sPAP can be estimated with acceptable precision given adequate TRV envelope and experienced sonographers. SPAP, TRV and RAP should be reported separately and commented on if necessary. In addition, TTE can discriminate fairly well between pre- and postcapillary PH in many situations, avoiding unnecessary right heart catheterisation.

Although the main weakness of 2–D TTE remains its inability to explore the complex 3-D RV morphology, the assessment of modern direct and indirect indices of RV remodelling and systolic function enable a comprehensive view of RV adaptation to PH, helping clinicians to estimate the outcome of their patients and their response to therapy. In the future, 3-D echo may circumvent this limitation. Currently, 3-D echo is not widely available and cannot be considered as part of a routine examination of the RV because it needs expensive matrix-array transducers, dedicated software for post-processing and specific learning to avoid pitfalls such as sternal shadowing or incomplete RV volume acquisition. In experienced hands, however, it demonstrates good agreement with CMR, which is the gold standard regarding RV and RA volumes as well as RVEF in PH patients [108].

The advantages of 3-D echo will probably appear more and more evident with time, the authors guess that it will soon be part of the complex pathways of PH diagnosis and follow-up.

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