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ECHOCARDIOGRAPHY (JM GARDIN AND AH WALLER, SECTION EDITORS)

Echocardiography in Pulmonary Arterial Hypertension

Francesco Ferrara[1] · Xiao Zhou[2] · Luna Gargani[3] · Karina Wierzbowska-Drabik[4] · Olga Vriz[5] · Bahaa M. Fadel[5] · Anna Agnese Stanziola[6] · Jaroslaw Kasprzak[4] · Mani Vannan[7] · Eduardo Bossone[8]

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Abstract

Purpose of Review Pulmonary arterial hypertension (PAH) is a devastating disease which can result in right heart (RH) failure and death. Herein, we discuss the current clinical applications of echocardiography in PAH.

Recent Findings Advanced echocardiographic techniques (strain, strain rate, 2D-speckle tracking strain, and three-dimensional echocardiography) may reveal in the near future additional important insights into RH structure and function.

Summary Although right-heart catheterization is mandatory for a definitive diagnosis, echocardiography (resting and exercise) represents a key noninvasive imaging test on the diagnostic-prognostic-therapeutic PAH algorithm.

Keywords Echocardiography · Pulmonary arterial hypertension · Exercise Doppler echocardiography · Strain · Three-dimensional echocardiography

Introduction

Pulmonary hypertension (PH) is a hemodynamic and pathophysiologic condition defined as an increase in mean pulmonary artery pressure (mPAP) of ≥ 25 mmHg at rest as assessed by right-heart catheterization (RHC) [1, 2]. PH is currently categorized into 5 groups based on distinct pathogenic, clinical features, and prognostic implications. These groups include pulmonary arterial hypertension (PAH) and secondary forms due to left heart, lung, and thromboembolic diseases [3]. PAH, defined hemodynamically as pre-capillary PH, MPAP ≥25 mmHg, and pulmonary capillary wedge pressure

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✉ Eduardo Bossone
ebossone@hotmail.com

Francesco Ferrara
fferrara1975@gmail.com

Xiao Zhou
zhouxiaosmile@hotmail.com

Luna Gargani
lunagargani@gmail.com

Karina Wierzbowska-Drabik
wierzbowska@ptkardio.pl

Olga Vriz
olgavriz@yahoo.com

Bahaa M. Fadel
fadelbahaa@gmail.com

Anna Agnese Stanziola
annastanziola@libero.it

Jaroslaw Kasprzak
kebtkebt@gmail.com

Mani Vannan
mvannan2560@gmail.com

[1] Cardiology Division, "Cava de' Tirreni and Amalfi Coast" Hospital, Heart Department, University of Salerno, Salerno, Italy

[2] Department of Cardiology, Chinese PLA General Hospital, Beijing, China

[3] Institute of Clinical Physiology—C.N.R., Pisa, Italy

[4] Department of Cardiology, Bieganski Hospital, Medical University of Lodz, Lodz, Poland

[5] Heart Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

[6] Department of Respiratory Diseases, Monaldi Hospital, University "Federico II", Naples, Italy

[7] Department of Cardiovascular Imaging, Piedmont Heart Institute, Atlanta, GA, USA

[8] Division of Cardiology, A. Cardarelli Hospital, Via A. Cardarelli, 9, 80131 Naples, Italy

(PCWP) ≤ 15 mmHg, has a prevalence of 15–60 subjects per million population [1, 2]. The initial symptoms are often non-specific, typically induced by exertion including shortness of breath, fatigue, weakness, angina, and syncope. Thus, a high index of clinical suspicion by the treating physician/team is necessary in order to make a timely diagnosis and initiate appropriate early therapeutic interventions [1, 2]. In this scenario, transthoracic Doppler echocardiography (TTE) represents a key screening tool due to its combination of accuracy, availability, lower cost, and non-ionizing exam [4, 5].

Herein, we discuss the current clinical applications (diagnostic and prognostic) of standard TTE, exercise Doppler echocardiography (EDE), and advanced ultrasound techniques (strain, three-dimensional echocardiography) in PAH.

Standard Echocardiography

Among patients at risk for, or with overt PH, standard, TTE is usually used to non-invasively estimate pulmonary hemodynamics and to assess the impact of PH on the right heart (RH) structure and function [4–6]. In daily practice, the calculation of systolic pulmonary artery pressure (sPAP) is based on the simplified Bernoulli equation applied to the peak tricuspid regurgitation velocity (TRV) where PA systolic pressure = 4 $(TRV)^2$ + right atrial pressure (RAP), and RAP is usually estimated by the dimension and collapsibility index of the inferior vena cava in the subcostal view (Figs. 1 and 2) [6]. TRV should be obtained from multiple views, searching for the best quality envelope and maximal CW Doppler velocity, and avoiding over gain and artifacts (fringes) [4–6]. In case peak, TRV is technically difficult to measure (trivial or mild tricuspid regurgitation), agitated saline administered by intravenous injection may be used in order to improve the Doppler signal. Moreover, TRV may be significantly underestimated in PH patients with severe tricuspid regurgitation. For these reasons, other echocardiographic Doppler variables reflecting RH pressure overload should always be considered in the TTE assessment of PH (Figs. 1 and 2) [4–6].

The pulsed wave (PW) Doppler interrogation of the right ventricular outflow tract (RVOT) in PH usually reveals a shorter acceleration time (< 100 milliseconds), which reflects an abnormal mPAP (RVOT-AT/mPAP negative correlation). A "notched" (mid or late) pattern of the RVOT PW Doppler profile reflects an increase in pulmonary vascular resistance (PVR) and is almost always present in PAH patients. An elevated ratio of peak mitral inflow to early diastolic annular velocity (E/e'), along with an increase in left atrial (LA) volume, may be useful to predict an increase of LA pressure, ruling in de facto a left heart etiology of PH [4–6]. However, it is important to point out that noninvasive TTE assessment of pulmonary pressures are generally accurate, but not precise, (Bland and Altman plots showed no bias but large limits of agreement) as compared to RHC values, which are considered to be the gold standard [7]. For this reason, TTE may be valid for population studies but cannot be used for the individual diagnosis of PH [7]. Furthermore, TTE, along with transesophageal echocardiography (TEE), can be helpful to identify intracardiac shunts (i.e., ventricular septal defect (VSD) or atrial septal defect (ASD)) and/or extracardiac shunts (e.g., patent ductus arteriosus (PDA)). In selected cases, cardiac magnetic resonance imaging (CMR) and/or cardiac-computed tomography (CT) may be requested in order to better detail the anatomic and functional characteristics of a cardiac congenital defect (Fig. 2).

Overall, TTE assessment of the right heart in PAH should include several complementary parameters of RH structure and function, providing direct and indirect signs of RH overload [4–6]. In particular, the assessment of RV function by standard TTE is based on key parameters exploring RV longitudinal motion (tricuspid annular plane systolic excursion (TAPSE) and RV tissue Doppler imaging (TDI) peak s')) and transverse motion (RV functional area change (FAC)) (Fig. 1) [6]. Table 2 reports the key TTE indices and signs for evaluation of patients

Fig. 1 Severe pulmonary arterial hypertension associated with mixed connective tissue disease in a 29-year-old woman in combination therapy with oral sildenafil + macitentan, prior to (panels **a**–**f**) and after initiation of epoprostenol therapy (**g**) for clinical and functional deterioration (WHO class III/IV). **a** 12-lead ECG showing sinus rhythm 75 beats per minute with right-axis deviation, accentuated P wave in lead II, V1 R wave predominance (R > S) in V1 with poor R wave progression in precordial leads, with V1–V3 ST depression due to right ventricular hypertrophy. **b** Reduced right ventricular longitudinal function as demonstrated by a reduced tricuspid annulus plane systolic excursion (TAPSE) of 14 mm. **c** Reduced right ventricular longitudinal function as demonstrated by a reduced RV S'-right ventricular systolic velocity of tricuspid annulus of 8 cm/s. **d** Enlarged end-diastolic areas of right ventricular inflow tract (25.1 cm2) and the right atrium (18.9 cm2). Large end-systolic area of the right ventricle (20.9 cm2) corresponds with low fractional area change FAC% of 16% (normal > 35%). **e** sPAP-systolic pulmonary artery pressure calculated from tricuspid regurgitation spectrum is 92 mmHg (estimated right atrial pressure of 8 mmHg). mPAP-mean pulmonary artery pressure can also be estimated from the mean transtricuspid systolic gradient, producing a value of 49 + 8 = 57 mmHg. Note late peaking of regurgitant flow typical for pulmonary hypertension. **f** Right ventricular index of myocardial performance (RIMP) by pulsed wave Doppler - tricuspid closure-to-opening time is 484 ms, with short right ventricular ejection time of 311 ms producing abnormally high RIMP = 0.56 (upper normal 0.43). Acceleration of flow in the right ventricular outflow tract is abnormally short. **g** Anteroposterior chest X-ray showing wide cardiac silhouette with enlarged pulmonary arteries and modest peripheral vascular attenuation note epoprostenol infusion catheter inserted in the subclavian vein. Right-heart catheterization, performed a day later, reconfirmed severe PAH with mPAP of 52 mmHg, with good agreement between echocardiographic and invasive data (see Table 1). After 5 months of intravenous treatment, the patient stabilized in class II with an increase in 6-min walk distance up to 570 m and lower NT-proBNP of 1573 pg/ml. Echocardiography confirmed that tricuspid regurgitation returned to moderate along with improvement in RV function documented by a TAPSE of 17 mm and RVS' of 10 cm/s, without significant change in Doppler echo estimates of pulmonary pressures (see Table 1)

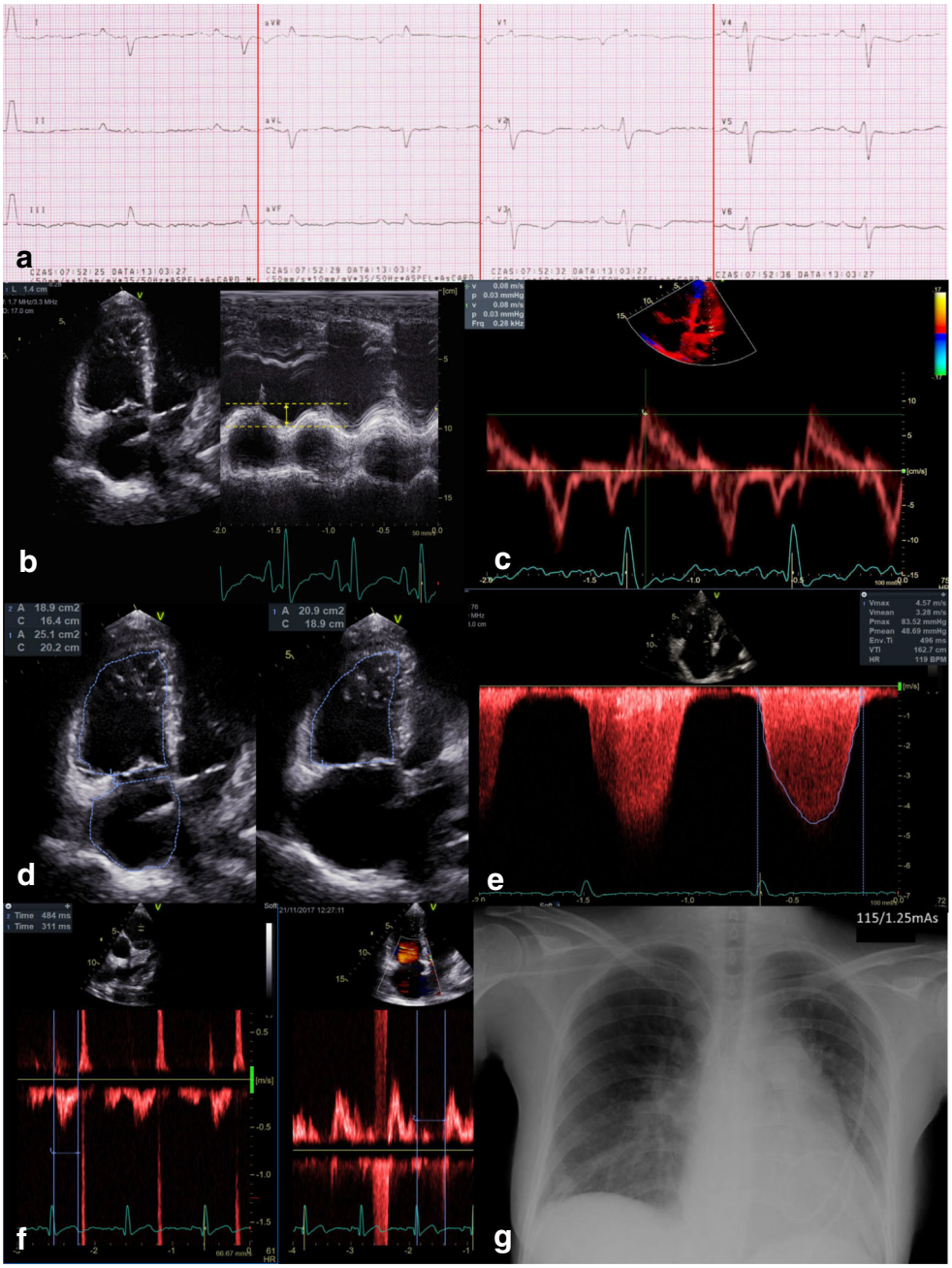
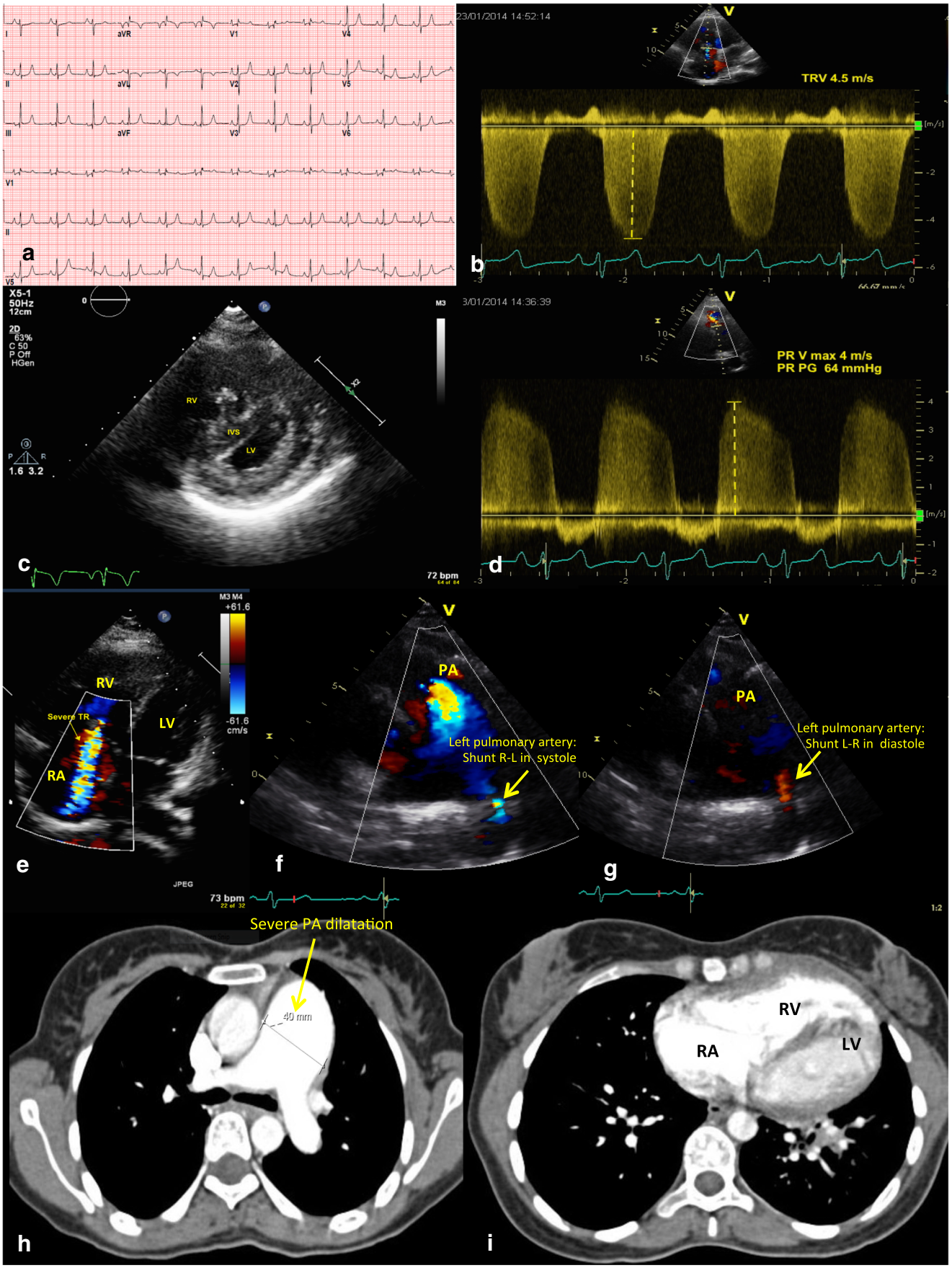


Table 1 Noninvasive and invasive parameters of pulmonary circulation

Parameter	Echocardiographic data prior to epoprostenol initiation	Right heart catheterization measurements on 11/22/2017	Echocardiographic data measured on epoprostenol infusion 03/27/2018
sPAP	92 mmHg	78 mmHg	86 mmHg
mPAP	48 mmHg (AT 68ms)	52 mmHg	40 mmHg (AcT 82 ms)
dPAP	28 mmHg	36 mmHg	32 mmHg
RAP from IVC assessment	8 mmHg	11 mmHg	3 mmHg
PVR (Wood units)	9.2 WU	8.3 WU	–
Proximal RVOT diameter	35 mm	–	34 mm
RVIT basal diameter	49 mm	–	48 mm
TAPSE	14 mm	–	17 mm
RV S'	8 cm/s	–	10 cm/s


a
b
TRV 4.5 m/s
c
RV
IVS
LV
d
PR V max 4 m/s
PR PG 64 mmHg
e
RV
LV
RA
Severe TR
f
PA
Left pulmonary artery:
Shunt R-L in systole
g
PA
Left pulmonary artery:
Shunt L-R in diastole
Severe PA dilatation
40 mm
h
i
RV
RA
LV

◀ **Fig. 2** Pulmonary arterial hypertension associated with congenital heart disease (patent ductus arteriosus (PDA), Eisenmenger syndrome and secondary polycythemia) in a 37-year-old woman (WHO class II) with a systemic blood pressure of 80/50 mmHg, heart rate of 90 beats/min without signs of fluid retention, such as pulmonary congestion or ankle swelling. **a** 12-lead ECG showing sinus rhythm 65 beats per minute with right axis deviation, accentuated P wave in lead II due to right atrial dilatation. **b** Severe increase of sPAP (systolic pulmonary artery pressure) = 110 mmHg calculated from tricuspid regurgitation velocity ($4TRV^2$ + right atrial pressure) (100 mmHg + estimated right atrial pressure of 10 mmHg) [2]. **c** Left ventricular (LV) D-shape with flattened interventricular septum (IVS) due right-heart pressure/volume overload. **d** Severe increase of mPAP (mean pulmonary artery pressure) = 74 mmHg, estimated from pulmonary regurgitation (PR) velocity systolic (4 PR peak $velocity^2$ + right atrial pressure) [53]. **e** Severe color tricuspid regurgitation (TR) with significant right ventricular (RV) and right atrial (RA) dilatation. **f** and **g** Patent ductus arteriosus with evident color bidirectional shunt (right to left in systole and left to right in diastole). G Computed tomography (CT) shows severe pulmonary artery (PA) dilatation = 40 mm. H CT shows severe RV and RA dilatation associated with evident RV free wall hypertrophy

with a clinical suspicion of PH, highlighting cutoff values, strengths, limitations, and clinical applications of each [6–13]. The current European Society of Cardiology (ESC) PH guidelines suggest grading the probability of resting PH based on TRV plus the presence of additional TTE signs and parameters of RH volume/pressure overload [2].

Stress Echocardiography

In the last few years, stress echocardiography has moved from being an imaging tool principally devoted to the detection of ischemic heart disease to many additional applications, including valvular heart disease and evaluation of the right heart-pulmonary circulation unit [14••, 15]. The versatility of EDE makes this examination very appealing for the evaluation not only of left ventricular structure, function, and wall motion abnormalities but also for a thorough non-invasive hemodynamic assessment [16]. The possibility to combine a morphological, functional, and hemodynamic evaluations of both the left and the right heart in a single non-invasive and non-ionizing examination confers unique potential upon EDE for the diagnosis and prognosis of several cardiac and respiratory conditions, including ischemic and valvular heart diseases, chronic heart failure, thromboembolic disease, lung disease, and PAH [14••, 15, 16]. Several questions remain however to be answered, and consequently, the concept of exercise evaluation in PH has not been endorsed by the latest ESC guidelines, even when PA pressures, resistance, etc. are estimated by right-heart catheterization (RHC), due to insufficient supportive data [2]. More recently, exercise PH has been defined as the presence of resting mPAP < 25 mmHg and mPAP > 30 mmHg during exercise with total pulmonary resistance > 3 Wood units, during RHC [17]. Recently, Bland and Altman analysis of sPAP, measured with TRV by EDE vs RHC during exercise, shows only minimal bias with acceptable accuracy but limits of agreement were broad indicating limited precision, mostly among the subset of patients with poor quality TR Doppler signals [18, 19•].

EDE has been tested in many different studies to see whether the development of increased values of sPAP with exercise could represent an early phase preceding overt PAH. Of course, this algorithm can be only applied to those conditions predisposing to the development of PAH—mainly connective tissue disease, and in particular, systemic sclerosis (SS)—and in family members of patients with heritable PAH. In the latter group, an abnormal increase of pulmonary pressure in response to exercise has been detected, compared to healthy control subjects [20]. This behavior was also associated with an increased prevalence of bone morphogenetic protein receptor type 2 mutations, underlining a role as a potential additional risk factor for the development of PAH. Of interest, in a large German family with heritable PAH, during the follow-up period, only those family members who had shown both bone morphogenetic protein receptor type 2 mutations and a hypertensive pulmonary pressure response during exercise subsequently developed overt PAH [21].

About 5–8% of systemic sclerosis patients may develop PAH according to most recent studies [22]. A higher number of patients may have PH due to interstitial lung disease and to left heart involvement, and often, PH in these patients accounts for multiple and partially overlapping mechanisms of pre- and post-capillary etiologies [23]. The percentage of systemic sclerosis (SSc) patients who show high sPAP values during exercise is around 50%, a percentage that clearly overestimates the subset of SSc patients who will develop PAH [24–27].

In this regard, it should be highlighted that pulmonary artery pressure is dependent not only on pulmonary vascular resistance (PVR), which is abnormally increased in PAH, but also on left atrial pressure and cardiac output (CO), as shown in both healthy [28] and in SSc subjects [24, 25]. It is therefore important to assess and integrate the different components that may influence exercise sPAP, to better understand the contribution of each single factor. It has been suggested that an increase in mPAP as a function of cardiac output (CO), with reported mPAP/CO slope > 3 mmHg·min·L-1, as a potential diagnostic EDE criterion for exercise-induced PH [29].

Moreover, EDE may be a useful tool for prognostic assessment in PH patients. In this regard, an exercise-induced sPAP increase may indicate RV contractile reserve and predicts survival in patients with severe PH associated with substantial resting RV dysfunction [30]. However, it should be underlined that, notwithstanding the very promising role and stimulating results, EDE has no clearly defined and unanimously accepted role in daily clinical practice, where the examination is usually performed to better clarify otherwise unexplained dyspnea on

Table 2 Key echocardiographic Doppler parameters for evaluation of patients with clinical suspicion of PAH

Key echo-Doppler indices	Cutoff values	Pitfalls and remarks	Ref.	Figure
Pulmonary hemodynamics				
sPAP (mmHg) $4 \times TRV^2 + RAP$	TRV > 2.8–2.9 m/s or not measurable sPAP > 34–36 mmHg	Sweep velocity should be at least 100 mm/s measuring only the well-defined dense spectral profile, avoiding artifacts (fringes), and overestimation.	6, 8	1 E 2 B
RAP (mmHg) IVC diameter and collapsibility	< 2.1 cm, collapse > 50%: RAP = 3–5 mmHg		6	–
mPAP (mmHg) (0.6 × sPAP +2) + RAP and/or 4 (PR peak velocity) ^{2} + RAP and/or 90–(0.62 × AT) + RAP (Mahan-Dabestani formula)	≥ 25 mmHg	The PR signal may be poor or parallel alignment of the Doppler signal may not be possible.	6	2 D
PVR TRV/VTI $_{RVOT}$ (cm) × 10 + 0.16	A normal PVR is < 1.5Wood units Significant increase of PVR is > 3 Wood units (240 dynes $ cm/s2)	Methods for estimating PVR are less well validated. Should not be used as a substitute for the invasive evaluation of PVR. The accuracy may be low in patients with markedly elevated PVR	6	–
AT_{RVOT}	< 100 m/s	Heart rate should be in the normal range of 60 to < 100 beats/min.	6, 9	1 F
FVE_{RVOT}	Mid-systolic notching	Lack of data in wide population of PH patients; not specific for thromboembolic diseases.	6	–
E/e' LAP = 1.9 + 1.24 E/e'	e' as mean between lateral and septal annular values average E/e'ratio > 10 LAP > 15 mmHg	Angle-dependent; proper attention to the location of the sample size. Left atrial volume indexed to BSA > 31 mL/m2 increases the accuracy for estimation of LAP	10	–
RV function				
TAPSE	< 16 mm	Angle- and load-dependent; not fully representative of RV global function.	6, 11	1 B
RV FAC 100 × (EDA–ESA)/EDA	< 35%	Poorly reproducible in case of sub-optimal image quality	6	1 D
RIMP (IVCT + IVRT)/ET	> 0.43 by PW-Doppler > 0.55 by TDI	Reproducible. Avoids geometric assumptions of complex RV geometry. Prognostic value. Varies with pressure and volume status. Unreliable when RA pressure is elevated. Cannot be used in atrial fibrillation	6	1 F
RV S' TDI Tricuspid annulus	< 10 cm/s	Angle-dependent; not fully representative of RV global function.	6	1 C
RV-PV coupling				
TAPSE/sPAP ratio	< 0.5	Conceptually, the lower the ratio, the worse the association of PH and RV dysfunction.	11	–
Indirect 2D signs				
RV dilatation	RV basal diameter at end-diastole > 42 mm RV/LV ratio > 1	Generally, all dimensional right-heart measurements are significantly lower in women. Should use measurements indexed to BSA.	6, 12	1 D
RV hypertrophy	RV subcostal wall thickness > 0.5 cm	Poorly reproducible in case of sub-optimal image quality	6	–
RA volume dilatation	> 36 mL/m2 in men > 31 mL/m2 in women	Measurements should preferably be indexed to BSA using single-plane area-length (A-L) technique. May be significantly underestimated compared to 3DE and MRI	12, 13	1 D
RVOT dilatation	RVOT PLAX proximal diameter > 3.3 cm		6, 12	–
PA dilatation	PA diameter > 25 mm		6, 12	–
LV eccentricity index LV-D shape	ratio between the LV anteroposterior and the septolateral dimensions > 1 in systole ± diastole		6	2 C
Pericardial effusion	–	Prognostic implications in PAH	2	–

Table 2 (continued)

Key echo-Doppler indices	Cutoff values	Pitfalls and remarks	Ref.	Figure
Nonconventional echo parameters of RV function				
RV LPSS	≥ − 19%	Vendor dependent		
Prognostic value, good sensitivity for estimate of RV function	6.12	3 B		
3D RV EF 100 × (EDV–ESV)/EDV	< 45%	Independent of geometric assumptions but dependent on image quality. Good correlation with RV EF by MRI. Lack of data in wide population and requires offline analysis and experience	6, 12	3 C

2D two-dimensional, *3D* three-dimensional, *3DE* three-dimensional echocardiography, *AT* acceleration time by PW Doppler, *BSA* body surface area, *E* mitral inflow E velocity as measured by PW Doppler, *e'* early diastolic velocity of the mitral annulus as measured by TDI, *ED* end diastole, *EDA* End-diastolic area, *EDV* end-diastolic volume, *EF* ejection fraction, *ESA* end-systolic area, *ESV* end-systolic volume, *ET* ejection time, *FAC* fractional area change, *FVE* flow velocity envelope *IVC* inférior vena cava, *IVCT* isovolumic contraction time, *IVRT* isovolumic relaxation time, *LAP* left atrial pressure, *LAVi* left atrial volume index, *LPSS* longitudinal peak systolic strain, *LV* left ventricle, *mPAP* mean pulmonary artery pressure, *MRI* magnetic resonance imaging, *sPAP* systolic pulmonary artery pressure, *PA* pulmonary artery, *PRV* peak pulmonary regurgitation velocity, *PLAX* parasternal long-axis, *PV* pulmonary vascular, *PVR* pulmonary vascular resistance, *PW* pulsed-wave, *RA* right atrium, *RAP* right atrial pressure, *RIMP* right ventricular index of myocardial performance, *RV* right ventricle, *RVOT* right ventricular outflow tract, *TAPSE* tricuspid annular plane systolic excursion (M-mode), *TDI* tissue Doppler imaging, *TRV* tricuspid regurgitation peak velocity, *VTI* velocity-time integral

exertion. Remaining challenges include proving the feasibility and reproducibility of these tests in clinical practice and exploring the full spectrum of pulmonary pressure—CO or pulmonary pressure—cardiac index slopes among healthy subjects and patient with various cardiorespiratory diseases [16, 31••].

Advanced Echocardiographic Techniques

The complex geometry and shape of the right heart (RH) may affect the ability of standard TTE to accurately quantify RH structure and function [6, 12]. The exponential development and implementation of advanced echocardiographic techniques (2D-speckle tracking strain (STE), strain rate, and three-dimensional echocardiography (3DE)) in various diseases states may result in a more comprehensive evaluation of the RH (Fig. 3) [32].

Strain

Strain has the advantage of being independent of angle, less dependent to load, and able to accurately measure regional myocardial deformation. Strain measurements should preferably be interpreted with the same machine and software or versus vendor-specific reference values, because of small but statistically significant variation among vendors. On the other hand, intra- and inter-observer variabilities in strain values, obtained from good-quality images, were generally acceptable. RV longitudinal strain correlates well with gold standard cardiac magnetic resonance (CMR)—derived RV ejection fraction (EF) [33]. In the setting of PH, conventional indices of RV systolic function, including RV ejection fraction (EF), may be normal despite abnormal RV strain. In this regard, in PAH patients, RV strain may detect silent RV dysfunction early in the disease course and may also be a marker of occult RV systolic dysfunction when all conventional indices are normal [34, 35]. Furthermore, an RV longitudinal peak systolic strain < 19% may be an even more powerful and incremental predictor of clinical outcomes in different PH etiologies in the setting of reduced RV systolic function [36–38]. Recently, two right atrial (RA) myocardial mechanics studies using 2D-STE demonstrated RA deformation damage in PH patients, implying an additive prognostic value [39, 40].

Three-Dimensional Echocardiography

3DE has demonstrated superior test-retest reproducibility compared with conventional 2D TDE and better agreement with CMR (gold standard) in the evaluation of RA volumes, RV volumes, and ejection fraction (Fig. 3) [41–45]. In experienced echo laboratories, 3DE may be implemented to

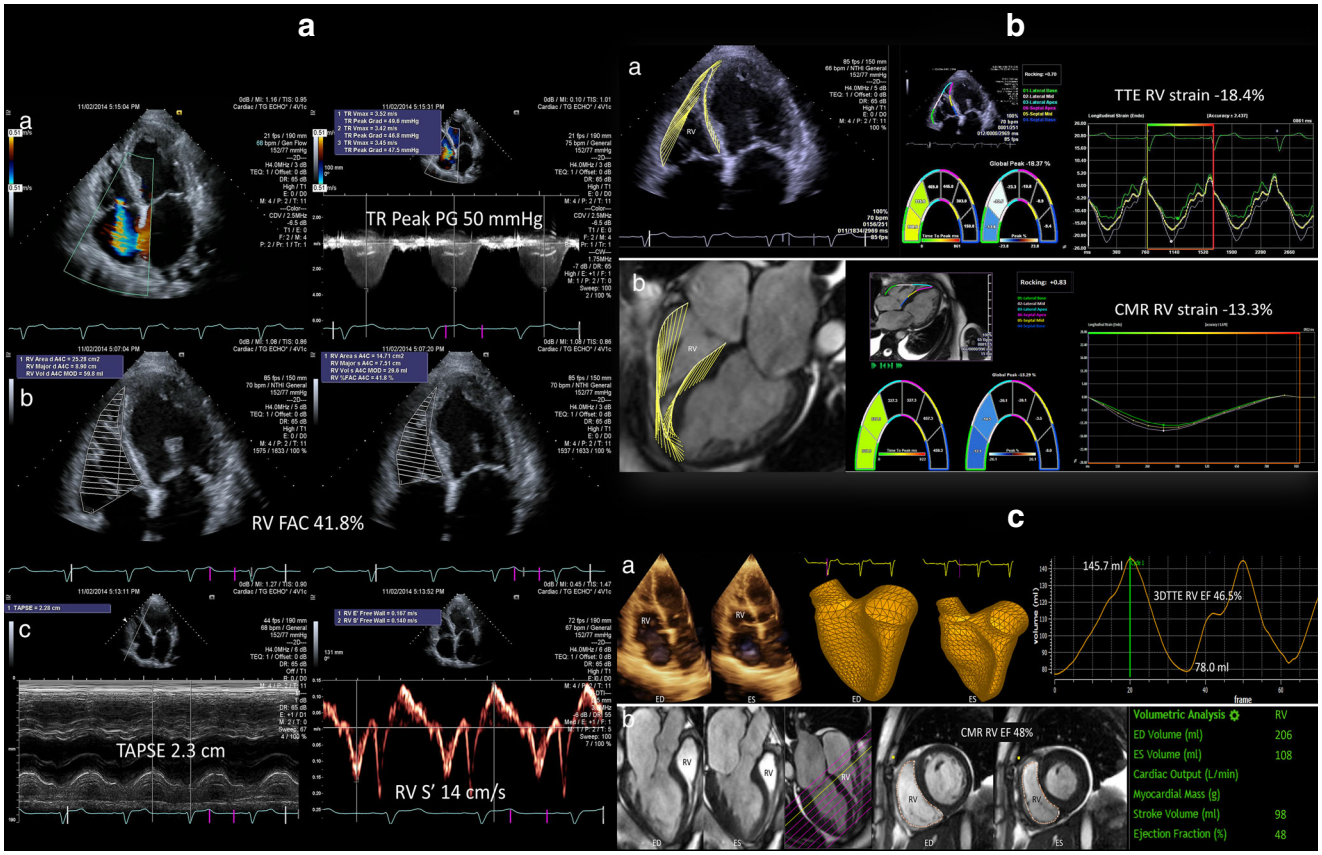


Fig. 3 72-year-old lady with long-standing asthma/COPD presented with increasing dyspnea, orthopnea, and ankle swelling. Left ventricular size and EF are normal (65%). **a** Findings from 2D/Doppler of the right heart. In (a), color-flow Doppler shows moderate TR and TR peak gradient of 50 mmHg. Calculated sPAP based on RA pressure estimate of 15 mmHg (based on dilated non-collapsing IVC) was ~65 mmHg, consistent with markedly elevated sPAP. (b) and (c) shows 2D indices of RV function, with normal FAC, TAPSE, and RV S'. **b** 2D RV strain using echo speckle-tracking in (a**)** and feature-tracking in CMR; In (b**),** 2D free-wall strain in 2D Echo and CMR are both reduced. The lower limit of 2D RV free wall strain is − 24%, and this is also currently used for CMR since there is no consensus on what is the cutoff for abnormal in CMR using a feature-tracking algorithm. **c** RV EF by 3DE and CMR. In (a**),** real-time 3DE of the RV in ED and ES and the automatically modeled RV in ED and Es are shown, from which the RV EDV, ESV, and EF are computed. RVEF is normal. In (b**),** CMR from the same patient shows similar data as 3D TTE, and the RV EF is normal and comparable to that obtained from 3D Echo

comprehensively investigate morpho-functional adaptations to pressure and/or volume overload among several cardiorespiratory conditions [41]. However, the "real" impact on the diagnostic-prognostic–therapeutic pathway in PAH remains to be explored in future studies [42, 44]. 2D and 3DE may generally suffice to comprehensively assess RV systolic function and strain, but when acoustic windows are suboptimal, CMR should be considered to obtain RV EF and strain (Fig. 3).

Echocardiography and Prognosis in PAH

PAH is a devastating disease characterized by progressive remodeling of the distal pulmonary arteries and elevated PVR, leading to RH failure and death [1, 2]. It is therefore essential to accurately monitor disease progression, estimate prognosis, and guide optimal clinical management. Thus, a comprehensive multiparametric prognostic assessment is required, including clinical symptoms and signs, functional capacity, cardiopulmonary testing, biomarkers, imaging indices, and hemodynamics [2, 46, 47]. In this regard, the presence of pericardial effusion, enlarged right atrial area and/or volume, and decreased TAPSE may provide important additional prognostic information in PAH patients [2].

Conclusion

Although RHC remains a "conditio sine qua non" for a definitive PAH diagnosis, echocardiography represents an essential step in the diagnostic algorithm. Furthermore, it is a useful tool to assess prognosis and guide therapeutic interventions. In the near future, the routine clinical implementation of EDE and advanced echocardiography techniques may provide important insights into the structure and function of the right heart-pulmonary circulation unit.

Compliance with Ethical Standards

Conflict of Interest Francesco Ferrara, Xiao Zhou, Karina Wierzbowska-Drabik, Olga Vriz, Bahaa M. Fadel, Anna Agnese Stanziola, Jaroslaw Kasprzak, Mani Vannan, and Eduardo Bossone declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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