Right Heart Stress Echocardiography

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The behavior of the right side of the heart during stress has been underemphasized and sparsely investigated by cardiologists and pneumologists. Reasons vary, but the right ventricle has traditionally been considered a passive conduit between the venous system and the lungs largely because of early animal experiments showing no increase of central venous pressure after the free wall of the right ventricle had been destroyed [1–3]. In addition, echocardiography of the right heart is less well standardized [4] as imaging of the left ventricle. Recent pathophysiological, clinical, and prognostic data have defined an important role for the right ventricle in many conditions, including ischemic heart disease and heart failure. Given that the right ventricle and the left ventricle share a common septum, have an overlapping blood supply, and are bound together by the pericardium, changes induced by myocardial ischemia and/or heart failure are reflected in pulmonary hemodynamics and right ventricular function [5]. Modern Doppler echocardiography allows a systematic evaluation of five key aspects of cardiopulmonary pathophysiology during stress: segmental right ventricular function; global right ventricular longitudinal function; coronary flow reserve in the posterior descending of the right coronary artery; indices of pulmonary hemodynamics, namely, pulmonary artery systolic pressure, pulmonary velocity time integrals, and pulmonary vascular resistances; and extravascular lung water in the lung, mirroring the distress of the alveolar–capillary membrane. Technical improvements were also matched by a greater understanding of the complexity and the clinical relevance of the adaptation of the right heart (functionally including pulmonary circulation and lung alveolar–capillary membrane) in several pathological conditions, from coronary artery disease to heart failure [5]. In many situations, it is not possible to fully understand heart disease if we do not look at the right heart and pulmonary stress hemodynamics.

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8.1 Regional Right Ventricular Function in Coronary Artery Disease

The right ventricle is less vulnerable to ischemia than the left ventricle for several anatomic and functional factors, including the rich system of Thebesian veins in the right ventricle (allowing perfusion of the papillary muscles of the right ventricle), the dual anatomic supply system (in which the left coronary branches perfuse almost one-third of the right ventricle), the rapid development of collateral vessels to the right ventricle given the lower resistance that favors a left-to-right transcoronary pressure gradient, and the relatively thin walls and lower stroke work and wall tension (with lower oxygen demand and less vulnerability to transmural perfusion heterogeneity during stress) [5]. Blood supply of the right ventricle is characterized by a rich collateral system and a perfusion during diastole and systole. The perfusion rate of the right ventricle at rest is 50 ml min^{-1} 100 g^{-1}, much lower than that of the left ventricle (120 ml min^{-1} 100 g^{-1}). However, right ventricular ischemia may occur during stress and is difficult to recognize, if not specifically looked for. It requires additional projections (subcostal view) to image RV ischemia and more experience to recognize it.

The evaluation of right ventricular size and function is made difficult by the retrosternal position, complex geometry, and heavy trabeculation of the right ventricle, which also partially overlaps with the silhouettes of the left ventricle. There is not one single echocardiographic view in which the complete right ventricle can be seen. For purposes of echocardiographic analysis, the right ventricle can be divided into four segments [6]: anterior wall, lateral wall, inferior wall, and wall of the outflow tract (Fig. 8.1).

Schematically, the right ventricle is composed of an inflow and an outflow tract. The former has an anterior and an inferior (also named diaphragmatic) wall. The inferior wall lies over the diaphragm. The acute margin of the heart is formed by the external edge of the right ventricle. From an echocardiographic perspective, it is called the lateral wall and it borders anteriorly with the anterior wall and posteriorly with the inferior wall. The outflow portion of the right ventricle is limited upward by the pulmonary valve and downward by the crista supraventricularis, the septal papillary muscle (Luschka's muscle), the anterior leaflet of the tricuspid valve, and the septal band. The outflow tract has an anterior wall (echocardiographically named wall of the outflow tract) and a posterior wall that is part of the interventricular septum. The inferior wall is irrigated by the marginal branches and the posterior descending artery, the lateral wall by the marginal branches, and the outflow tract and the anterior wall by the posterior and anterior descending artery. Although the interventricular septum is part of the right ventricle, the evaluation of its function is usually included in the analysis of the left ventricle. In right-dominant hearts (85 % of cases), the right ventricle is nourished by the right coronary artery. The development of contraction abnormalities of the right ventricle (more often lateral and inferior segments) is a hallmark of coronary artery involvement by coronary vasospasm in ergonovine-induced [7] or tight stenosis in dobutamine-induced ischemia [8, 9] (Table 8.1). These alterations appear later than in the left ventricle [10], are best

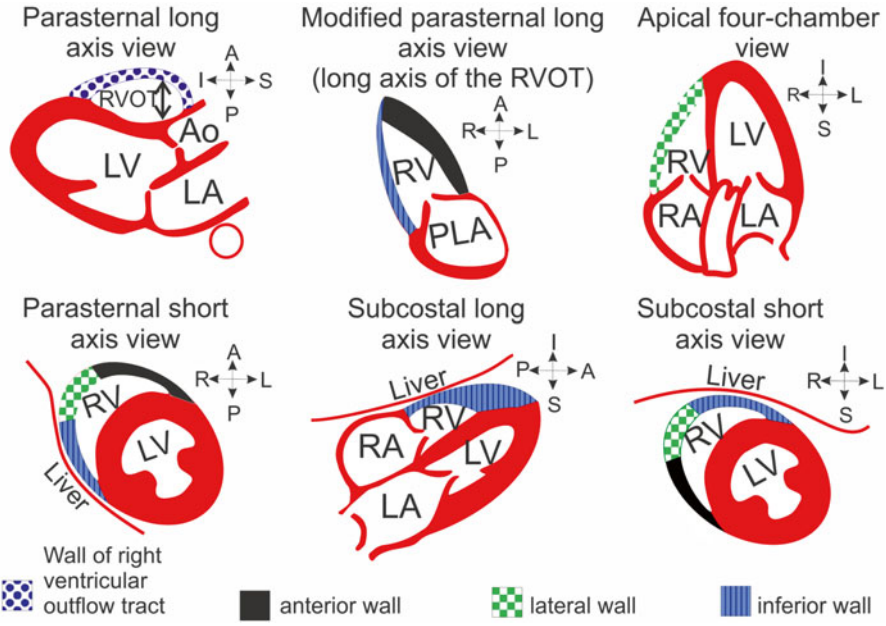

Fig. 8.1 Systematic approach to the right ventricular function during stress echocardiography. *A* anterior, *AO* aorta, *I* inferior, *L* left, *LA* left atrium, *LV* left ventricle, *P* posterior, *R* right, *RA* right atrium, *RV* right ventricle, *RVOT* right ventricular outflow tract, *S* superior

Table 8.1 Differences between right and left ventricular ischemia during stress echocardiography

	Right	Left
Prevalence in RCA disease	40–60 %	70–90 %
Prevalence in LCA disease	0–20 %	70–90 %
ECG abnormalities	Right precordial leads	Standard leads
Isolated presentation	Rare	Frequent
Feasibility to be detected	60–80 %	90–98 %
Prognostic value	Additive to left	Established

recognized from a modified parasternal and subcostal long-axis view (Fig. 8.2), and can be accompanied by severe right ventricular and right atrial enlargement [8, 11], sometimes with reduction of the tricuspid annular plane systolic excursion (TAPSE) with *M*-mode, which is an index of global longitudinal right ventricular function.

Rest or stress-induced right ventricular enlargement is not necessarily due to coronary artery disease but can be due to other conditions such as stress-induced pulmonary hypertension which may nevertheless be of prognostic significance. Isolated right ventricular ischemia occurs in 2 % of patients with right coronary artery stenosis when assessed by wall motion abnormalities [11] but increases to 5–10 % if assessed by failure of TAPSE to increase >2 mm [12] or other indices of

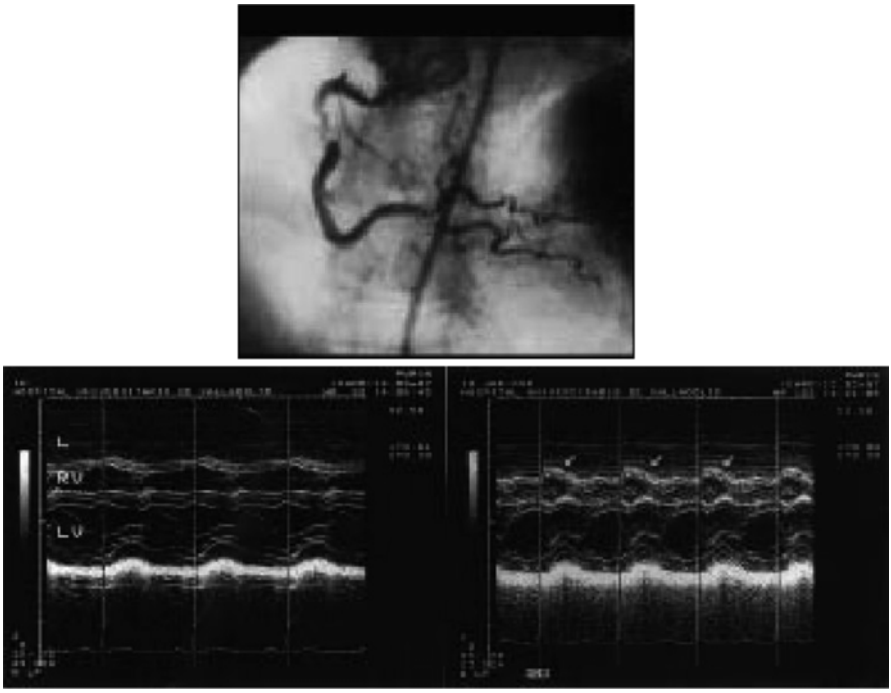

Fig. 8.2 *M*-mode study from the subcostal window. Resting exam (*left*) shows normal right ventricular wall motion. During dobutamine infusion (*right*), dyskinesis of the inferior wall of the right ventricle is clearly seen (*arrows*). *Vertical lines* correspond to ventricular systole. *L* liver, *LV* left ventricle, *RV* right ventricle (By courtesy of Alberto San Roman et al., Ref. [10])

RV longitudinal function [11]. Right ventricular dysfunction is found in 20 % of patients with concomitant inferior wall ischemia, in whom it contributes to a negative prognostic outlook [11].

8.2 Global Right Ventricular Function

The global inotropic reserve of the right ventricle can be measured as the increase in ejection fraction, or in fractional area change, or in a simpler and at least equally accurate way as augmented descent of the right ventricular base or TAPSE. The latter index of global right ventricular function can be calculated from the apical 4-chamber view and 2D-targeted *M*-mode tracings (Fig. 8.2) by recording the free wall long-axis amplitude of movement (normally 15–20 mm). A good relationship has been reported between TAPSE and the right ventricular ejection function measured by radionuclide ventriculography in a manner independent of geometric assumptions [13, 14]. Conceptually, TAPSE (or, if available, peak systolic S wave velocity of Doppler tissue imaging of the lateral tricuspid annular motion) assesses longitudinal function of the right ventricle in the same way as MAPSE (mitral

annular plane systolic excursion) by simple *M*-mode or myocardial velocity imaging does of the left ventricle [15]. The assessment of TAPSE avoids the approximation, mistakes, and computational burden inherent to the calculation of ejection fraction in the right ventricle, whose crescentic and irregular shape eludes any geometric modeling [16], although real-time 3D echocardiography has potential to solve or at least limit this problem. Moreover, its simplicity makes it easy to calculate and translates into a very low-intra- and interobserver variability even when measured by untrained readers during stress [17], an important issue when searching for end points in clinical trials. The indices of right ventricular function all increase significantly during exercise stress in healthy subjects, but their increase is blunted in pulmonary hypertension [18] or severe dilated cardiomyopathy with RV involvement [19, 20]. Interestingly, the right ventricular contractile reserve is preserved in chronic mountain sickness in spite of reduced resting RV function, suggesting that the lower resting values may represent a physiologic adaptation to chronic hypoxic conditions rather than impaired RV function [21].

8.3 Coronary Flow Reserve of the Right Coronary Artery

Stress testing of coronary flow reserve has now become a clinical reality with last-generation, fast, high-dose vasodilatory stress echocardiography coupled with second harmonic imaging technology and pulsed Doppler of the middistal left anterior descending coronary artery [22, 23]. Under normal conditions, in the absence of stenosis, coronary blood flow can increase at least threefold over resting values when hyperemia is induced pharmacologically, for instance, with administration of exogenous adenosine or dipyridamole, which accumulates endogenous adenosine. Coronary flow reserve is the capacity of the coronary circulation to dilate and can be expressed by the difference between the hyperemic flow and the resting flow curve. This pathophysiological concept recently entered the stress echocardiography laboratory, and the combined assessment of regional wall motion by 2D echocardiography and pulsed Doppler imaging of the left anterior descending coronary artery is the recommended state-of-the-art stress echocardiography protocol in the latest recommendations (2008) of the European Association of Echocardiography [24]. More recently, the posterior descending artery of the right coronary artery has been consistently imaged, with a success rate around 75 % [25, 26], usually from a modified apical 2-chamber view with counterclockwise rotation and anterior angulations of the probe [27] (Fig. 8.3). The information of right coronary artery flow reserve is derived as the ratio of peak diastolic flow velocity during stress over rest. A concordant reduction in both left anterior descending and posterior descending arteries is associated with a worse prognosis than a reduction in either one coronary artery – both in coronary artery disease [28] and in dilated cardiomyopathy patients [29]. In addition, a reduction in right coronary artery reserve is associated with conditions of right ventricular pressure overload and may help in the functional characterization, for instance, of congenital heart disease patients [30].

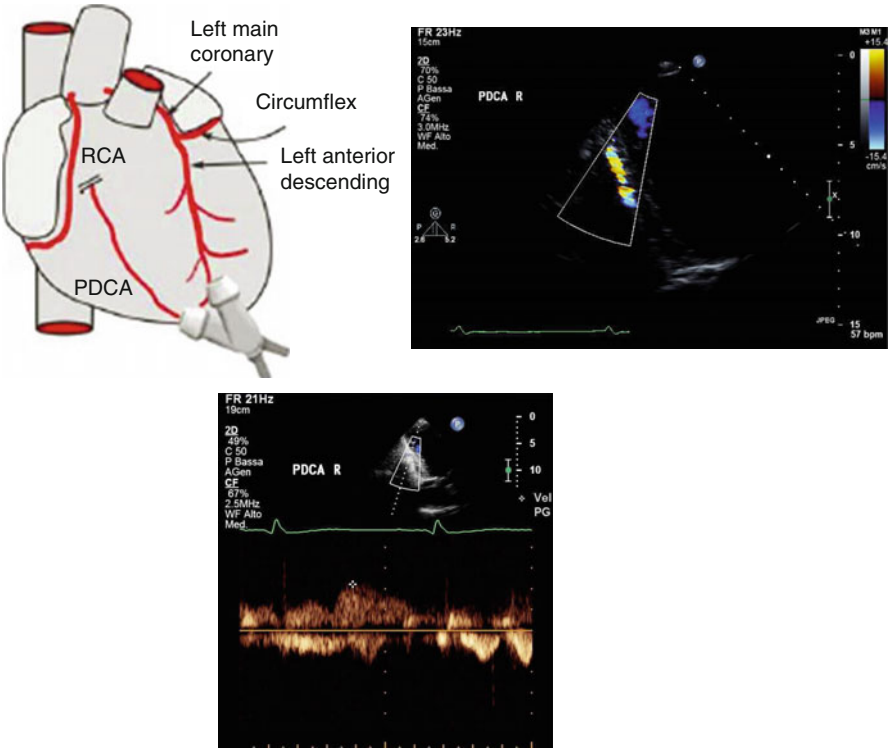

Fig. 8.3 *Upper left panel*: artist's drawing illustrating transducer beam orientation to the posterior descending coronary artery. The middistal tract is imaged from a modified apical 2-chamber view with counterclockwise rotation and anterior angulations of the probe. *Upper right panel*: the corresponding echocardiographic image of posterior descending color flow. *Lower panel*: the corresponding pulsed Doppler flow signal at rest, on which the peak diastolic flow velocity is measured. The variation in diastolic flow velocity between rest and peak vasodilation (following adenosine or dipyridamole infusion) gives an index of coronary flow reserve

8.4 Pulmonary Hemodynamics

Pulmonary artery systolic pressure can be estimated from peak tricuspid regurgitation (TR) jet velocities according to the well-validated modified Bernoulli's equation [31]: pulmonary artery systolic pressure = $4(V)^2$ + right atrial pressure, where V is the peak velocity (in m/s) of the tricuspid valve regurgitant jet (Table 8.2), and right atrial pressure is estimated from inferior vena cava diameter and respiratory changes, yielding a value from 5 (inferior vena cava diameter <17 mm, >50 % reduction with inspiration) to 20 mmHg (inferior vena cava diameter >17 mm, no reduction with inspiration) [16] (Table 8.3). Technically adequate signals have complete envelopes with well-defined borders, a sweep velocity of at least 100–200 mm s^{-1}, and can be obtained (often without need of contrast) at baseline and at peak exercise stress in the majority of patients (Fig. 8.4). The assessment of

Table 8.2 Noninvasive assessment of pulmonary pressure by Doppler echocardiography

		Normal values (rest)
PASP	4×TR peak velocity^2+RAP	<35
PAP m	79–0.45 (RVOT AT) 4×peak pulmonary regurgitation velocity	<25
PEDP	4×(pulmonary regurgitation end-diastolic velocity)+RAP	<15
PVR	10×TR velocity/$RVOT_{TVI}$	<2.0

PASP pulmonary artery systolic pressures, *PVR* pulmonary vascular resistances, *PEDP* pulmonary end-diastolic pressure, *PAP* pulmonary artery pressure, *TR* tricuspid regurgitation

Table 8.3 Echocardiographic estimation of the right atrial pressure (*RAP*) by measuring the diameter of the inferior vena cava and the respiratory motion of the inferior vena cava

Inferior vena cava diameter (cm)	Respiratory collapse (%)	RAP (mmHg)
<1.7	≥50 %	5
>1.7	≥50 %	10
>1.7	≤50 %	15
>1.7	0	20

From Lang et al. [16]

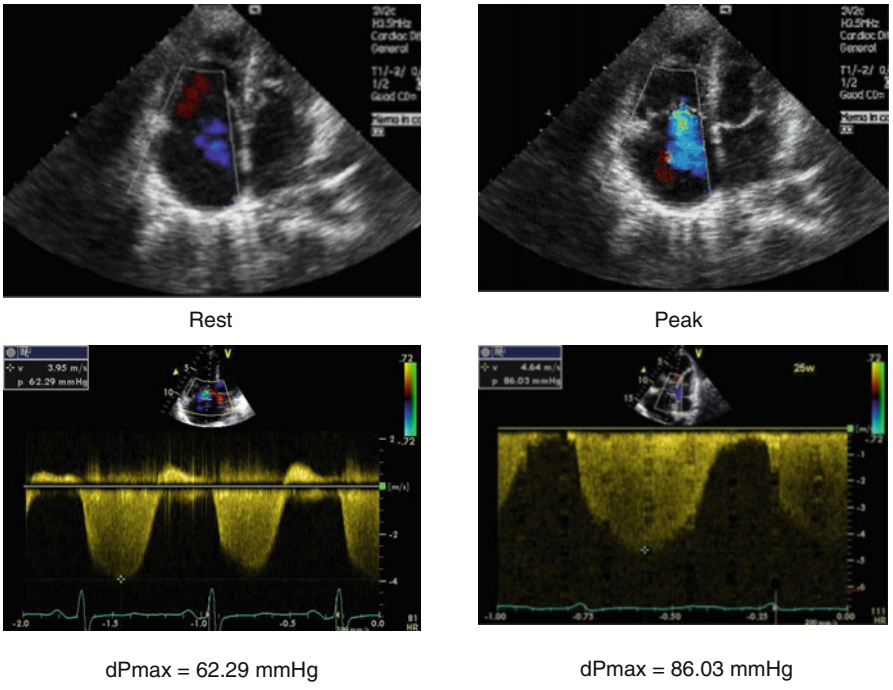

Fig. 8.4 Patients with resting pulmonary artery systolic pressure (estimated from jet velocity of tricuspid regurgitation) of 64 mmHg. During mild exercise, the patient experiences severe dyspnea and dramatic rise in pulmonary artery systolic pressure

pulmonary artery systolic pressure (PASP) depends on the presence of an at least trivial TR, which is found in about 40–85 % of normal subjects [32] and 80–90 % of patients with pulmonary hypertension [33, 34]. Furthermore, training is required to be able to assess TR velocity during exercise correctly. Over- and underestimation of TR velocity is a frequent problem. In the case of missing TR, subjects can be asked to drink 500–1000 ml before assessment which increases the preload and the size of the right atrial area and usually helps for the test to be successful. The quality of the TR velocity recording may be enhanced with contrast echocardiography by injecting agitated saline solution or other contrast echocardiographic agents intravenously [35]. However, an estimate of PASP can be obtained in the absence of TR from the blood pool and – more simply – with pulsed-wave Doppler tissue imaging, the isovolumic relaxation time of the tricuspid annulus of the right ventricle can be derived [36–38]. Pulmonary hypertension causes a significant delay in the onset of right ventricular filling. A third approach is based on the assessment of pulmonary forward flow [38]. Generally, the shorter the acceleration time (measured from the onset of Q wave on ECG to the onset of pulmonary flow velocity), the higher the pulmonary vascular resistance and hence the pulmonary arterial pressure. However, assessment of acceleration time especially during exercise has a high inter- and intraobserver variability.

Notably, the pulmonary artery diastolic pressure (PADP) can be estimated at rest from the velocity of the end-diastolic pulmonary regurgitant jet (Vedpr), using the modified Bernoulli's equation [PADP = 4 * (Vedpr)^2 + right atrial pressure [39] (Table 8.2). When used with the tricuspid regurgitant jet to estimate pulmonary artery systolic pressure, the yield for direct information on pulmonary artery pressures increases to 90 % [40].

The simple ratio of peak TR velocity (in m/s) to RVOT VTI (in cm) multiplied by 10 allows for the evaluation of pulmonary artery pressures in hemodynamic terms, namely, the basic relationship of Δpressure = flow * resistance [41, 42] (Table 8.2). A ratio greater than 1.8 resistance units is predictive of an abnormal pulmonary vascular resistance by cardiac catheterization and may predict which pre-liver transplant patients, who often have elevated pulmonary artery pressures due to increased cardiac output with or without pulmonary vascular changes that results in portopulmonary hypertension, need catheter-based evaluation [43]. The method is easy to incorporate into a standard echocardiography exam and helps to identify a group of patients with apparently increased PASP (which may be influenced by right ventricular stroke volume) as normal [41]. This method does have an inability to replicate higher values of Wood's units and may be further limited in patients with very dilated pulmonary arteries or RVOTs and with severe pulmonic regurgitation. Overall, the most reliable method to measure PASP or mean pulmonary artery pressure during exercise is to use continuous-wave Doppler echocardiography.

Pulmonary arterial hypertension is defined as a group of diseases characterized by a progressive increase of pulmonary vascular resistances leading to right ventricular failure and death [44]. Pulmonary hypertension is defined by a mean pulmonary arterial pressure over 25 mmHg at rest [44]. Transthoracic echocardiography is a key screening tool in the diagnostic algorithm [45–48]. It not only provides an estimate of pulmonary artery pressure at rest and during exercise, but it may also

help to exclude any secondary causes of pulmonary hypertension, predict the prognosis, monitor the efficacy of specific therapeutic interventions, and detect the preclinical stage of disease [47, 49]. By transthoracic echocardiography, normal values are defined by pulmonary artery systolic pressure of less than 35 mmHg at rest [45, 50]. The reliability of tricuspid regurgitation velocity (TRV) cut-off values, using right heart catheterization (RHC) as reference, has previously been assessed in SSc patients [51, 52]. A TRV of ≥3.4 m/s with an assumed right atrial pressure of 5 mmHg (thus corresponding to a PASP of 50 mmHg) has been recommended as cut-off value for performing RHC to diagnose or exclude PH in the ESC/ERS guidelines [44]. However, transthoracic Doppler echocardiography (TDE) at rest using these cut-off-values was not reliable enough to detect early forms of associated pulmonary arterial hypertension in systemic sclerosis [53]. The DETECT Study performed RHC in each systemic sclerosis patient and showed that of 85 patients with manifest associated pulmonary arterial hypertension in systemic sclerosis only 29.8 % had a TRV >3.4 m/s at rest. More than 40 % of patients would have been overseen using TDE only [53].

Up to now, there is no firm consensus on which PASP threshold is diagnostic for exercise-induced pulmonary hypertension, particularly if stress echocardiography is applied. There are only few invasive and noninvasive studies analyzing the normal values for pulmonary artery pressures during exercise [45, 50]. Usually, in healthy subjects the systolic pressures do not exceed 40 mmHg even during heavy exercise [42, 54]. However, in well-trained athletes [45, 46] and those older than 55 years, systolic pressures as high as 55–60 mmHg are encountered [34]. Pulmonary hypertensive response during exercise (as shown in Fig. 8.6) can be clinically important in several conditions [4], including pulmonary hypertension due to mitral valve disease (regurgitation or stenosis) [55], heart failure [56, 57], congenital heart disease, connective tissue diseases, autoimmune diseases (e.g., lupus or systemic sclerosis) [46, 58, 59], after lung transplantation [60] and, possibly, healthy subjects with susceptibility to high-altitude pulmonary edema [61].

The assessment of PASP or mean pulmonary artery pressure during exercise by exercise Doppler echocardiography may help to identify asymptomatic gene carriers in families with pulmonary arterial hypertension who may be at risk of developing clinically overt disease over the years [33, 62]. Also in patients with systemic sclerosis, the abnormal pulmonary pressure response to exercise has been identified as a risk factor for the development of a manifest pulmonary hypertension [59]. Only out of the group of systemic sclerosis patients with elevated pressures during exercise did some (10 %) develop manifest pulmonary hypertension within a 3-year period. Unfortunately, at present using echocardiography and right heart catheterization at rest, more than 80 % of patients with pulmonary hypertension will not be diagnosed until right heart failure has occurred with the consequence of a markedly impaired life span. Thus, the assessment of PASP during stress echocardiography may be a promising method for detecting pulmonary hypertension at an early stage.

Furthermore, stress echocardiography may also be useful in detecting subjects susceptible to pulmonary hypertension in special environmental and physical conditions [63]. Subjects susceptible to high-altitude pulmonary edema showed similar abnormal PASP response to exercise in normoxia and during prolonged hypoxia

(12 % volumes of oxygen corresponding to a 4.500-m altitude) [63]. Although echocardiography during exercise may be a promising approach for detecting early stages of pulmonary hypertension, most guidelines recommend echocardiography at rest only [44, 48]. The accuracy of stress Doppler echocardiography for this indication has not been assessed in a larger group of patients and/or susceptible subjects.

From our point of view, PASP of >40 mmHg at rest and of >45 mmHg during low-dose exercise (25–50 W over 2 min) seem to be reasonable cut-off values for the noninvasive detection of manifest pulmonary hypertension, as they are in line with exercise pathophysiological mechanisms [64] and methodological prediction formulas of mean pulmonary arterial pressure [65–67]. The thresholds are based on publications, stating that healthy subjects do not exceed these values at rest [33] or during low-dose exercise [68] defined as CO below 10 l/min. Furthermore, using the Chemla formula (PAPm = 0.61*PASP + 2 mmHg) [67] or the Syyed formula (PAPm = 0.65*PASP + 0.55 mmHg) [65] which both revealed a high accuracy and precision [66], PAPm of 25 mmHg at rest is equal to a PASP of 38 mmHg; PAPm of 30 mmHg during exercise would reflect a PASP of 45.9 mmHg. These PASP-cut-off values are also within the recommended values mentioned in the ERS/ESC guidelines for pulmonary hypertension [33].

The technique has pitfalls. From the pathophysiological viewpoint, on the basis of the fundamental equation of flow ($F = \Delta/R$), the abnormal exercise-induced increase in pressure can be linked to a supernormal increase in flow (e.g., in athletes) or to a normal increase in flow but with a subnormal fall in resistances due to a limited capability of pulmonary vessel recruitment and vasodilation (e.g., in chronic obstruction pulmonary disease with parenchymal pulmonary hypertension or congenital heart disease).

Furthermore PASP values during exercise have been shown to be directly linked to left atrial pressure [69] and left ventricular diastolic function and the presence of interstitial lung disease [70]. The current European Respiratory Society/ESC guidelines for the diagnosis of pulmonary arterial hypertension do not specify an indication for performing SE, because of limited information regarding standard values for PASP during exercise and the lack of prospective prognostic data [44], in spite of the acknowledged great potential for detecting the preclinical stages of disease via the exercise-induced increase in PASP disproportionate to the increase in cardiac output [4, 71].

The Doppler assessment of PASP has imperfect agreement with the gold standard of right heart catheterization, remains unfeasible in 15 % of patients with inadequate tricuspid regurgitation jet, and is unreliable in massive tricuspid regurgitation. During stress, we still lack accepted cut-off values of normal and abnormal responses. PASP values are linearly dependent on cardiac output, and multipoint pulmonary artery pressure-flow relationship should also be integrated with the evaluation of pulmonary vascular resistances. Post-exercise measurements are unreliable because of rapid return to baseline of pulmonary hemodynamics.

The prognostic meaning of exercise-induced increase in PASP varies radically depending on the clinical context. In patients with left heart failure or significant

Table 8.4 The clinical applications of PASP stress test

Disease	Level of evidence		
	Appropriate	Uncertain	Inappropriate
Symptomatic, mild mitral stenosis	√		
Asymptomatic, severe mitral insufficiency	√		
Heart failure		√	
Suspected PAH in normal resting TTE		√	
Reevaluation of exercise-induced PH on therapy		√	
Proven resting PH			√

PASP pulmonary artery systolic pressure, *HAPE* high-altitude pulmonary edema, *PAH* pulmonary arterial hypertension

mitral valve disease, PASP increase reflects an increase in left atrial pressure and impaired LV diastolic reserve and is a predictor of poorer prognosis. Instead, in patients with severe pulmonary hypertension and right heart failure, it indicates a preserved right ventricular contractile reserve and indicates a better prognosis [72].

At present, the only application endorsed by general cardiology guidelines [73] is the exercise Doppler study in symptomatic individuals with mild mitral stenosis and asymptomatic severe aortic insufficiency and mitral regurgitation [73] (Table 8.4). In these patients, valve surgery is considered reasonable (class II a, level of evidence C) for asymptomatic patients with preserved left ventricular function and pulmonary artery systolic pressure greater than 60 mmHg during exercise [73].

Thus, the European Society of Cardiology's updated guidelines strongly recommend exercise echocardiography in patients with valvular heart disease [73]. Exercise stress echocardiography may provide prognostic information in asymptomatic severe aortic stenosis by assessing the increase in mean pressure gradient and change in left ventricular function with exercise. In asymptomatic patients with moderate or severe mitral regurgitation without left ventricular dysfunction/dilatation, exercise echocardiography may identify a subset of patients who are at a higher risk of developing symptoms. In patients with mitral stenosis who are asymptomatic, the development of symptoms during exercise is strongly associated with the changes in the systolic pulmonary arterial pressure [74].

The indication to perform the study on patients with suspected pulmonary hypertension and normal or indeterminate findings after resting echocardiography study [75] remains uncertain. Other promising indications remain investigational at present.

8.5 B-Lines

B-lines detected by lung ultrasound (LUS), also called ultrasound lung comets, represent a useful, practical, appealingly simple way to image directly the extravascular lung water [76, 77]. Because the current technology for measuring pulmonary edema can be inaccurate (chest X-rays), cumbersome (nuclear medicine or

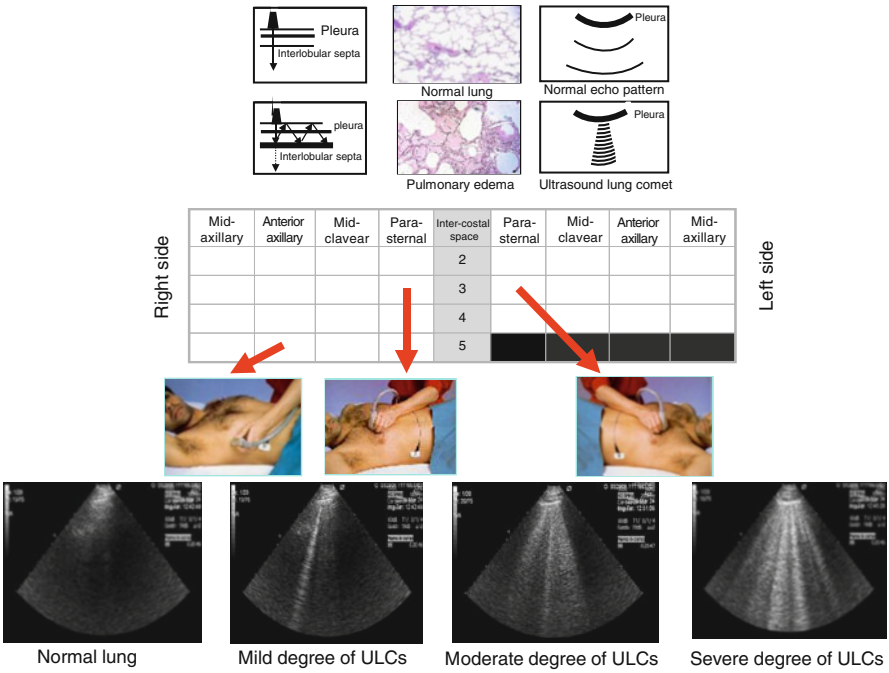

Fig. 8.5 How B-lines are generated (*upper panel*), counted (*middle panel*), and displayed (*lower panel*). The normal lung is "black" (no signal); the abnormal wet lung is "*black and white*" (with *white rockets* departing from the pleural line); and the lung with overt pulmonary edema is "*white*" (increase of coalescing comets on chest sonography)

radiology techniques), or invasive (indicator dilution), there is a great potential for technology that could quantify lung edema noninvasively in real time with a simple, semiquantitative, user-friendly, radiation-free direct imaging of extravascular lung water (Fig. 8.5). The cardiac transducer is employed to scan the anterior chest, and the number of B-lines in each intercostal space is summed up to generate a simple score. This can be extremely important in intensive care, for instance, in detecting acute respiratory distress syndrome, or in cardiology departments for identifying a cardiogenic cause of dyspnea but also in the stress testing laboratory [78]. In fact, membrane alveolar–capillary distress is a recognized adverse prognostic determinant in patients with heart failure. Indeed, a non-physiologic abrupt increase in pulmonary capillary wedge pressure can cause ultrastructural changes in the wall of pulmonary capillaries resulting in interstitial and alveolar edema. Particularly in patients with heart failure, a marked increase in pulmonary artery pressure and pulmonary capillary wedge pressure is observed during exercise even at very low levels creating an alveolar–capillary membrane dysfunction that contributes to symptom exacerbations and exercise intolerance (Fig. 8.6). Exercise may in fact determine the sudden appearance of B-lines on the chest in heart failure patients, in whom an increase in capillary wedge pressure may occur with absence of inducible ischemia,

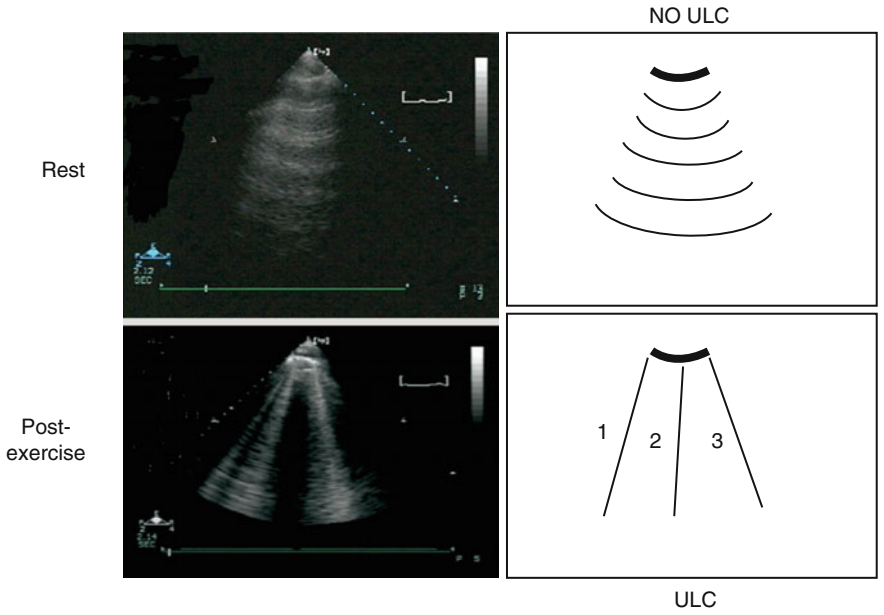

Fig. 8.6 Lung ultrasound (third right intercostal space) at rest (*left upper panel*) and immediately after exercise (*left lower panel*). On the right panels, the schematic drawing showing at rest normal, parallel, horizontal A-lines (*right upper panel*) and three vertical B-lines departing from the pleural line after exercise (*right lower panel*). The exercise-induced appearance of B-lines (also called ultrasound lung comets, ULC) reflects the acute increase of extravascular lung water. (Modified from Agricola et al., [78])

or in patients with extensive induced ischemia, in whom B-lines increase has the same conceptual meaning of the increased lung-to-heart ratio observed during sestamibi or thallium stress scan [78]. B-lines are usually accompanied by a marked stress-induced rise in E/e', which is a marker of raised left ventricular filling pressures and/or of PASP [79]. Another interesting model is an environmental stress-induced pulmonary edema. In high-altitude trekkers, healthy elite apnea and scuba divers or underwater fishermen [80–82], and extreme athletes involved in sports such as triathlon or marathon [83], B-lines can be detected in the presence of and, more often, in the absence of symptoms of pulmonary edema.

Therefore, stress lung ultrasound is useful in two separate settings, heart failure and extreme physiology (Table 8.5). In heart failure, B-lines may be helpful to titrate diuretic therapy or dialysis session, which should be increased in the presence of subclinical pulmonary edema present at rest or induced by exercise. LUS is performed in the stress echo lab with the standard high-end echocardiographic instruments and add as ancillary information to the standard evaluation of regional and global wall motion obtained during stress testing. In extreme physiology settings, B-lines can be obtained with portable pocket-size instruments, which are usable even in hostile environments. With batteries, power source, image storage (USB or laptop), and ultrasound gel, the total weight does not exceed 15 Kg. The technique can be easily learned by absolute beginners after an intensive 1-day training and

Table 8.5 Main applications of stress lung ultrasound

Setting	Heart failure	Extreme physiology
Environment	Stress laboratory	Ecological
Instrument	High cost, high weight	Low cost, pocket size
Subjects	HF patients	Divers, trekkers, runners
Technique	Stress echo + LUS	LUS
Location	Indoor	Outdoor
Target	Pulmonary edema	Non-cardiogenic pulmonary edema

also performed with e-learning interactive infrastructure. LUS can be performed within few minutes and hence reduces the time of patient exposure, which is especially important in cold mountain environments [79]. LUS in extreme physiology setting is therefore the best example of a new paradigm of "ecological" stress, under real-life conditions. This is especially important in extreme physiology setting, where changing levels of exercise, temperature, humidity, and distress are virtually impossible to reproduce in the stress testing lab. LUS stress echo is the paradigm of "next-generation" stress echo, leaving the controlled, artificial conditions of the laboratory to enter the universe of ecological, real-life world of stress.

B-lines may arise not only from water-thickened but also from fibrous-thickened subpleural septa, which are an important sign of alveolar–interstitial syndrome, for instance, in interstitial lung disease of systemic sclerosis [84]. Fibrotic B-lines are diuretic resistant, whereas watery B-lines of pulmonary edema are reduced by diuretics or dialysis [76].

Conclusion

It is now time to remember, also in the stress echocardiography laboratory, the "forgotten" right heart, which can be extensively studied in its regional and global, segmental, and longitudinal function, as well as in the novel dimension of coronary flow reserve of the right coronary artery and pulmonary hemodynamic and alveolar–capillary membrane response. The versatility of this information can help to better characterize a variety of patients, from coronary artery disease to dilated cardiomyopathy, from valvular heart disease to pulmonary hypertension, and from systemic sclerosis to healthy subjects susceptible to high-altitude pulmonary edema [85, 86]. From a practical viewpoint, it is certainly not feasible to do everything to all patients, since there are so little time during stress and so many things to see. Therefore, the variable of potential diagnostic interest should be strategically tailored to the individual patient (Table 8.6). The integration of right heart evaluation (including right ventricle, right coronary artery, pulmonary hemodynamics, and alveolar–capillary membrane) will allow the characterization of an exciting new target to be included in stress echocardiography. It was said several years ago in 1994 that "*the pulmonary circulation in patients with chronic pulmonary disease is often considered a no-man's land, falling between the domains of the respirologist and the cardiologist and understood only by the physiologist*!" [87]. It can be said today that a functional dynamic evaluation of

Table 8.6 Right heart stress echocardiography: targets and tools

	Method	Disease	Stress
Segmental function	2D	CAD	Any
Global function	*M*-mode	DCM	Dob (ex)
RCA coronary flow reserve	Color (PW) Doppler	CAD/DCM	Dip (ado)
PASP	CW Doppler (TR)	Primary or secondary pulmonary hypertension	Ex
B-lines	Lung ultrasound	Heart failure, HAPE	Hypoxia (ex)

CAD coronary artery disease, *CW* continuous wave, *DCM* dilated cardiomyopathy, *Dip* dipyridamole, *Dob* dobutamine, *Ex* exercise, *HAPE* high-altitude pulmonary edema, *PASP* pulmonary artery systolic pressure, *PW* pulsed wave, *TR* tricuspid regurgitation

right ventricular function, right coronary artery flow reserve, pulmonary hemodynamics, and extravascular lung water can offer a unique opportunity to the cardiologist and the pneumologist to better understand the cardiovascular physiology in a variety of cardiovascular and lung diseases.

Table of Contents Video Companion

See in the section illustrative cases: case number 29 (diastolic dysfunction by Maria Joao Andrade MD, Carnaxide–Lisbon, Portugal), case number 31 (comets during exercise stress in heart failure patient), and case numbers 32–35 (pulmonary pressure in aortic stenosis).

See also in the section selected presentations: B-lines, in and out the stress echo lab.

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