Stressing the Cardiopulmonary Vascular System: The Role of Echocardiography

Lawrence G. Rudski, MD, Luna Gargani, MD, PhD, William F. Armstrong, MD, PhD, Patrizio Lancellotti, MD, PhD, Steven J. Lester, MD, Ekkehard Grünig, MD, Michele D'Alto, MD, PhD, Meriam Åström Aneq, MD, PhD, Francesco Ferrara, MD, PhD, Rajeev Saggar, MD, Rajan Saggar, MD, Robert Naeije, MD, PhD, Eugenio Picano, MD, PhD, Nelson B. Schiller, MD, and Eduardo Bossone, MD, PhD, FCCP, FESC, FACC, *Montreal, Quebec, Canada; Pisa, Naples, and Salerno, Italy; Ann Arbor, Michigan; Liège and Brussels, Belgium; Scottsdale and Phoenix, Arizona; Heidelberg, Germany; Linköping, Sweden; and Los Angeles and San Francisco, California*

The cardiopulmonary vascular system represents a key determinant of prognosis in several cardiorespiratory diseases. Although right heart catheterization is considered the gold standard for assessing pulmonary hemodynamics, a comprehensive noninvasive evaluation including left and right ventricular reserve and function and cardiopulmonary interactions remains highly attractive. Stress echocardiography is crucial in the evaluation of many cardiac conditions, typically coronary artery disease but also heart failure and valvular heart disease. In stress echocardiographic applications beyond coronary artery disease, the assessment of the cardiopulmonary vascular system is a cornerstone. The possibility of coupling the left and right ventricles with the pulmonary circuit during stress can provide significant insight into cardiopulmonary physiology in healthy and diseased subjects, can support the diagnosis of the etiology of pulmonary hypertension and other conditions, and can offer valuable prognostic information. In this state-of-the-art document, the topic of stress echocardiography applied to the cardiopulmonary vascular system is thoroughly addressed, from pathophysiology to different stress modalities and echocardiographic parameters, from clinical applications to limitations and future directions. (J Am Soc Echocardiogr 2018;■:■-■.)

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The past decade has seen an increased awareness of the importance of interactions between the right heart and the pulmonary vascular bed, or the cardiopulmonary vascular system.[1] Prognosis is closely related to right heart function and pulmonary circulation in a variety of conditions, including left-sided heart failure (HF),[2] valvular heart disease (VHD),[3] and, most classically, precapillary pulmonary hypertension (PH).[4] Despite recognition of the cardiopulmonary vascular system's influence, great challenges exist in its noninvasive assessment.

Stress echocardiography has been a mainstay in the evaluation of various left-sided pathologies.[5-9] These studies have helped clinicians in diagnosing functionally significant obstructive coronary artery disease (CAD) and in guiding the timing of therapeutic procedures and have contributed in the prognostic stratification. More recently, stress echocardiographic applications beyond CAD have gained attention for the significant potential clinical implication of applying such a dynamic and versatile technique to many different conditions.[10,11]

In this state-of-the-art document, we review the physiopathology of the cardiopulmonary vascular system, the echocardiographic measures of right ventricular (RV) function and hemodynamics, and how they fare in response to stress testing. Clinical applications including the role in diagnosis and prognosis are reviewed, and limitations and knowledge gaps are discussed to lay out future research.

From the Azrieli Heart Center and Center for Pulmonary Vascular Diseases, Jewish General Hospital, McGill University, Montreal, Quebec, Canada (L.G.R.); the Institute of Clinical Physiology, National Research Council, Pisa (L.G., E.P.); the Department of Cardiology, Second University of Naples–Monaldi Hospital, Naples (M.D.); and the Heart Department, University Hospital, Salerno (F.F., E.B.), Italy; the Department of Internal Medicine, Division of Cardiovascular Disease, University of Michigan Medical Center, Ann Arbor, Michigan (W.F.A.); the Department of Cardiology, University of Liège Hospital, GIGA-Cardiovascular Sciences, Liège (P.L.); and the Free University of Brussels, Brussels (R.N.), Belgium; the Division of Cardiovascular Diseases, Mayo Clinic, Scottsdale (S.J.L.); and the Lung Institute, Banner University Medical Center–Phoenix, University of Arizona, Phoenix (Rajeev Saggar), Arizona; Centre for Pulmonary Hypertension, University Hospital Heidelberg, Heidelberg, Germany (E.G.); the Department of Clinical Physiology, Institution of Medicine and Health Sciences, Linköping University, Linköping, Sweden (M.A.A.); and the Lung & Heart-Lung Transplant and Pulmonary Hypertension Programs, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles (Rajan Saggar); and the Cardiovascular Research Institute, Health eHeart Study, Division of Cardiology, Department of Medicine, University of California, San Francisco, San Francisco (N.B.S.), California.

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Drs. Rudski and Gargani contributed equally to this work.

Reprint requests: Eduardo Bossone, MD, PhD, FCCP, FESC, FACC, via Principe Amedeo, 36, 83023 Lauro (AV), Italy (E-mail: ebossone@hotmail.com).

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Abbreviations

2D = Two-dimensional
3D = Three-dimensional
AS = Aortic stenosis
CAD = Coronary artery disease
CHD = Congenital heart disease
CO = Cardiac output
Ea = Arterial elastance
EDE = Exercise Doppler echocardiography
Ees = End-systolic elastance
EVLW = Extravascular lung water
FAC = Fractional area change
HF = Heart failure
LA = Left atrial
LAP = Left atrial pressure
LV = Left ventricular
mPAP = Mean pulmonary artery pressure
MR = Mitral regurgitation
MS = Mitral stenosis
NYHA = New York Heart Association
PAH = Pulmonary arterial hypertension
PH = Pulmonary hypertension
PVR = Pulmonary vascular resistance
RA = Right atrial
RHC = Right heart catheterization
RV = Right ventricular
$RVOT_{TVI}$ = Right ventricular outflow tract time-velocity integral
RVSP = Right ventricular systolic pressure
sPAP = Systolic pulmonary artery pressure
SSc = Systemic sclerosis
SV = Stroke volume
TAPSE = Tricuspid annular plane systolic excursion
TRV = Tricuspid regurgitation velocity
VHD = Valvular heart disease
Vo_2 = Oxygen uptake

PHYSIOPATHOLOGY

Stress testing is traditionally applied in medicine to uncover alterations in function at early stages of disease. An exercise-induced increase in mean pulmonary artery pressure (mPAP) >30 mm Hg had previously been included in the definition of PH.[12] The practice of exercise measurements of the pulmonary circulation[13] was discouraged in the last American and European guidelines on PH because of uncertainty about exact cutoff values and prognostic implications.[14,15] The rationale and clinical relevance of testing the pulmonary circulation under stress conditions still hold.[16,17] Data continue to accumulate in support of the notion that exercise Doppler echocardiography (EDE) is useful to evaluate and unmask abnormalities of pulmonary vascular function as well as the state of the right heart.[18,19]

RV Function

The right ventricle is coupled to the pulmonary circulation. RV-arterial coupling depends on the adequacy of the matching of contractility to afterload.[20-22] The gold standard of contractility is end-systolic elastance (Ees), or the ratio of end-systolic pressure to end-systolic volume. An acceptable gold standard of afterload is arterial elastance (Ea), or the ratio of end-systolic pressure to stroke volume (SV). Both Ees and Ea can be measured on a simple pressure-volume loop, which describes ventricular pressure as a function of ventricular volume during a cardiac cycle. The optimal RV-arterial coupling allowing flow ejection at a minimal energy cost corresponds to an Ees/Ea ratio of 1.5 to 2.0.[20-22] In patients with PH, the right ventricle basically adapts to the increase in pulmonary arterial afterload by an increased Ees to preserve Ees/Ea.[23] Insufficient RV systolic function adaptation to afterload results in the Starling mechanism with increased RV volumes to preserve flow output at the price of systemic congestion and negative ventricular interaction.[22] Therefore, an assessment of RV function can be made with afterload-dependent indices but also, more accurately, with indices integrating RV function and RV afterload, with a possibly more realistic estimate of Ees/Ea.[24] An exercise increase in RV systolic pressure (RVSP) predicts survival in patients with severe PH, with a cutoff value of change in systolic pulmonary artery pressure (sPAP) > 30 mm Hg.[4] However, RVSP is an indirect estimate of RV contractile reserve and, in fact, correlates poorly with Ees in exercising patients with PH.[25] Furthermore, exercise changes in RVSP vary considerably in healthy subjects, so that it is difficult to define limits of normal of the response.[26] Because the blunting of the increase in Ees to preserve the Ees/Ea ratio in PH is associated with an increase in RV dimensions, assessment of RV function during exercise probably best integrates estimates of both contractility and dimensions. Accordingly, surrogates to the Ees/Ea ratio such as the ratio between RVSP and RV end-systolic area[27,28] or tricuspid annular plane systolic excursion (TAPSE) and RVSP[29] have been proposed. The clinical relevance of exercise changes in echocardiographic estimates of RV-arterial coupling remains to be established.

Acute Changes in Right Heart Function after Extreme Exercise

The right ventricle is a high-volume pumping chamber facing a low-impedance circuit. With chronic endurance exercise challenges, the right-sided chambers remodel, resulting in significant ventricular enlargement (~20%), demonstrated by traditional two-dimensional (2D) as well as novel three-dimensional (3D) measures.[30] This increase in RV volume is associated with little, if any, change in parameters of RV systolic function, including RV ejection fraction and TAPSE. A decrease in 2D strain has been demonstrated in strength-trained but not in endurance-trained athletes, with both groups having preserved isovolemic acceleration and normal N-terminal pro–brain natriuretic peptide levels.[31]

Experimental data on racehorses have demonstrated that intense exercise can cause stress failure of pulmonary capillaries, resulting in exercise-induced pulmonary hemorrhage.[32] Elite human athletes

HIGHLIGHTS

- The right heart and pulmonary circulation play a key role in cardiorespiratory diseases.
- The cardiopulmonary vascular system can be assessed at rest and during exercise by echo.
- This evaluation allows a significant insight into cardiopulmonary physiology.
- It also helps establish the etiology of pulmonary hypertension and other conditions.
- The cardiopulmonary vascular system behavior provides significant prognostic information.

also develop changes in the structure of the capillary wall at maximal exercise, as evidenced by red blood cells in their alveoli.[33] Lung ultrasound has detected preclinical pulmonary edema through the appearance of B-lines in up to 20% of elite athletes, including apnea divers and high-altitude trekkers,[34,35] indicating acute distress of the alveolar-capillary membrane.

Several groups have studied the effects of acute extreme exercise on the right ventricle. Neilan *et al.*[36] found decreases in RV systolic strain rate and diastolic function. Lord *et al.*[37] demonstrated acute RV dilatation concomitant with decreased RV systolic tissue Doppler velocity, fractional area change (FAC), and free wall strain, with incomplete resolution of several of these parameters 6 hours after exercise. La Gerche *et al.*[38] correlated the acute reduction in RV ejection fraction with both serum troponin levels and N-terminal brain natriuretic peptide levels. Recurrent episodes of extreme endurance events have occasionally been associated with evidence of RV myocardial fibrosis, particularly in the RV septum, leading to the proposal of an exercise-induced form of arrhythmogenic RV cardiomyopathy.[39] The main publications on pulmonary pressure response to EDE in normal subjects and athletes are listed in Table 1.

Pulmonary Vascular Function

Pulmonary vascular function is defined by the relationship between a pulmonary vascular pressure difference (mPAP minus left atrial pressure [LAP]) and pulmonary blood flow to calculate pulmonary vascular resistance (PVR).[40] Doppler echocardiography allows noninvasive hemodynamic estimation of mPAP, sPAP, LAP, and pulmonary blood flow from the cardiac output (CO).[41] At rest, these measurements have been shown by rigorous Bland and Altman analysis to be accurate (no significant bias) but to suffer from limited precision (extended limits of agreement) compared with invasive measurements of pulmonary artery pressure (PAP), LAP estimated from pulmonary capillary wedge pressure, and thermodilution CO taken as gold standards.[42] Standard routine right heart catheterization (RHC) measurements with thermodilution fluid-filled catheters have been shown to be accurate but also to suffer from limited precision compared with true gold-standard measurements of PAP and left ventricular (LV) end-diastolic pressure with high-fidelity micromanometer-tipped catheters and CO by the direct Fick method.[42] Thus, Doppler echocardiography is adequate to study the pulmonary circulation at rest for population studies but, like RHC, must be used with caution for individual decision making.

No rigorous systematic evaluation of Doppler echocardiographic measurements of pulmonary vascular pressure and flows compared with invasive gold standards has been reported during exercise. However, available data suggest adequate accuracy to answer clinical or physiological questions. For example, the slope of linear fitting of mPAP/CO relationships in healthy subjects has been shown to be on average 1.5 mm Hg/L/min in invasive and in Doppler echocardiographic studies.[18,40] The upper normal limit of invasive or noninvasive mPAP/CO relationships is 3 mm Hg/L/min, corresponding to a total PVR (mPAP/CO) of 3 Wood units.[18,40] The upper normal limit of pulmonary capillary wedge pressure or LAP estimated from the E/e′ ratio has yet to be defined.

Because of the obligatory interdependence of the three components of the PVR equation, EDE requires the measurements of mPAP, LAP, and CO. Sometimes CO is replaced by oxygen uptake (Vo_2) or workload. These variables are linearly related but not interchangeable, because of significant variability. For example CO at 200 W in healthy volunteers may vary from 14 to 24 L/min,[43] and mPAP-Vo_2 may show a plateau or an uptake pattern[44] of still uncertain relevance. Because PAP is determined by CO, not by VO_2 or workload, measuring CO is preferable.[40] It is also important to measure pulmonary vascular pressures and CO during, not immediately after, exercise. CO and mPAP decrease rapidly to near normal values within the first 5 min of recovery from a maximum exercise test.[45] Finally, because the principal objective of the exercise stress test is to expose the pulmonary circulation to increased CO, it is important that the exercise mode be dynamic (bicycle or treadmill). Resistive exercise (weightlifting) may confuse measurements of the pulmonary circulation because of ergo-reflex-related activation of the sympathetic nervous system, increased systemic vascular resistance and intrathoracic pressure changes.[40]

Alveolar-Capillary Membrane

The cardiopulmonary vascular system evaluation includes the two separate variables of pulmonary vascular reserve and RV function. There is, however, a third key player represented by the alveolar-capillary membrane integrity, which contributes to extravascular lung water (EVLW) accumulation that can be imaged through ultrasound B-lines.[46,47] B-lines are present in one third of patients with compensated HF at rest and in two thirds after exercise.[48] Their presence at rest and after exercise predicts more severe functional and prognostic stage in HF.[49,50] Although the increase in LV filling pressures is associated with a larger number of B-lines, the entity of this correlation is only modest, because B-lines image EVLW, not pressure, and the integrity of the alveolar-capillary membrane can show large individual variations. This means that high levels of EVLW can be found even with modest increases in pulmonary capillary wedge pressure and vice versa. Therefore, the possibility to integrate the rest and stress assessment of pulmonary hemodynamics and RV contractile reserve with B-lines, as a measure of EVLW and a proxy of alveolar-capillary membrane integrity, is extremely appealing for further studies on pre- and postcapillary PH. This may prove insightful considering that the hemodynamic features of precapillary, combined, and postcapillary PH show a pathophysiological continuum.[51]

STRESS MODALITIES

Among other stress tests, EDE has the advantage of being noninvasive, being relatively low cost, and providing detailed hemodynamic information together with assessment of LV and RV function and valvular function.

Imaging the right ventricle is more problematic than imaging the left ventricle because of its retrosternal position, its complex structure, its asymmetric shape and contraction pattern, and the failure of any single

Table 1 Pulmonary pressure response to exercise in normal subjects and athletes

Study	Patients/gender height (cm); weight (kg)	Age (y)	Exercise protocol workload (W/METs)	RAP estimate (mm Hg)	Baseline sPAP (mm Hg)	Peak sPAP (mm Hg)	ΔsPAP	Remarks
Normal subjects								
Himelman *et al.* (1989)	12/11 M —	27–68	Supine bicycle 158 ± 49	From IVC	22 ± 4	31 ± 7	11 ± 7	
Oelberg *et al.* (1998)	10/6 M 167 ± 8; 69.9 ± 14.7	52.3 ± 10.9	Upright bicycle	From IVC	17 ± 8	19 ± 8	—	
Bossone *et al.* (1999)	14/14 M 180.9 ± 6.8; 77.9 ± 8.8	18.9 ± 0.9	Recumbent bicycle 240	Fixed value (5)	9	21 (95% CI, 9–19)	—	
Grünig *et al.* (2000)	11/11 M 179 ± 6; 76 ± 7	37 ± 11	Supine bicycle 198 ± 8	From IVC	27 ± 4	36 ± 3	8 ± 2	
Kiencke *et al.* (2008)	9/— BSA 1.90 ± 0.07 m^2	32 ± 3	Supine bicycle —	—	17 ± 3	—	11 ± 5	SV: 73 ± 13 mL at rest SV: 98 ± 19 mL at peak
Grünig *et al.* (2009)	191/91 F 173 ± 9; 68±12	32 ± 10	Supine bicycle 125	From IVC	20.4 ± 5.3	35.5 ± 5.4	—	
Mahjoub *et al.* (2009)	70/36 F BMI 24.6 ± 4.2 kg/m^2	48 ± 16	Semisupine bicycle 152 ± 47	Fixed value (5)	27 ± 4	51 ± 9	27 ± 8	On multivariate analysis, age, LV mass, and sPAP at rest were independent predictors of sPAP at peak exercise
Möller *et al.* (2010)	88/49 F 171.2 ± 10; 64.2 ± 13	18.3 ± 3.5	Supine bicycle 25 W/2 incr.	From IVC	21.8 ± 3.6	39 (17–63)	—	
Argiento *et al.* (2010)	25/12 F 178 ± 12; 70 ± 15	36 ± 14	45° cycle 170 ± 51	From IVC	19 ± 5	46 ± 11§	—	CO at rest 4.7 ± 1.0 CO at peak 18.0 ± 4.2
La Gerche *et al.* (2010)	15/13 M BSA 1.94 ± 0.14	38 ± 6	Semisupine bicycle 190 ± 30	No added value	21.6 ± 3.8	47.0 ± 6.5	—	CO at rest 5.0 ± 0.6 CO at peak 12.4 ± 3.2
D'Alto *et al.* (2011)	88/78 F 161.5 ± 8; 64.1 ± 11.3	55.3 ± 12.4	Supine bicycle 89 ± 28	From IVC	20.6 ± 3.7	25.9 ± 3.3	—	CI: 3.1 ± 0.8 ΔCI: 4.6 ± 2.3
Argiento *et al.* (2012)	124/62 M 173 ± 9; 70 ± 11	37 ± 13	Supine bicycle 175	From IVC	15.5 ± 2.6 M* 15.1 ± 2.9 F*	36.0 ± 5.9 M* 30.5 ± 7.2 F*	—	1.46 ± 0.48 M† 1.55 ± 0.60 F†
Athletes								
Bossone *et al.* (1999)	26/26 M 182.9 ± 4.7; 85.4 ± 5.8	20.3 ± 1.7	Recumbent bicycle 240	Fixed value (5)	21	41 (95% CI, 21–41)	—	Ice hockey players
La Gerche *et al.* (2010)	40/36 M BSA 1.94 ± 0.16 m^2	36 ± 8	Semisupine bicycle 284 ± 34	No added value	21.5 ± 3.8	60.7 ± 12.4	—	Endurance sport
Bidart *et al.* (2012)	15/— —	38.7	Recumbent bicycle 246.7	No added value	19.4	54.8	—	Exercise TRV/$RVOT_{TVI}$ < 0.2 m/sec/cm
Claessen *et al.* (2015)	61‡/46 175 ± 12; 79 ± 14	46 (32–57)	Upright cycle ergometer	No added value	37.7 ± 22.9	64.8 ± 25.1	—	sPAP/CO 6.8 ± 6.2 mm Hg/L/min

BMI, Body mass index; *BSA*, body surface area; *CI*, cardiac index; *F*, female; *incr.*, increments; *IVC*, inferior vena cava; *M*, male; *RAP*, RA pressure.

*mPAP (mm Hg) was calculated as 0.6 × sPAP +2.

†mPAP-CO (mm Hg/L/min).

‡Study population: 19 endurance athletes, nine healthy nonathletes, eight BMPR2 mutation carriers, five post–pulmonary embolism patients, 14 patients with chronic thromboembolic PH, six post–pulmonary endarterectomy.

§The average slope mPAP/CO was 1.37 ± 0.65 mmHg · min^{-1} · L^{-1}.

Table 2 Comparison between different exercise tests for the assessment of cardiopulmonary vascular system

Test	Availability	Hemodynamic information	RV function	Anatomy	Prognostic information	Invasiveness	Costs
Exercise RHC	++	++++	+	++	+++	+++	$$
EDE	+++	++	+++	+++	++	+	$
Cardiopulmonary exercise	+++	+	+	+	++	+	$
Exercise CMR	++	+	++++	++++	+	+	$$
Exercise CMR with simultaneous invasive pressure registration	+	++++	++++	++++	+	+++	$$$

+, Scarce; ++, reasonable; +++, good; ++++, optimal; *RHC*, right heart catheterization; *CMR*, cardiac magnetic resonance.

2D view to fully reflect RV geometry and function. Views less applicable to the left ventricle, such as subcostal imaging, are frequently essential for the right ventricle, and the inability to completely characterize the right ventricle both at rest and with stress is higher than that for the left ventricle. When the clinical question is the presence or absence of CAD, the echocardiographic examination is tailored, with respect to type of stress and imaging views, to the left ventricle, and secondary attention is paid to the right ventricle. For patients known to be free of obstructive CAD, stress echocardiography can be tailored to a detailed assessment of RV size and function, development or worsening of tricuspid regurgitation, and pulmonary hemodynamics. Potentially all the traditional stress modalities can be used to evaluate the right ventricle. However, because of the complex interaction of pharmacologic agents with the pulmonary circulation, and the fact that from a clinical standpoint, establishing a link between physiologic stress and RV adaptation is essential, exercise modalities are preferred in virtually all instances (Table 2). From an imaging perspective, supine bicycle exercise is the best technique; however, treadmill exercise may more accurately reproduce symptoms (Table 3).

Exercise Echocardiography

When evaluating patients for CAD or functional limitations related to fatigue or dyspnea, an exercise format is preferred, because it is the most physiologic stressor, and there is rough parity among treadmill echocardiography, supine bicycle echocardiography, and upright bicycle echocardiography.[5,6] Studies have documented the ability to detect RV ischemia using all of these techniques.[52-54]

Although LV function with stress is heavily dependent on the presence or absence of provoked ischemia and less so on conditions of afterload, the function of the nonpreconditioned right ventricle during stress may be more heavily dependent on changes in PVR, resulting in exercise-induced PH. Secondary abnormalities of RV function will mimic the effects of RV ischemia. As such, it is crucial to have a thorough comprehensive understanding of any preexisting entities such as mitral valve disease or pulmonary vascular disease, which could have a secondary, nonischemic effect on RV function.

If the clinical question is that of RV adaptation to disease likely to result in elevation of pulmonary pressure, the stress modality should be tailored to image the right ventricle. This is often best accomplished using semisupine bicycle exercise, which affords the advantages of continuous online monitoring, as well as enhanced monitoring for development of functional tricuspid regurgitation and PAP.

Pharmacologic Stress Echocardiography

Limited data are available about detection of RV ischemia[53,55] and subclinical impairment in RV contractile reserve during dobutamine stress echocardiography.[56] The pharmacologic effects of dobutamine on the pulmonary circulation are complex and may result in either vasodilation or vasoconstriction of the pulmonary arterial circuit, depending on dose and the presence or absence of preexisting disease. As such, the effect of dobutamine on RV function could be either by way of induction of myocardial ischemia or a purely secondary effect related to acute increase in afterload due to dobutamine effect on the pulmonary circulation.

The effects of vasodilator drugs, such as dipyridamole, on the pulmonary circulation are complex, and these agents are therefore not recommended for evaluation of RV function. Selective pulmonary vasodilator effect of endogenous and exogenous adenosine has been used, however, to lower PVR[57] and to assess the reversibility of PH.[58]

ECHOCARDIOGRAPHIC MEASUREMENTS DURING EXERCISE

RV Contractile Reserve

RV contractile reserve can be defined as the ability of the ventricle to increase global function during stress. A few echocardiographic studies have specifically evaluated RV contractile reserve during stress. Global RV contractile reserve can be measured as the change (peak stress minus rest value) of TAPSE (from simplest M-mode tracings), tricuspid annular systolic velocity S′ (from tissue Doppler), FAC (from 2D imaging), or ejection fraction (best assessed from more complex and time-consuming 3D imaging). The assessment of TAPSE (or S′) and, to a lesser extent, FAC avoids the approximations, mistakes, and computational burden inherent to the calculation of ejection fraction in the right ventricle, whose crescentic and irregular shape eludes any simple geometric modeling. All indices of RV function increase significantly during exercise or dobutamine stress in healthy subjects, but their increase is blunted in PH[56] or severe dilated cardiomyopathy with RV involvement.

Because of the influence of load on TAPSE, FAC, and ejection fraction (even when the latter is calculated by 3D imaging), they tend to reflect RV arterial coupling (as well as preload) rather than measures of RV contractility per se. To distinguish between genuine RV dysfunction and/or pathologic increases in pulmonary vascular load, whenever possible it would be appropriate to combine sPAP and RV end-systolic area to calculate RV end-systolic pressure-area relation or TAPSE/sPAP as a surrogate of RV contractility.[27,29]

Exercise-induced increase in sPAP has been proposed as a possible measure of RV contractile reserve during EDE[4]: high ΔsPAP (sPAP increase > 30 mm Hg, suggesting preserved RV contractile reserve) was an independent prognostic marker of survival in patients with

Table 3 Stress modalities for the cardiopulmonary vascular system

	Treadmill exercise echocardiography	UBE	SBE	DSE	VSE	Caveats
Detection of RV ischemia	+	+	+	+++	NE	• Exercise modalities preferred for all patients capable of exercise. • Nonexercise modalities provide no direct link of echocardiographic findings to symptoms. • Examination usually tailored to evaluation of LV ischemia.
Exercise-induced PH	++	++	+++	NE	NE	• Online monitoring of TR and RVSP may be easier with SBE than UBE.
Exercise-induced dyspnea/fatigue	+++	+++	++	NE	NE	• Online monitoring of TR and RVSP may be easier with SBE than UBE. • UBE may more reliably reproduce actual symptoms experienced by the patient. • Non-exercise modalities provide no direct link of echo findings to symptoms.
RV adaptation to inducible LV disease (ischemia, cardiomyopathy or pressure overload)	NE	++	++	+	NE	• Provocation of LV decompensation takes precedence over monitoring of right ventricle. • If LV status already fully characterized, one can tailor examination to the right ventricle.
RV adaptation to mitral valve disease	NE	++	+++	NE	NE	• For MS: assessment of mitral gradients, RV function, TR, and RVSP are needed. • For MR, more attention to quantifying severity of regurgitation is also needed.
RV adaptation to pulmonary disease	NE	+++	++	NE	NE	• UBE is often better tolerated in severe lung disease than SBE. • Tailor examination to RV function, TR, and RVSP.
Monitoring of detailed function parameters (strain, strain rate etc)	+	++	+++	NE	NE	• Image quality and stability must be optimized for detailed analysis of deformation parameters (usually feasible only with supine imaging). • No data to support nonexercise stress modalities in clinical practice.

DSE, Dobutamine stress echocardiography; *NE*, not evaluated; *SBE*, supine bicycle exercise echocardiography; *TR*, tricuspid regurgitation; *UBE*, upright bicycle exercise echocardiography; *VSE*, vasodilator stress echocardiography.

Table 4 Echocardiographic indices for the evaluation of patients undergoing right heart stress echocardiography (in addition to standard LV evaluation, including LV E/e′ and LA volume)

	Key indices	Complementary indices	Research tools
Baseline	sPAP/mPAP RAP CO RV FAC TAPSE RV dimensions RA volume PVR	RV S′ DTI RV E/e′ RV e′/a' ACT PA diameter PR early diastolic velocity RV end-systolic pressure-area ratio TAPSE/sPAP	3D RV volumes Strain
During stress (i.e., 50 W)	sPAP CO	mPAP TAPSE RV FAC RV S′ DTI RV E/e′ RV e′/a' PVR ACT	3D RV volumes Strain
Peak stress	sPAP/mPAP CO TAPSE	RV FAC RV S′ DTI RV E/e′ RV e′/a' PVR ACT RAP RV end-systolic pressure-area ratio TAPSE/sPAP	3D RV volumes Strain
Recovery (5 min)	sPAP CO	mPAP TAPSE RV S′ DTI RV E/e′ RV e′/a' PVR ACT PA diameter PR early diastolic velocity RV end-systolic pressure-area ratio TAPSE/sPAP	3D RV volumes Strain

ACT, Acceleration time; *DTI*, tissue Doppler imaging; *PA*, pulmonary artery; *PR*, pulmonic regurgitation *RAP*, RA pressure.

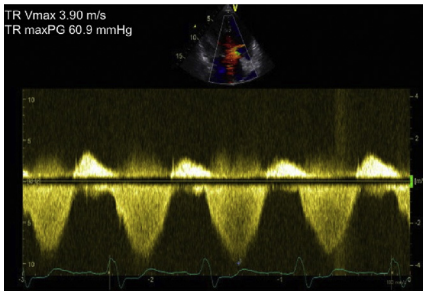
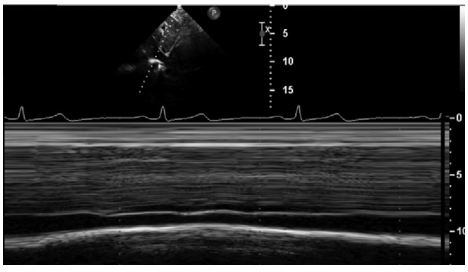
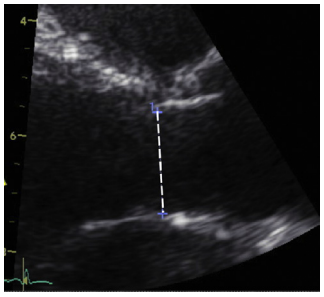
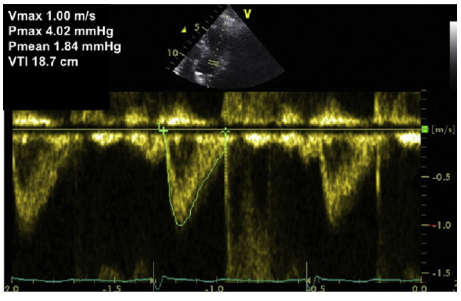
invasively confirmed pulmonary arterial hypertension (PAH) or inoperable chronic thromboembolic PH. A good reason for choosing exercise sPAP increase to estimate RV contractile reserve is that sPAP increase is closely related to RV function, because the ability of the right ventricle to increase pressure depends on the maintenance of RV arterial coupling[23] and the ability to maintain or increase SV during exercise without dilating.[59] Janicki *et al.*[60] have shown that the exercise-induced pulmonary arterial pressure-flow relationship in PH is very steep. Thus, a large increase in sPAP implies the capacity of the right ventricle to eject a large SV despite high pressures, reflecting preserved RV contractile reserve.

Exercise increase in TAPSE and tissue Doppler S′ have also been proposed.[26] The magnitude of increase is significantly higher in control subjects compared with patients with PH: in healthy subjects, exercise augments TAPSE by about 20% relative to baseline (~5 mm) and S′ by about 80% (~10 cm/sec).[61]

Noninvasive Hemodynamics

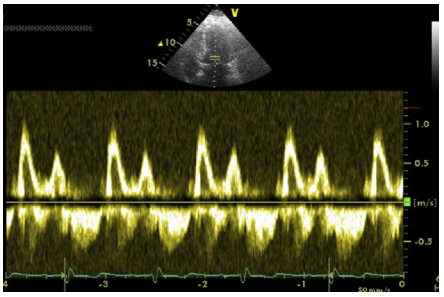
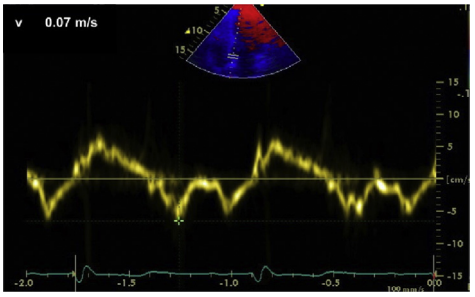
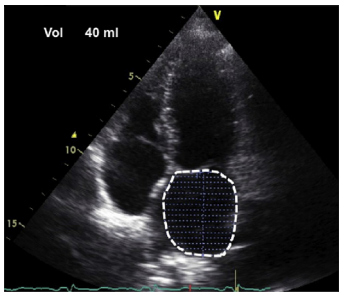
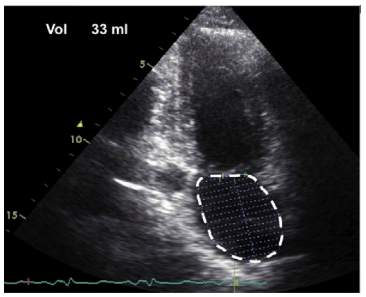
Doppler echocardiography allows a noninvasive hemodynamic estimation of many parameters at rest. Most of them can be assessed at peak exercise with high feasibility. Specific technical information about these measurements and their limitations has been detailed in the guidelines for the echocardiographic assessment of the right heart in adults.[41] In the absence of flow obstruction between the right ventricle and pulmonary artery, the tricuspid regurgitation velocity (TRV) will have a linear positive correlation with sPAP. Flow velocities are directly related to the flow volume and indirectly related to the cross-sectional area through which flow passes. Therefore, when the right ventricle or tricuspid annulus is dilated (increased regurgitant orifice area) and/or RV function or contractility is depressed, the strength of the positive correlation between TRV and sPAP is diminished. Moreover, an increase in sPAP may be "physiologic" and secondary to increased pulmonary flow, as occurs in anemia,

Table 5 Echocardiographic key indices

Key indices	Baseline	During stress (i.e., 50 W)	Peak stress	Recovery (5 min)
sPAP, mPAP, RAP	✓	✓	✓	✓
TRV peak velocity  RAP from IVC dimensions and collapsibility[41]  $sPAP = 4\ TRV^2 + RAP$ $mPAP = 0.61 \times sPAP + 2$ mm Hg or $mPAP = 4\ PRV^2 + RAP$				
CO	✓	✓	✓	✓
Zoom on LVOT diameter in early-mid systole  $LVOT_{TVI}$ derived by PW Doppler tracing the modal velocity  $SV = D^2 \times 0.785 \times LVOT_{TVI}$ $CO = SV \times HR$				

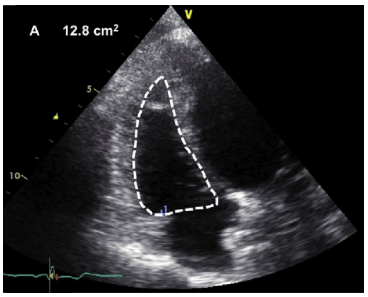
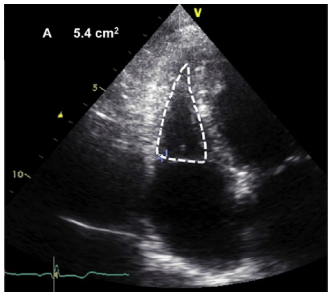
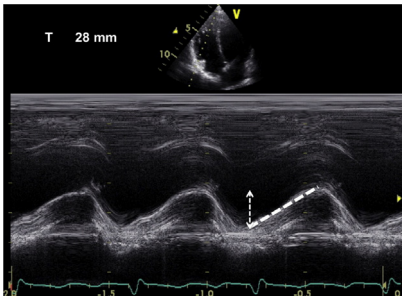
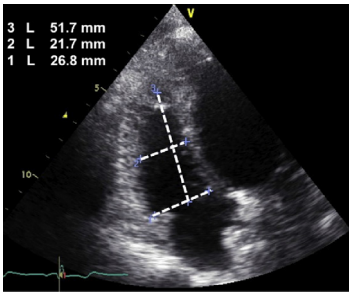
(*Continued*)

Table 5 (*Continued*)

Key indices	Baseline	During stress (i.e., 50 W)	Peak stress	Recovery (5 min)
LV E/e′	✓	✓		
E from PW Doppler on mitral valve inflow				
				
e′ as mean DTI between lateral and septal wall values				
				
LA volume (indexed)	✓			
Mean volume between apical four-chamber view (modified Simpson rule) and two-chamber view				
				
				

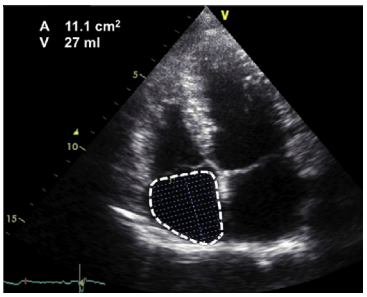
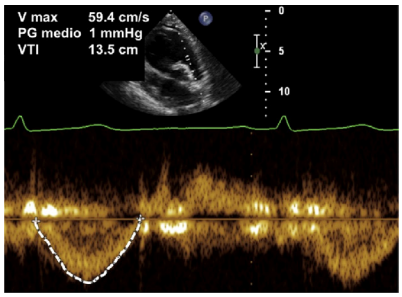
(*Continued*)

Table 5 (*Continued*)

Key indices	Baseline	During stress (i.e., 50 W)	Peak stress	Recovery (5 min)
RV FAC	✓			
RV EDA  				
RV ESA FAC = (EDA − ESA)/EDA × 100  				
TAPSE	✓		✓	
M-mode of the total excursion of the tricuspid annulus  				
RV dimensions	✓			
RV basal, RV midcavity, and RV longitudinal dimensions in a dedicated apical four-chamber view  				

(*Continued*)

Table 5 (*Continued*)

Key indices	Baseline	During stress (i.e., 50 W)	Peak stress	Recovery (5 min)
RA volume	✓			
Area lenght or disk summation techniques in a dedicated apical four-chamber view				
				
PVR	✓			
$RVOT_{TVI}$ from parasternal short-axis view				
				
$PVR = [TRV/(RVOT_{TVI} \times 10)] + 0.16$				

DTI, Doppler tissue imaging; *EDA*, end-diastolic area; *ESA*, end-systolic area; *HR*, heart rate; *$LVOT_{TVI}$*, LV outflow tract velocity-time integral; *PRV*, pulmonary regurgitation velocity; *PW*, pulsed-wave.

hyperthyroidism, obesity, or exercise,[62] or "pathologic" and related to an increase in resistance. sPAP should thus be interpreted in the context of both measures of flow (CO) and resistance.

Exertional dyspnea in the presence of normal resting biventricular function and sPAP is a common symptom in individuals presenting for evaluation by stress echocardiography. A rise in sPAP with exercise should be considered pathologic when it is disproportionate to the rise in CO and secondary to an increase in PVR. The RV outflow tract time-velocity integral ($RVOT_{TVI}$) is a good surrogate for transpulmonary flow, and dividing TRV by $RVOT_{TVI}$ will correct for flow-mediated changes in sPAP by providing an estimate of PVR.[1,2] Both elite athletes and patients with chronic obstructive pulmonary disease may substantially increase their sPAP with exercise. However, differently from those with pulmonary disease who show a marked exercise-induced increase in the $TRV/RVOT_{TVI}$ ratio, in athletes, $TRV/RVOT_{TVI}$ does not demonstrably change with exercise.[3,4] Resistance to transpulmonary flow may be either precapillary (associated with an increased PVR) or postcapillary (secondary to increased LAP).

Exercise PH, which is common in subjects with normal LV ejection fractions, is strongly associated in this population with E/e′ ratio, age, systolic blood pressure during exercise, and sex.[63] Exercise PH may thus explain an individual's symptom of exertional dyspnea and also provides prognostic information in subjects with preserved LV ejection fractions, particularly in those with increases in estimated LV filling pressure during exercise.[64]

Heterogeneity in both the hemodynamic mechanism and potential underlying clinical condition makes the search for the underlying pathophysiologic mechanism clinically imperative.

The key echocardiographic indices of the cardiopulmonary vascular system to be assessed during stress echocardiography, in addition to a standard LV evaluation, are indicated in Tables 4 and 5.

CLINICAL APPLICATIONS

Stress echocardiography for assessing the cardiopulmonary vascular system can be very useful when evaluating symptoms such as dyspnea or fatigue with exertion. The clinician should be aware of the secondary effects of both left-sided heart disease and exercise PH on the right ventricle.

This is also why there are no clear standardized cutoff values for "pathologic" peak sPAP, and although a tentative summary of existing data can be established (Table 6), the sPAP value alone should be used with caution and interpreted in the more general

clinical context of the patient and other echocardiographic and Doppler data.

Pulmonary Arterial Hypertension

In addition to the role of echocardiography in the noninvasive diagnostic algorithm, monitoring, and follow-up of PAH, methods have been investigated for screening at-risk populations, including patients with connective tissue disease (especially systemic sclerosis [SSc]) and family members of patients with heritable PAH. According to current guidelines, screening is possible in well-defined patient groups at high risk for developing PAH, but this approach is not feasible in the wider population.[13] Even though stress testing is not recommended by current guidelines, many data point out the advantages of this method for screening purposes in at-risk groups. Further prospective studies are warranted to evaluate the sensitivity and specificity of exercise tests as well as their predictive value. The main publications on sPAP response to EDE in patients at high risk for PAH and in patients with overt PAH are listed in Table 7.

Screening in Heritable PAH. PAH is a rare disease that is a model for dysfunctional right heart and pulmonary circulation. Despite significant improvements and modern therapy, the disease is still associated with impaired quality of life and poor prognosis. It has been hypothesized that an earlier diagnosis may mitigate the disease time course. Most recent data from large PAH registries have confirmed that >85% of patients are still diagnosed at late disease stages with World Health Organization functional class II to IV, severely enlarged right heart, and impaired RV function.[65] Therefore, great attempts has been made to detect preclinical disease stages noninvasively. To date, physical examination, electrocardiography, resting echocardiography, and lung function and laboratory tests have failed to provide acceptable sensitivity and specificity. In contrast, patients with normal electrocardiographic findings without strain, normal plasma brain natriuretic peptide levels, and normal echocardiographic findings at rest have only a 5% chance of having manifest PAH.[66]

Screening assessments have been performed in family members of patients with idiopathic PAH. In these subjects, a higher proportion showed a hypertensive pressure response to exercise compared with unrelated healthy control subjects. During exercise, 31.6% of relatives exceeded the 90th percentile of mean maximal TRV of >3.08 m/sec seen in control subjects.[67] This clinical phenotype was associated with an increased prevalence of bone morphogenetic protein receptor type 2 mutations and might therefore be an additional risk factor for the development of PAH. This assumption is also supported by follow-up data from a large German family with heritable PAH with a median follow-up time of 12 ± 6.6 years. During the follow-up period, only those family members who had shown both bone morphogenetic protein receptor type 2 mutations and a hypertensive pressure response during exercise developed a manifest disease.[68]

Screening in SSc. Patients with SSc are at increased risk for developing PAH, with a prevalence ranging from 8% to 12%.[69,70] The prognosis of these patients is severely impaired, with a 3-year survival rate of 47% to 56% compared with patients with SSc without PAH (94%).[71,72] In patients with SSc, a hypertensive response to exercise has shown prognostic relevance and might also be an important marker for early clinical or preclinical stage of the disease.[73-76] An sPAP increase of 18 mm Hg has shown sensitivity of 50% and specificity of 90% for subsequent development of PAH and is an independent predictive factor of PAH.[74] An abnormal increase in sPAP immediately after exercise has been also associated with alterations in RV function at rest and a blunted increase in RV function during exercise.[77] Patients with SSc and increased sPAP response to exercise are also impaired in their physical exercise capacity,[78] and postexercise sPAP inversely correlates with the maximum workload achieved and exercise time.[79] In this regard, patients with "borderline" mPAP at rest (21–24 mm Hg) and a hypertensive response during exercise present a very interesting phenotype[78]; their pulmonary arterial pressure increase significantly differs from the increase of normal subjects (~5 vs 3 mm Hg/L/min). This hemodynamic finding could be caused by early pulmonary vasculopathy or by concomitant cardiac or pulmonary disease.

The percentage of exercise increase in sPAP is high in SSc and clearly overestimates the subset of patients who will develop resting PAH.[79-81] Because elevated sPAP in SSc may occur also as a consequence of interstitial lung disease or LV systolic and/or diastolic dysfunction, caution should be taken to distinguish the different etiologies of PH. Echocardiographic assessment of increased PVR during exercise has been proposed to detect patients at higher risk for developing resting PAH but warrants further confirmation.[76,82-84] Additional information can be found in Supplemental Figures 1-7 and Videos 1-2 (available at www.onlinejase.com).

Congenital Heart Disease. The dynamic assessment of pressures, gradients, and flows represent the main clinical application of stress echocardiography in congenital heart disease (CHD). Stress echocardiography has been used for unmasking coronary artery involvement in Kawasaki disease,[85] for assessing the severity of LV outflow obstructions such as subaortic stenosis and aortic coarctation,[86] and for evaluating contractile reserve in systemic right ventricle[87] and tetralogy of Fallot.[88] Recently, stress echocardiography by semisupine bicycle exercise has been used for evaluating the response to exercise in young patients who underwent endovascular stenting for coarctation of the aorta.[89] This study demonstrated reduced systolic and diastolic myocardial reserve in patients with coarctation of the aorta compared with control subjects. However, the prognostic clinical implications require further study.

Early detection of pulmonary vascular involvement is a key point in evaluating patients with CHD. Nevertheless, the dynamic increase of pulmonary pressure and resistance during stress echocardiography might have a different predictive value depending on the underlying disease. Gabriels *et al.*[76] observed that patients with corrected atrial septal defect and abnormal pulmonary hemodynamic response to stress were unlikely to develop PAH at 3.7-year follow-up. Similarly, in 76 consecutive patients with open or closed systemic-to-pulmonary shunts, van Riel *et al.*[90] observed that the Master two-step test was able to detect an abnormal pulmonary vascular response among a significant number (21%) of patients with CHD during routine follow-up. Van de Bruaene *et al.*[91] found altered pulmonary hemodynamics during exercise in patients who underwent atrial septal defect closure later in life (>34 years). Patients with steeper increases of pulmonary pressure on EDE were considered to have early pulmonary vascular disease, though a clear threshold value for dynamic PAP increase in CHD is not yet defined.

Stress echocardiography is an emerging tool also in the pediatric population. However, despite the significant advances in stress imaging techniques, there are still relatively few studies published in children,[92-95] and limits of normal as well as clinical relevance of this technique requires additional evaluation. Additional information can be found in Supplemental Figures 8-13 and Videos 3-4 (available at www.onlinejase.com).

Table 6 Summary of proposed cutoff values

Condition	Proposed cutoff	Clinical correlation	Reference
Normal subjects (<55–60 y of age and <150-W workload)	Peak sPAP < 43 mm Hg		67
Well-trained athletes (>150-W workload)	Peak sPAP < 60 mm Hg		62
Screening in heritable PAH	Peak sPAP > 43 mm Hg	• Associated with increased prevalence of BMPR2 mutations • Contributes to predict manifest PAH	67,68
Screening in SSc	ΔsPAP > 18 mm Hg	• Contributes to predict manifest PAH (sensitivity of 50% and specificity of 90%) • Correlates with impaired physical exercise capacity	74,75
HFrEF	Peak sPAP > 60 mm Hg	• Associated with dynamic MR and exercise-limited dyspnea	100
MS (with discrepancy between Doppler findings and clinical symptoms or signs)	Peak sPAP > 60 mm Hg	• Recommended to evaluate the response of the mean mitral gradient and PAP	108
Primary MR (severe, asymptomatic)	Peak sPAP > 60 mm Hg	• Associated with markedly reduced 2-y symptom-free survival	114
AS (severe, asymptomatic)	Peak sPAP > 60 mm Hg	• Associated with a two-fold increased risk for cardiac events	8

BMPR2, Bone morphogenetic protein receptor type 2; *HFrEF*, HF with reduced ejection fraction.

PH due to Left Heart Disease

LV Dysfunction. PH and RV dilation and failure are frequent in patients with LV systolic and diastolic dysfunction and are independently associated with a worse outcome.[96-98] LV systolic dysfunction, diastolic filling abnormalities, and the degree of functional mitral regurgitation (MR) are key factors in generating histologic and hemodynamic changes of the cardiopulmonary vascular system, depending on the chronicity and severity of the process.

In patients with HF, sPAP is highly dynamic, and exercise PH seems due mainly to increased LV filling pressure and not to an abnormal rise in PVR.[99] Interestingly, the parameters that determine increased resting sPAP are not necessarily the same as those determining exercise PH,[100] underlining again the complexity and the importance of stress testing to better understand the physiopathology and explain symptoms. Increased resting sPAP is not the primary cause of exercise-limiting dyspnea in stable patients with chronic HF, whereas in those patients in whom exercise leads to an acute increase in LAP transmitted backward to the pulmonary circulation, a significant exercise-induced dyspnea is reported, mostly related to the presence and degree of dynamic MR.[100] Many data also show that resting sPAP values are not closely related to exercise-induced PH development, which is instead determined mostly by lack of LV contractile reserve, diastolic dysfunction, and worsening MR. Left intraventricular dyssynchrony at rest may also exacerbate the rise in sPAP during exercise.[101]

The resting TAPSE/sPAP ratio has been proposed as an estimation of the cardiac length-force relationship to provide a more comprehensive noninvasive assessment of RV contractile state and reserve. This parameter seems to be an independent predictor of cardiac death in patients with HF, irrespective of LV morphologic characteristics and degree of dysfunction, and has the advantage of being applicable to both HF with reduced and preserved ejection fraction.[24] Exercise TAPSE and sPAP have also demonstrated to be independent hemodynamic determinants of the rate of oxygen consumption increase to the work rate ($\Delta V_{O_2}/\Delta$ work rate slope), an indicator of cardiovascular efficiency. This underlines the pathophysiologic link between aerobic function and the uncoupling of the cardiopulmonary vascular unit.[102] The main publications on sPAP response to EDE in patients with HF are listed in Table 8.

Lung ultrasound B-lines have been recently proposed as the sonographic sign of EVLW in patients with HF.[46-48] Dynamic increase in EVLW is a well-established event, contributing to symptom exacerbation and exercise intolerance.[103] Exercise increase in B-lines correlates with exercise increase in E/e′ ratio and sPAP, and provides the additional information of EVLW development (pulmonary congestion) to the more established noninvasive assessment of increased LV filling pressures (hemodynamic congestion).[104] Moreover, it brings valuable prognostic information.[49] Additional information can be found in Supplemental Figures 14-19 and Videos 5-6 (available at www.onlinejase.com).

Valvular Heart Disease. The usefulness of EDE in the management of VHD has been highlighted in many studies.[7,105] Beyond the assessment of symptoms and changes on electrocardiography, the evaluation of VHD severity and the evolution of sPAP during exercise provide additional and incremental prognostic information, which aid in clinical decision making.[18,106] Current American and European guidelines do not formally include exercise-induced PH as a criterion that may indicate surgery.[107-109]

Aortic Stenosis. PH is rare (6%) in patients with asymptomatic aortic stenosis (AS); however, when present, PH is a strong predictor of reduced exercise capacity and poor outcome.[8,110] In asymptomatic AS, PH is often uncovered during an exercise test and is usually defined as sPAP > 60 mm Hg. Exercise PH is related to the level of sPAP at rest, sex, and the level of LV relaxation (e′ velocity) and left atrial (LA) compliance.[8] For a given increase in LV filling pressure, patients with limited changes in LA dimensions during exercise (i.e., exhausted LA compliance reserve) displayed higher increases in pulmonary pressure; this was even truer if LA emptying was no longer facilitated by recruitable LA function. Lancellotti *et al.*[8] reported a high rate of cardiac death (12%) and significantly reduced cardiac event–free survival in truly asymptomatic severe AS and exercise-induced

Table 7 Pulmonary pressure response to exercise in patients at high risk for PAH and in patients with overt PAH

Study	Associated disease (patients; gender)	Age (y) height (cm)/weight (kg)	Exercise protocol	RAP estimate (mm Hg)	Baseline sPAP (mm Hg)	Peak sPAP (mm Hg)
Himelman *et al.* (1989)	COPD (*n* = 36; 15 female)	32–80 —	Supine bicycle (10 or 25 W/2 incr.)	From IVC	46 ± 20 22 ± 4 (control)	83 ± 30 31 ± 7
Oelberg *et al.* (1998)	Asymptomatic ASD (*n* = 10; 4 female)	52.9 ± 11.2 167 ± 7/82 ± 20	Upright bicycle (10 W/2 incr.)	From IVC	31 ± 8 17 ± 8 (control)	51 ± 10 19 ± 8
Grünig *et al.* (2000)	HAPE-S (*n* = 9; male)	45 ± 8 182 ± 8/82 ± 9	Supine bicycle (25 W/2 incr.)	Fixed value (5 mm Hg)	28 ± 4 27 ± 4 (control)	55 ± 11 36 ± 3
Grünig *et al.* (NR) 2000	Relatives of iPAH patients (*n* = 52)	—	Supine bicycle (25 W/2 incr.)	Fixed value	24 ± 4 (NR) 23 ± 3 (AR)	37 ± 3 56 ± 11 (AR)
Collins *et al.* (2006)	Scleroderma (*n* = 51; 49 female)	53.9 ± 12.0 —	Treadmill (5.9 ± 1.9 METs)	Fixed value (10 mm Hg)	24 ± 8	38 ± 12
Alkotob *et al.* (2006)	Scleroderma (*n* = 65; 56 female)	51 ± 12	Treadmill (1–13.4 METs)	Fixed value (5 mm Hg)	25 ± 8	39 ± 8
Kiencke *et al.* (2008)	HAPE-S (*n* = 10)	33 ± 2	Supine bicycle	—	19 ± 4 17 ± 3 (control)	23 ± 6 11 ± 5
Steen *et al.* (2008)	Scleroderma (*n* = 54; 51 female)	—	Treadmill (85% predicted maximal HR)	Fixed value (10 mm Hg)	34.5 ± 11.5	51.4
Grünig *et al.* (2009)	Relatives of iPAH patients (*n* = 291; 125 female)	37 ± 16 169 ± 9/69 ± 15	Supine bicycle (25 W/2 incr.)	From IVC	20.7 ± 5.4 20.4 ± 5.3 (control)	39.5 ± 5.6 35.5 ± 5.4
Reichenberger *et al.* (2009)	Scleroderma (*n* = 33; 31 female)	54 ± 11	Supine bicycle (30 W/2 incr.)	From IVC	23 ± 8	40 ± 11
Möller *et al.* (2010)	ASD and VSD (*n* = 44; 25 female)	17.5 ± 3.3 167 ± 8.8/ 59 ± 11	Supine bicycle (25 W/2 incr.)	From IVC	20.7 ± 5.3 21.8 ± 3.6 (control)	37 (24–76) 39 (17–63)
Kovacs *et al.* (2010)	Connective tissue disease (*n* = 52; 42 female)	54 ± 11 167 ± 8/69 ± 12	Supine bicycle (25 W/2 incr.)	From IVC	27 ± 5* 23 ± 3† 23 ± 3‡	55 ± 10* 29 ± 8† 30 ± 7‡
D'Alto *et al.* (2011)	SSc (*n* = 172; 155 female)	51.8 ± 21.5 163 ± 9/66 ± 14	Supine bicycle (25 W/2 incr.)	From IVC	26.2 ± 5.3 20.6 ± 3.7 (control)	36.9 ± 8.7 25.9 ± 3.3
Gargani *et al.* (2013)	SSc (*n* = 164; 150 female)	58 ± 13 162 ± 7/62 ± 11	Semisupine bicycle (25 W/2 incr.)	From IVC	27.9 ± 5.4	49.6 ± 12.9
Grünig *et al.* (2013)	PAH, CTPEH (*n* = 124; 87 female)	54 ± 16 167 ± 7/74 ± 17	Supine bicycle (25 W/2 incr.)	From IVC	64 ± 17	98 ± 25¶

Codullo *et al.* (2013)	SSc (n = 170; 153 female)	55.2 ± 13	Supine bicycle	From IVC (5 mm Hg)	23.7 ± 8.1[#] 29.5 ± 5.5[**]	33.1 ± 2.6[#] 47.7 ± 12.2[**]
Voilliot *et al.* (2014)	SSc (n = 45; 34 female)	54 ± 3 (BMI 24 ± 5 kg/m^2)	Semisupine bicycle (25 W/2 incr.)	From IVC	25 ± 7	46 ± 14
Nagel *et al.* (2015)	SSc (n = 76; 64 female)	58 ± 14 1.8 ± 0.2	45° cycle ergometer	From IVC	25.6 ± 7.3[§] 52.0 ± 18.0[‖]	49.9 ± 12.7[§] 83.9 ± 18.9[‖]

AR, Abnormal response to exercise; *ASD*, atrial septal defect; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *CTEPH*, chronic thromboembolic PH; *HAPE-S*, high altitude pulmonary edema susceptible; *HR*, heart rate; *incr.*, increments; *iPAH*, idiopathic PAH; *IVC*, inspiratory collapse of the inferior vena cava; *NR*, normal response to exercise; *RAP*, RA pressure; *VSD*, ventricular septal defect; –, data not available.
[*]Exercise sPAP > 40 mm Hg.
[†]Exercise sPAP < 40 mm Hg, peak V_{O_2} < 75%.
[‡]Exercise sPAP < 40 mmHg, peak V_{O_2} > 75%.
[§]No PH group of 54 patients (mPAP < 25 mm Hg).
[‖]Twenty-two patients with manifest PH (mPAP > 25 mm Hg).
[¶]In the multivariate Cox model analysis adjusted for age and sex, sPAP increase during exercise and peak V_{O_2} per kilogram remained independent prognostic markers (hazard ratios, 2.56 for peak V_{O_2} per kilogram and 2.84 for sPAP increase).
[#]Patients (n = 164) with complete follow-up who did not develop PH.
[**]Patients (n = 6) who did develop PH.

PH. Overall, exercise PH doubled the risk for cardiac events at 3-year follow-up, with an incremental prognostic value beyond peak aortic jet velocity. Large increase in transaortic pressure gradient, exercise PH, and impaired LV contractile reserve provide the clinician with a straightforward evaluation of the LV burden due to increased afterload in AS. The presence of exercise PH should encourage closer monitoring. Conversely, patients with no exercise PH can be followed up safely.[105]

Mitral Stenosis. EDE is useful for assessing the functional significance of mitral stenosis (MS), particularly when discrepancies between clinical and resting echocardiographic data exist.[107,108] The level of sPAP is an indicator of the overall hemodynamic burden of MS and has an important impact on individual outcome.[111] Exercise PH may relate to reduced LA compliance, increased LAP, lower pulmonary vascular compliance, and increased PVR in relation to severe MS.[112] However, the clinical interpretation of the development of exercise PH should be performed cautiously in patients with MS. Indeed, according to exercise load and time, some patients may reach the threshold of PH, whereas their functional capacity and pulmonary function are not impaired. In a recent study, Brochet *et al.*[113] reported that the relative increase in sPAP in the early exercise stages (≤60 W) but not peak exercise PH (sPAP > 60 mm Hg) was associated with a higher rate of exercise dyspnea and/or mitral valve intervention during follow-up. Therefore, the evaluation of the kinetics of exercise-induced changes in sPAP may be more useful for risk stratification and the management of patients with MS.

Primary MR. In asymptomatic primary MR with normal ejection fraction, exercise PH can be observed in a large proportion of patients (46%).[114] The increase in sPAP often relates to dynamic MR.[115] Interestingly, exercise PH is more accurate than resting sPAP in predicting the occurrence of symptoms and cardiovascular events during follow-up. Exercise PH also represents an independent predictor of mitral valve surgery requirement, especially when combined with exercise RV dysfunction (TAPSE < 19 mm).[116] Compared with patients without exercise PH or RV dysfunction, patients with one of these two conditions have an intermediate outcome. The negative predictive value of exercise PH persists postoperatively with a significant reduction in event-free survival and higher rate of late atrial fibrillation or cardiac-related hospitalization.[117] In the previous European Society of Cardiology guidelines, isolated exercise PH was a class IIb indication for mitral valve repair in asymptomatic patients without LV dysfunction or dilatation,[118] but it was not confirmed in the 2017 guidelines.[107] A close follow-up in a heart valve clinic[119] should still be recommended.

Secondary MR. In secondary MR, dynamic MR and increased LAP mainly determine exercise increase in sPAP.[100,120] The magnitude of rise in sPAP during exercise is more pronounced in patients with exercise-limiting dyspnea and is involved in the pathogenesis of acute pulmonary edema, irrespective of the LV function.[121,122] The best predictive cutoff value for the increase in sPAP in patients with recurrent pulmonary edema is 21 mm Hg.[122] Of note, exercise PH is observed in about 40% of patients with chronic LV systolic dysfunction.[123] Exercise PH negatively influences the outcome regardless of the degree of baseline MR.[124] It is associated with a 3.7-fold increased risk for combined cardiac events and a 5.3-fold increased risk for cardiac-related death during follow-up.[123] Conversely, the lack of exercise PH confers a good prognosis. The risk for cardiac event during follow-up also increases exponentially with the level of exercise sPAP. Beyond 70 and 80 mm Hg, the risk for an event increases by 50%

Table 8 Pulmonary pressure response to exercise in left heart disease

Study	Patients/gender BMI/BSA	Age (y)	EF (%)	Exercise protocol Workload (W/METs)	RAP estimate (mm Hg)	Baseline sPAP (mm Hg)	Peak sPAP (mm Hg)	Remarks
HF								
Lancellotti *et al.* (2003)	Survivors, 89/60 M Nonsurvivors, 9/6 M	65 ± 11 69 ± 9	38 ± 5 36 ± 7	Tilting bicycle (25 W/2 incr.)	—	26 ± 10 22 ± 9	44 ± 18 48 ± 16	Degree of MR provides independent prognostic information
Tumminello *et al.* (2007)	46/— —	66 ± 10	30 ± 6	Semisupine bicycle (25 W/2 incr.)	Fixed value (10)	31 ± 11	52 ± 18	Increase in sPAP relates to dynamic MR and exercise-limited dyspnea
Ennezat *et al.* (2008)	104/75 M	54 ± 12	26 ± 10	Tilting bicycle (20 W/3-min step)	—	29 ± 9	44 ± 18	Exercise TDE data do not provide additional prognostic information over resting TDE parameters
Marèchaux *et al.* (2008)	85/64 M —	57 ± 13	26 ± 8	Tilting bicycle (25 W/2 incr.)	No added value	27 ± 8	43 ± 18	RV systolic dysfunction is inversely related to exercise-induced PH
Bandera *et al.* (2014)	136*/86 M Group A†, 36/20 F Group B†, 100/30 F	64 ± 11 67 ± 10 61 ± 12	47 ± 14 52 ± 16	Tilting bicycle 68 ± 28 91 ± 40.1	From IVC	37 ± 17 33 ± 14	61 ± 19 51 ± 18	Peak sPAP (OR, 1.06; 95% CI, 1.01–1.11; P = .01) and exercise TAPSE (OR, 0.88; 95% CI, 0.80–0.97; P = .01) as main cardiac determinants of $\Delta V_{O_2}/\Delta WR$ flattening
Degenerative asymptomatic MR (at least moderate)								
Magne *et al.* (2010)	78/44 M BMI 26 ± 4 kg/m^2	61 ± 13	69 ± 6	Tilting bicycle (25 W/2 incr.)	Fixed value (10)	39 ± 11	62 ± 17	Exercise PH is associated with markedly low 2-y symptom-free survival
Kusunose *et al.* (2013)	196/126 M BMI 26 ± 4 kg/m^2	56 ± 13	65 ± 3	— METs 8.6 (7.2–10.5)	From IVC	39 ± 8	56 ± 13	Exercise TAPSE (HR, 0.32; 95% CI, 0.18–0.56; P < .001) and exercise sPAP (HR, 1.03; 95% CI, 1.02–1.05; P < .001) were independently associated with event-free survival

Asymptomatic severe AS								
Lancellotti *et al.* (2012)	105/62 M BSA 1.8 ± 0.2 m^2	71 ± 9	67 ± 7.6	Tilting bicycle (4.8 ± 1.2 METs)	Fixed value (10)	38 ± 8	62 ± 16	Exercise PH is associated with a 2-fold increased risk for cardiac events
Asymptomatic MS								
Brochet *et al.* (2011)	48/16 M —	51 ± 14	—	Semisupine bicycle (>60 W) 48%	Fixed value (10)	36 ± 5	68 ± 7	Onset of dyspnea was associated with a high increase of relative sPAP (>90% at 60 W; OR, 2.31; 95% CI, 1.2–4.8; $P = .02$)

BMI, Body mass index; *BSA*, body surface area; *EF*, ejection fraction; *F*, female; *HR*, hazard ratio; *IVC*, inferior vena cava; *M*, male; *OR*, odds ratio; *RAP*, RA pressure; *TDE*, transthoracic Doppler echocardiography; *WR*, work rate.
*The underling diseases were HF with reduced ($n = 54$ [40%]) or preserved ($n = 8$ [6%]) EF, history of stable CAD ($n = 18$ [13%]), high-risk patients with hypertrophic cardiac remodeling ($n = 33$ [24%]), hypertrophic or restrictive cardiomyopathy ($n = 5$ [4%]), and mitral or tricuspid valvular regurgitation ($n = 18$ [13%]).
†Change in V_{O_2}/change in WR flattening (group A), not flattening (group B).

and 100%, respectively. Therefore, the presence of elevated exercise sPAP can unmask a subset of patients who may benefit from targeted therapeutic approaches.

PH due to Lung Disease

Exercise echocardiography in chronic lung disease population is feasible, providing not only continuous mPAP/CO relationship but also concomitant assessment of RV afterload, function, and deformation. The term *cor pulmonale* classically refers to RV maladaptation in response to chronic respiratory disease.[125] However, most current literature in chronic lung disease focuses on the clinical application of cardiopulmonary exercise testing and/or invasive RHC to stress the right heart during exercise. The identification of exercise PH may in fact serve as a sensitive index to detect early RV maladaptation in patients with underlying parenchymal lung disease.

Abnormal pulmonary hemodynamics are frequent in the setting of lung disease and correlate with exercise capacity.[126,127] For instance, in interstitial lung disease, mPAP/CO slope ≥ 3 mm Hg/L/min during exercise is associated with higher V_D/V_T (dead space volume/tidal volume) and lower peak V_{O_2} and CO.[128] The mPAP response to exercise should be interpreted relative to changes in CO and averaged over the respiratory cycle.[18,40] However, during exercise, the majority of patients with chronic lung disease, including sleep apnea, tend to have normal to mild PH, typically arising from a high CO state.[129-131] Nevertheless, aberrant increases in sPAP can be accompanied by a lower SV, relative to healthy control subjects, suggesting an abnormal pressure-flow relationship. Unfortunately, these pressure assessments are often influenced by intrathoracic pressure swings during exercise.[132,133] Others have suggested that the diseased lung itself may exert an external constraint on the heart. These effects can directly modify cardiac performance, as seen during echocardiographic studies in patients with acute bronchoconstriction, in whom acute RV dilation occurs only during inspiration and normalizes in expiration.[134,135]

Despite the reliance on echocardiographic estimation of sPAP for the evaluation of PH, in patients with chronic respiratory disease, sPAP estimations have only a moderate correlation compared with RHC measurements ($r = 0.69$).[136] In fact, RVSP is a poor predictor of PH in idiopathic pulmonary fibrosis.[137] However, rather than relying on single absolute sPAP values, exercise Doppler echocardiographic assessment of RV dysfunction and dilatation may better stratify a subpopulation with idiopathic pulmonary fibrosis at increased risk for death independent of mPAP.[138]

Importantly, PH may worsen during exercise, sleep, and exacerbations of the underlying chronic lung disease. In this regard, PH manifest during exercise in patients with chronic obstructive pulmonary disease is best discriminated by a ratio of RV preejection period to time to peak velocity ≥ 3 and/or time to peak velocity < 100 msec.[139] Similarly, in idiopathic pulmonary fibrosis with otherwise normal RV markers of function and afterload (i.e., RV size and function, TAPSE, and sPAP), speckle-tracking 2D strain echocardiography identified early impairment of cardiac function (RV free wall strain ≤ −12%) as an independent predictor of cardiac-related mortality.[140]

LIMITATIONS AND FUTURE DIRECTIONS FOR STRESSING THE RIGHT VENTRICLE

The status of the right ventricle has changed from being considered a passive reservoir to a chamber that carries the potential for adversely affecting the clinical outcome in several diseases. Experience with

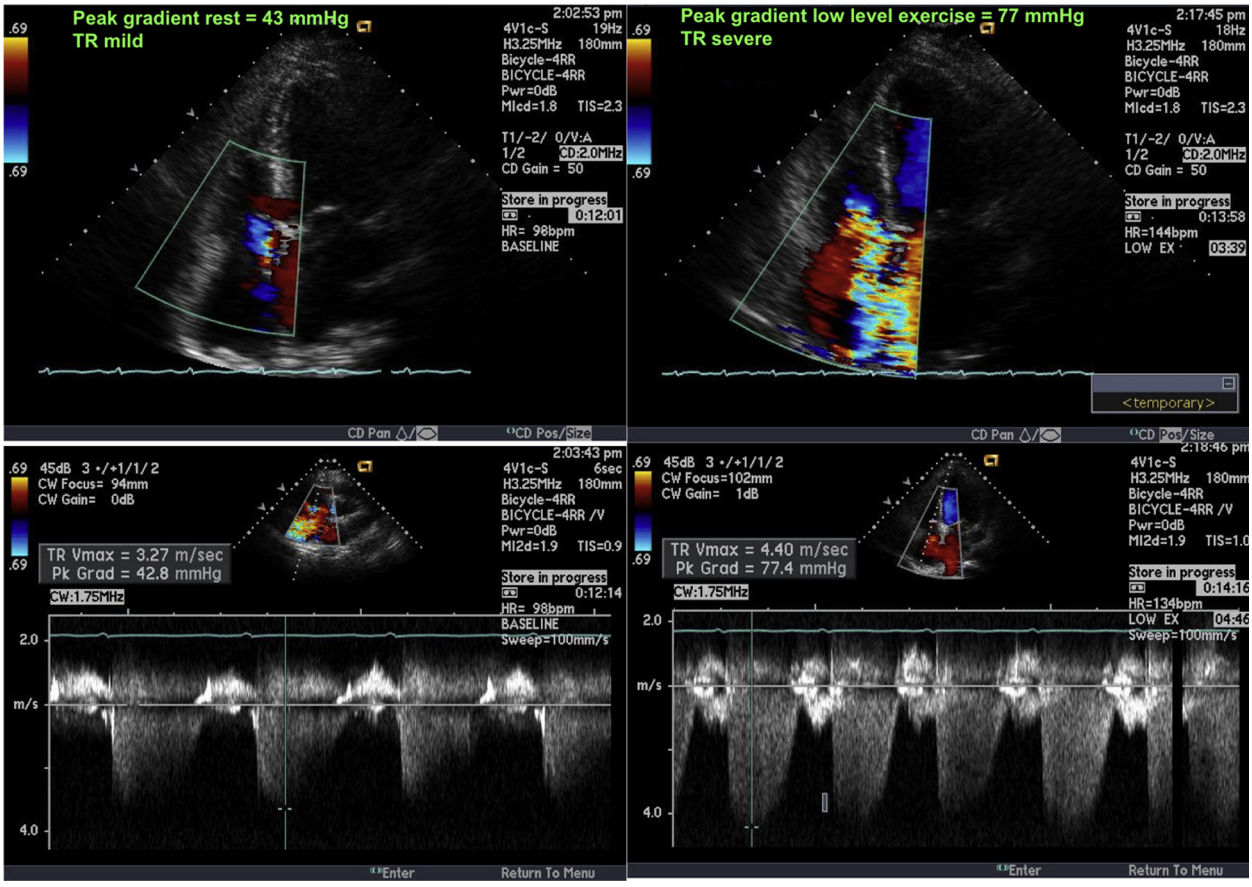


Figure 1 (*Top left*) Still frame from 2D real-time image of four-chamber apical view showing normal RV size and shape and mild tricuspid regurgitation (TR). (*Top right*) At peak exercise the right ventricle dilates, function qualitatively decreases, and moderate to severe TR appears by color flow. (*Bottom left*) Rest Doppler shows moderately elevated pulmonary pressure at 43 mm Hg (+RA). (*Bottom right*) At peak exercise, PAP is 77 mm Hg + RA, the TR jet is denser consistent with an increase in regurgitant volume, and there is a shape change such the configuration of the continuous-wave signal has a sharper peak (despite a sweep speed of 100 mm/sec), possibly indicating a TR v wave.

exercise and the right heart began more than three decades ago when sites began performing supine bicycle exercise in conjunction with echocardiography and Doppler. The impetus was the realization that, in addition to segmental wall motion evaluation for ischemia, hemodynamics such as sPAP and transaortic pressure gradients could be derived during ramped dynamic exercise (Figure 1).

Proper noninvasive evaluation of the right ventricle during stress is enhanced by measuring comprehensive hemodynamics during stress. Measurement of peak RVSP by echocardiography is contentious and frequently taken to task for its allegedly poor correlation with invasive hemodynamics.[141] But careful review of those plotted data shows a variation between individual estimations as high as 20 mm Hg in the moderately elevated range of PAP and a few so-called leverage points in the higher range of pressure, where the actual number is less important. Adding to the natural variation of peak RV pressures is the difficulty in measuring right atrial (RA) pressure from the inferior vena cava. Furthermore, peak RV pressure by catheter is highly sensitive to phases of respiration. For this reason, it is not by chance that guidelines define PH using mPAP and not peak pressure. Nonetheless, many practitioners go no further than using "peak PAP" as the sole nugget of information about the state of the pulmonary circulation rather than part of the comprehensive view derived from Ohm's law: pressure = flow × resistance. Exercising amplifies some of the limitations of imaging the right heart by larger lung movements during the effort, hiding parts of the RV wall, and probe repositioning required for visualizing both the inflow and outflow tract is time consuming. Furthermore, the act of image acquisition of the RV at rest and even more so during exercise requires strong operator skills sets. When the pulmonary pressure response is a main clinical issue, saline contrast enhancement can be used to improve tricuspid regurgitation signals, taking care to measure the envelope and not the outlying signals.

However, echocardiography is a noninvasive, low-cost technique that allows measurements of pulmonary hemodynamics and myocardial contractility, thus remaining the method of choice for stress testing the right ventricle. The complex RV shape as a half-moon wrapped around the left ventricle is incompatible with a Euclidian mathematical model as used for the left ventricle; its shape has restricted the measurement of RV volumes on 2D images. However, the introduction of 3D imaging could overcome this limitation. Three-dimensional echocardiographic imaging has successfully been used for the left ventricle for the past decade but is still lagging regarding the right ventricle. Recently a 3D modality that is capable of accounting for the RV triangular shape with an inflow and an outflow

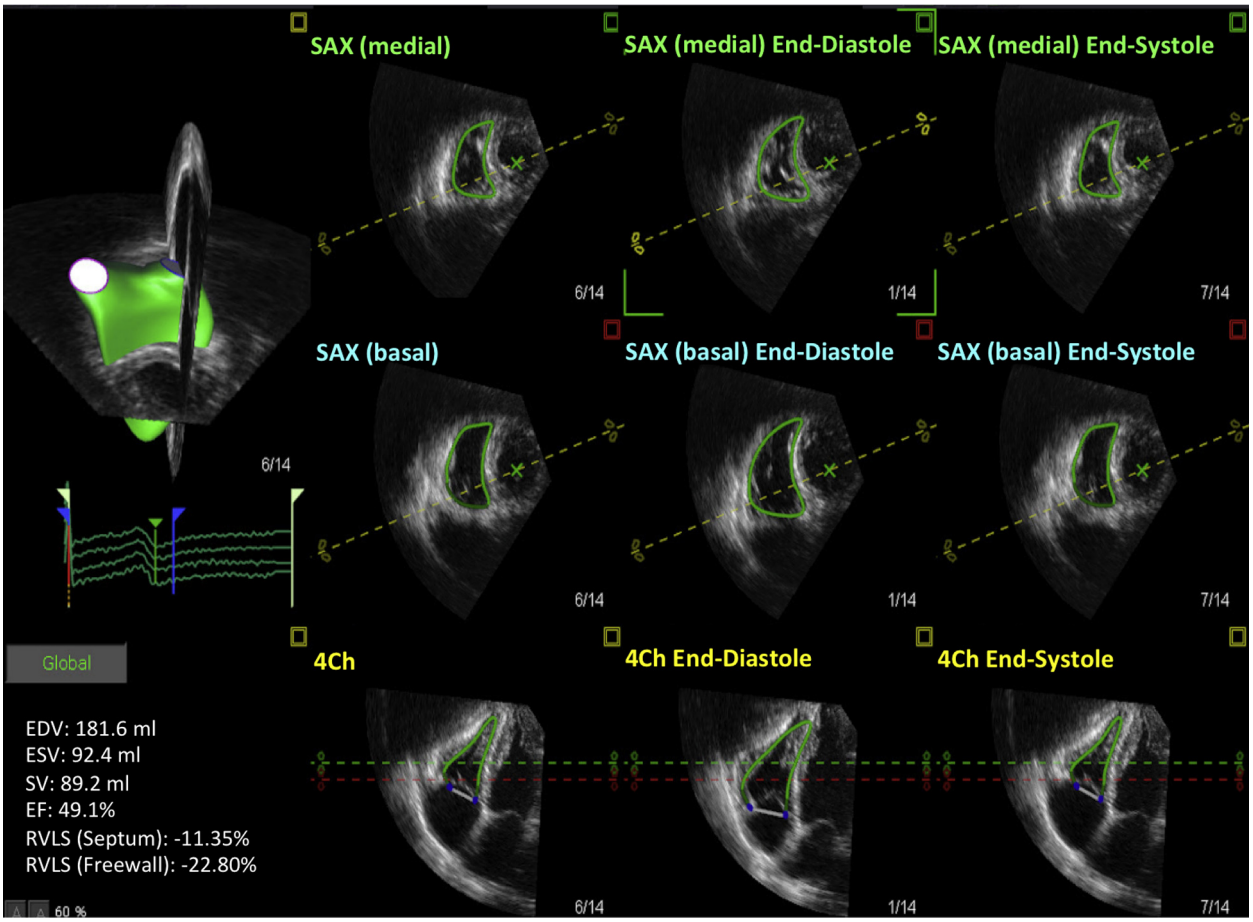


Figure 2 Three-dimensional image encompasses the entire RV chamber and allows display and analysis of multiple projections. Independent of geometry, these projections can be combined into a 3D display and viewed in real time. The quantitative values at the *bottom left* of the image accurately reflect RV size. *4Ch*, Four-chamber; *SAX*, short-axis.

tract has been developed.[142] Programs for quantitation of the right ventricle from 3D data sets have been introduced. These data sets allow volumetric calculations and have sufficient data to allow a 3D printer to produce an entire right ventricle (Figures 2 and 3). However, feasibility data during stress are not available, and these techniques should be considered research tools at the moment. Underestimation of RV volume by 2D imaging is improved on 3D echocardiography but, compared with magnetic resonance imaging, is not completely resolved.[143]

Strain analysis has enhanced the diagnostic possibilities of ventricular function.[144] Evaluation of strain using speckle-tracking has been introduced for RV analysis, with promising results. However, the software usually used is adapted for the left ventricle and is challenged by the 3- to 4-mm-thin RV wall that requires tracking speckles through an adequate sample. An attempt to use the strain function during exercise has shown large variability of the results due to difficulties in image acquisition and the software making it, at times, less valuable in use for clinical practice.[37] An improvement of RV adapted software tracking may extend the use of this valuable modality. Combining 3D echocardiography and strain analysis could open a new avenue in the global evaluation of the right ventricle.

NEXT-GENERATION STRESS ECHOCARDIOGRAPHY: WHAT TO DO NOW

There is little doubt that there is presently a gap between the wealth of information that stress echocardiography can provide about the cardiopulmonary vascular system and the limited role in general cardiology guidelines and clinical practice. The field has evolved rapidly, but as a consequence of this rapid growth, the clinical use of stress echocardiography often lacks the necessary supportive evidence and is slowed by confusion on methodologic issues, lack of large-scale studies, deregulated indications, and missing standardization in the way the examination is performed, analyzed, and used. Yet the advantages of stress echocardiography make it especially attractive in an era of increasing societal concerns on health care costs and cumulative effects of ionizing radiation exposure.

In the panel of evaluated variables, the common reductionist approach identifying sPAP with pulmonary vascular reserve should be replaced with a more comprehensive approach so that the test will remain simple and feasible but allow a more integrated, pathophysiologically plausible approach to the different key players of the cardiopulmonary vascular system[145] (Table 9).

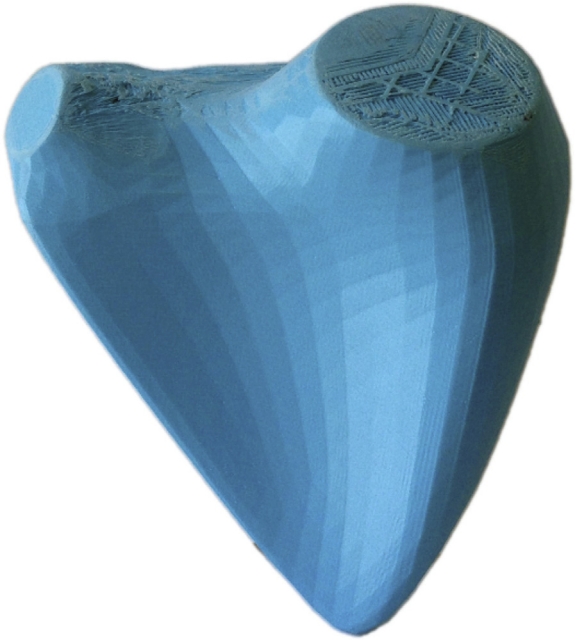


Figure 3 The 3D data set was used in conjunction with a 3D printer to produce a model of the right ventricle. Images courtesy Berthold Klas and Bernhard Mumm (TomTec, Unterschleissheim, Germany).

Table 9 Stressing the cardiopulmonary vascular system

	What we have	What we need
Approach	Reductionist	Comprehensive
Pulmonary vascular reserve	sPAP	sPAP/CO, mPAP/CO
RV contractile reserve	TAPSE	sPAP/RVESA, TAPSE/sPAP
Alveolar-capillary membrane	Missing	B-lines (EVLW)
Type of studies	Efficacy	Effectiveness

RVESA, RV end-systolic area.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.echo.2018.01.002.

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APPENDIX

Case 1: Connective Tissue Disease

This case presents a 53-year-old woman with SSc. Dyspnea was present (New York Heart Association [NYHA] class II). There were no risk factors for CAD. Pulmonary function test results were normal (Supplemental Figures 1-7, Videos 1 and 2).

Resting echocardiography showed normal LV and LA dimensions, normal ejection fraction, no regional wall motion abnormalities, normal RV and RA dimensions, TAPSE of 20 mm, and sPAP of 30 mm Hg (27 mm Hg RV/RA gradient + 3 mm Hg RA pressure).

Exercise was stopped at 50 W for dyspnea. At peak stress, sPAP was 49 mm Hg, TAPSE was 22 mm, E/e′ ratio was 7.2, ΔmPAP/ΔCO was 3.38, and TAPSE/sPAP decreased from 0.61 to 0.45 from rest to peak exercise. ΔmPAP/ΔCO was >3 mm Hg/L/min without significant increase in E/e′ ratio.

Close clinical and imaging follow-up was suggested.

Case 2: CHD

This case presents a 64-year-old woman with patent ductus arteriosus with a small left-to-right shunt, not corrected. Dyspnea was present (NYHA class II). Arterial hypertension was present (Supplemental Figures 8-13, Videos 3 and 4).

Resting echocardiography showed normal LV and LA dimensions, normal ejection fraction, no regional wall motion abnormalities, normal RV and RA dimensions, TAPSE of 24 mm, FAC of 50%, and sPAP of 28 mm Hg.

At peak stress, sPAP significantly increased to 61 mm Hg, TAPSE was 26 mm, ΔmPAP/ΔCO was 5 mm Hg/L/min, and TAPSE/PASP decreased from 0.86 to 0.43 from rest to peak exercise.

Close clinical and imaging follow-up was suggested.

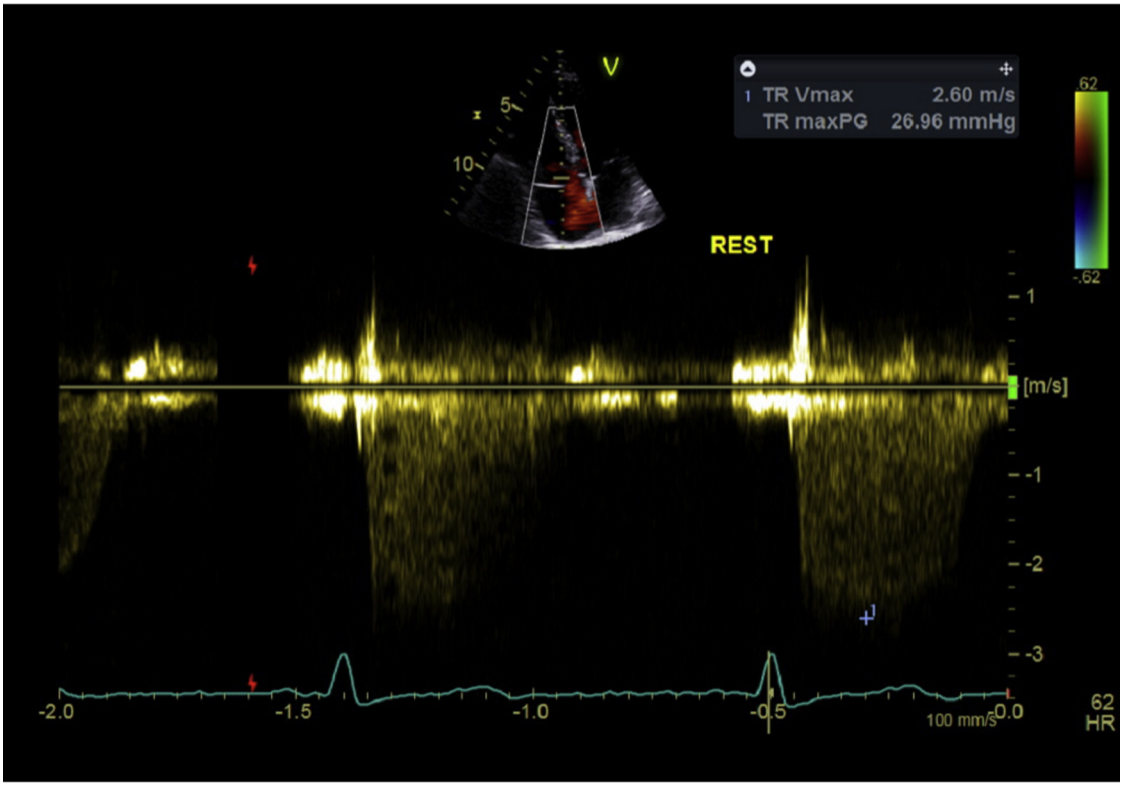
Case 3: HF

This case presents a 72-year-old woman with left bundle branch block and hypertensive heart disease. There was no significant coronary stenosis on angiography. Dyspnea was present (NYHA class II) with optimal medical therapy (Supplemental Figures 14-19, Videos 5 and 6).

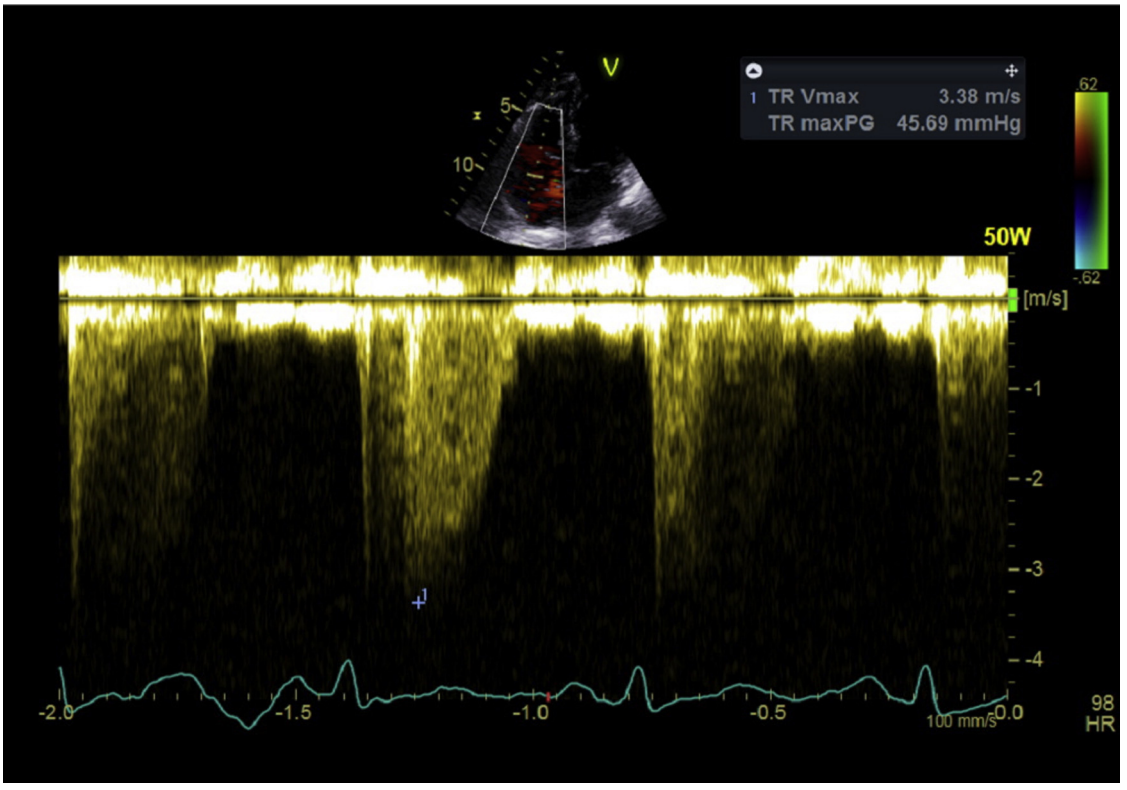
Resting echocardiography showed reduced ejection fraction, paradoxical interventricular septal motion, normal RV and RA dimensions, TAPSE of 24 mm, and sPAP of 36 mm Hg.

At peak exercise, MR worsened, there was no increase in estimated CO, sPAP significantly increased to 73 mm Hg, TAPSE was 25 mm, ΔmPAP/ΔCO was 5 mm Hg/L/min, and TAPSE/PASP decreased from 0.53 to 0.34 from rest to peak exercise.

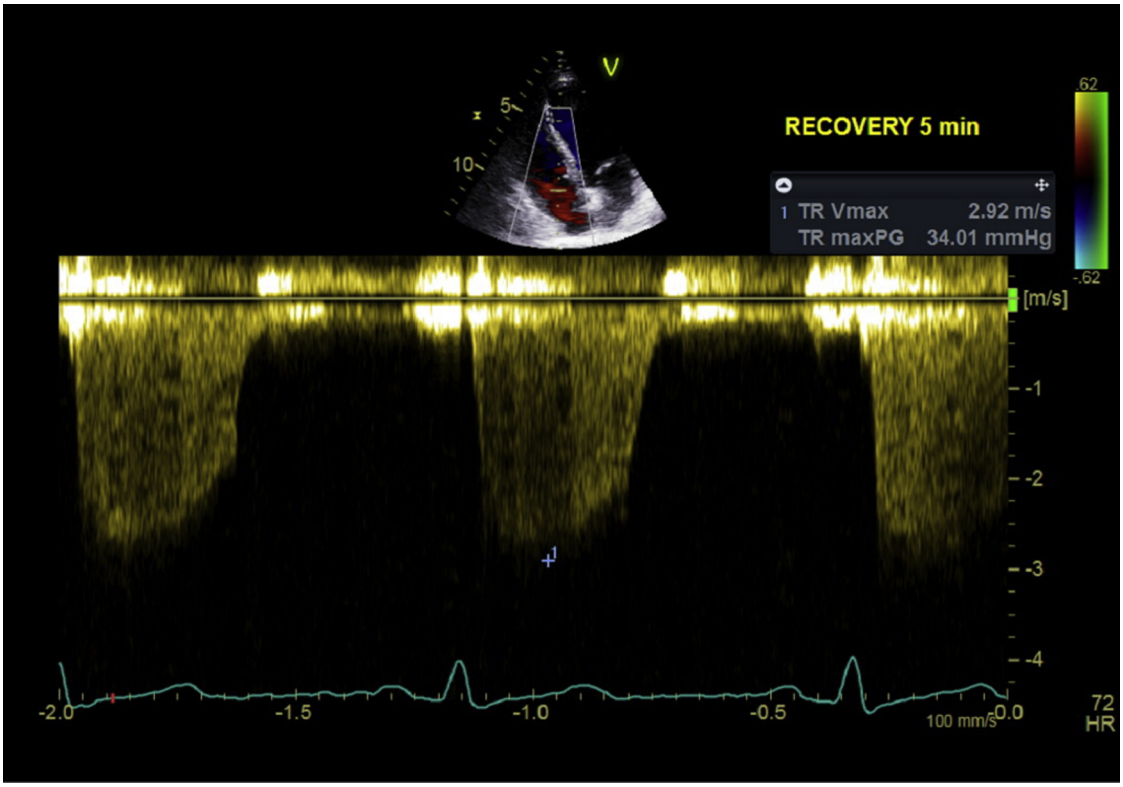
On the basis of integration of the clinical and rest and stress echocardiographic evaluation, the patient was referred for cardiac resynchronization therapy.



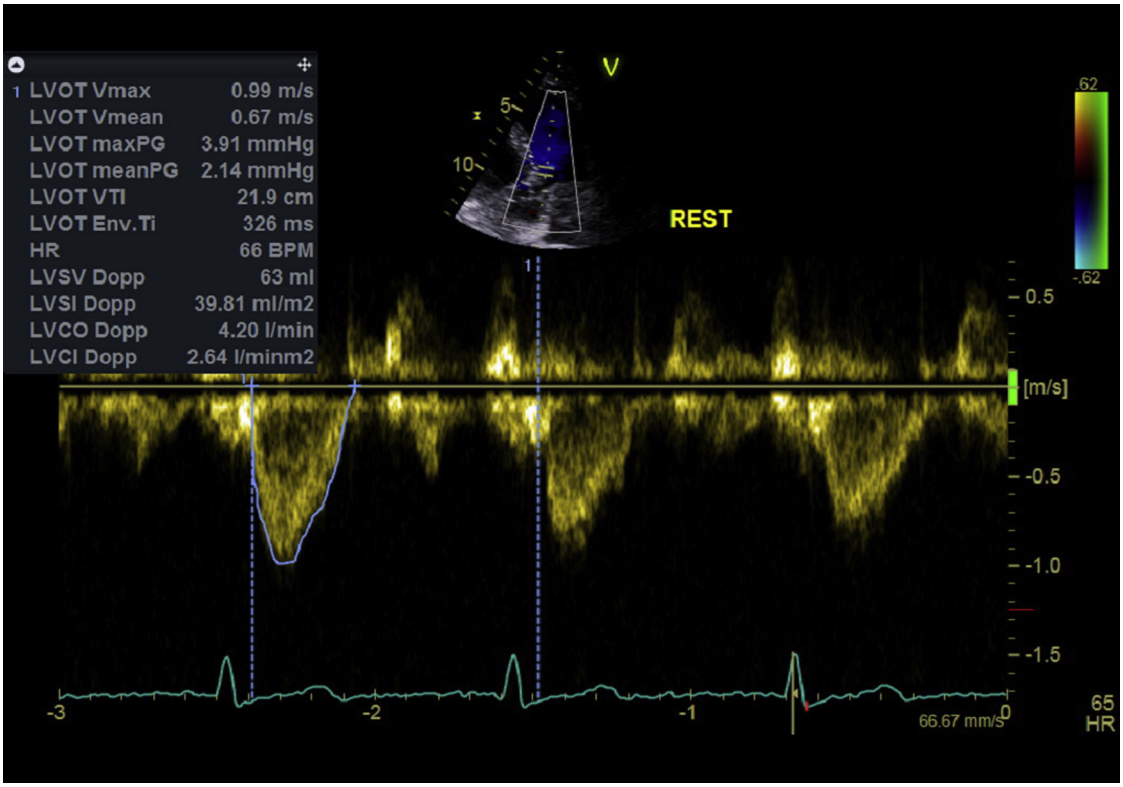
Supplemental Figure 1 SSc. Tricuspid regurgitation maximal velocity at rest.



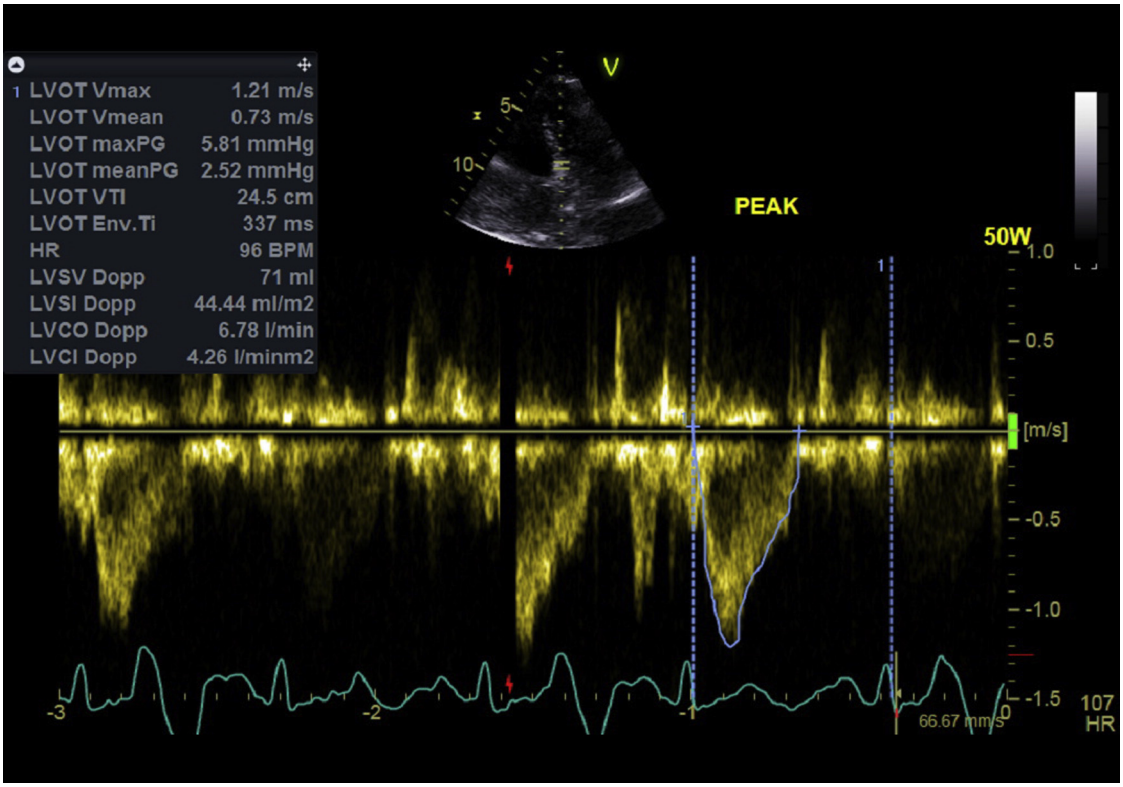
Supplemental Figure 2 SSc. Tricuspid regurgitation maximal velocity at peak stress.



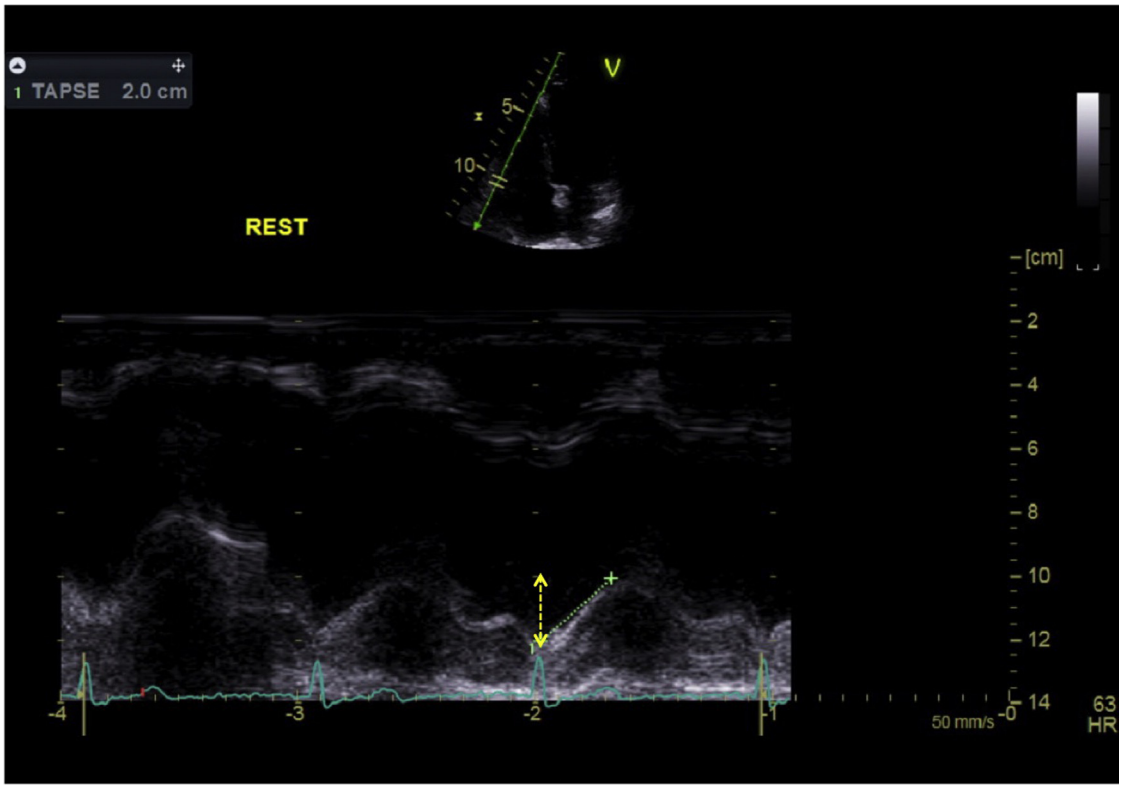
Supplemental Figure 3 SSc. Tricuspid regurgitation maximal velocity at 5-min recovery.



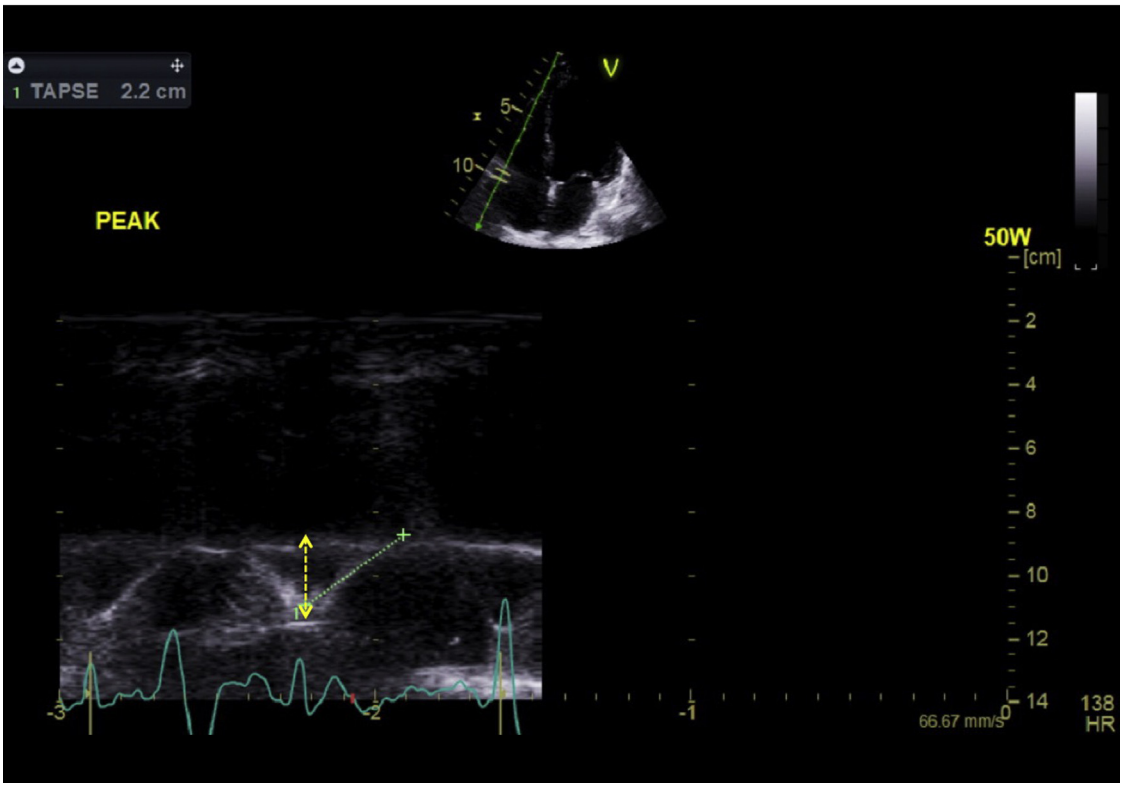
Supplemental Figure 4 SSc. Velocity-time integral Doppler spectrum at rest (to calculate CO).



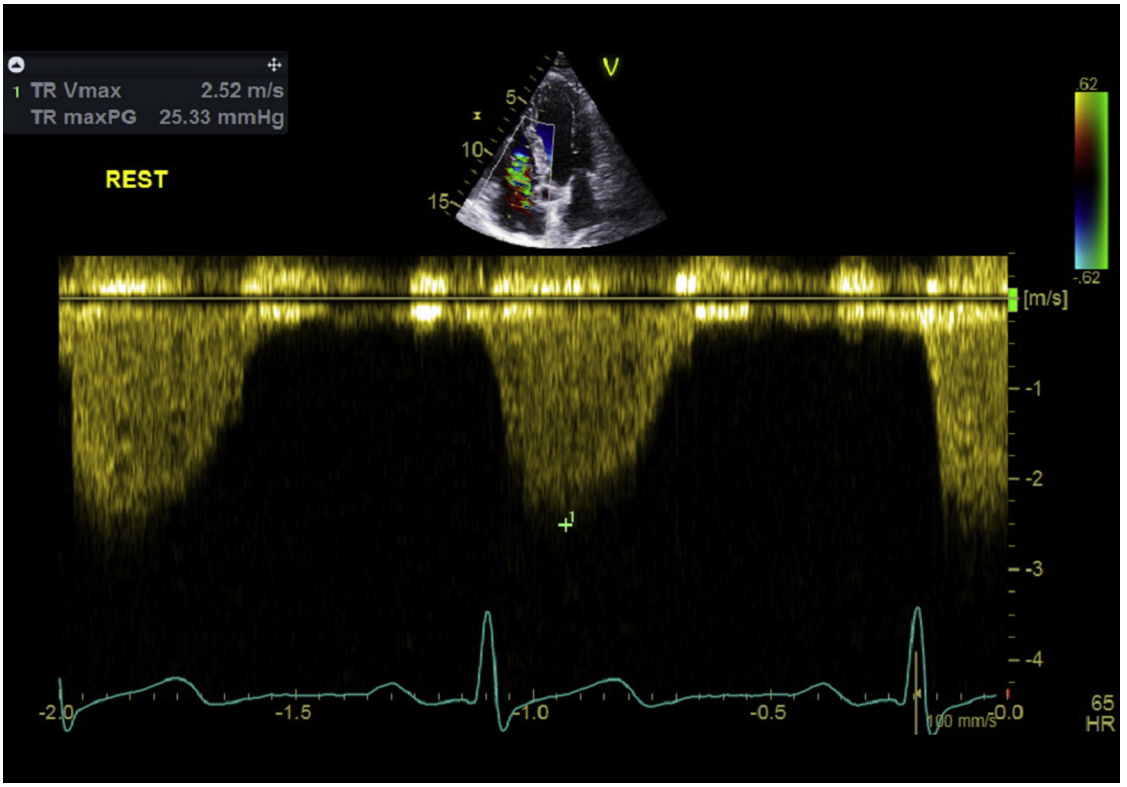
Supplemental Figure 5 SSc. Velocity-time integral Doppler spectrum at peak stress (to calculate CO).



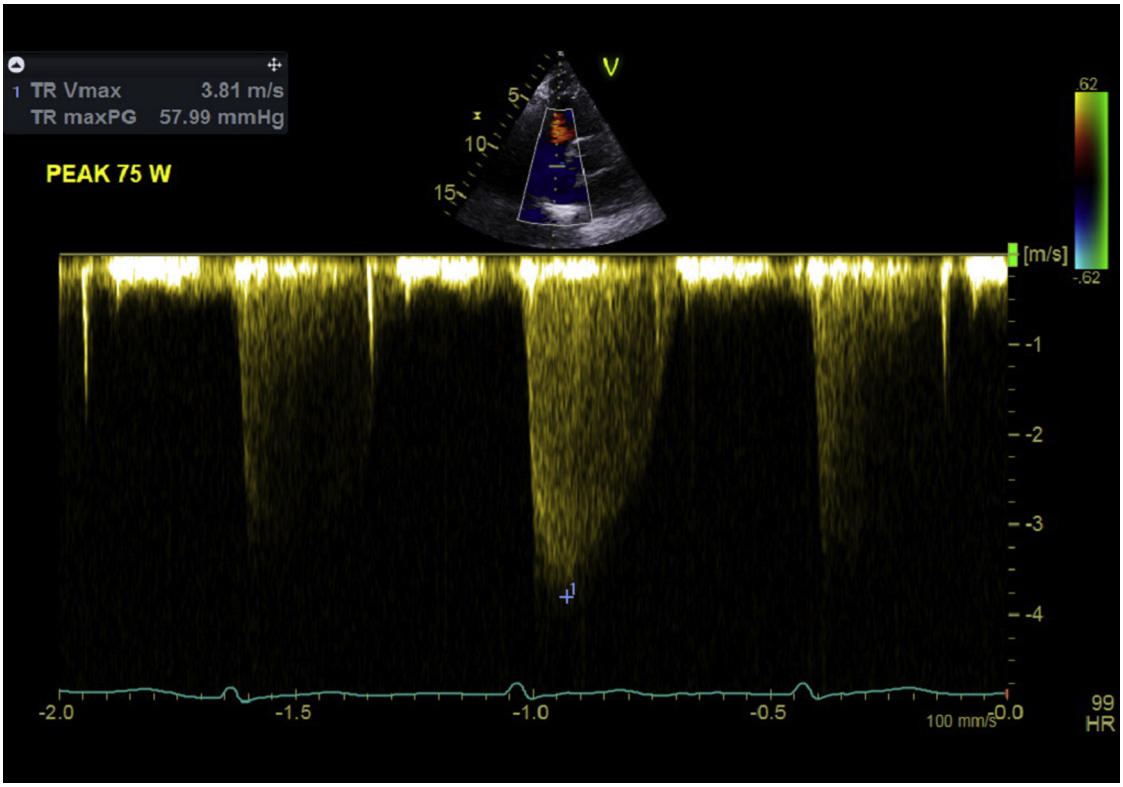
Supplemental Figure 6 SSc. TAPSE at rest.



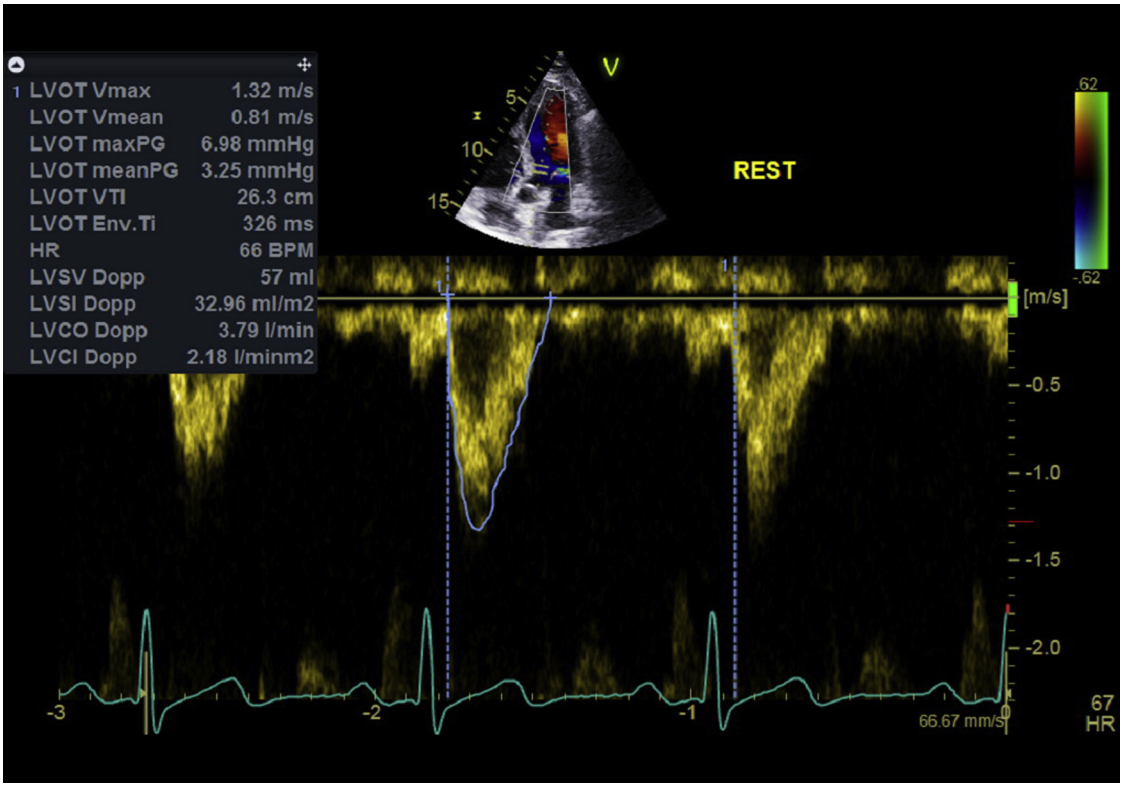
Supplemental Figure 7 SSc. TAPSE at peak stress.



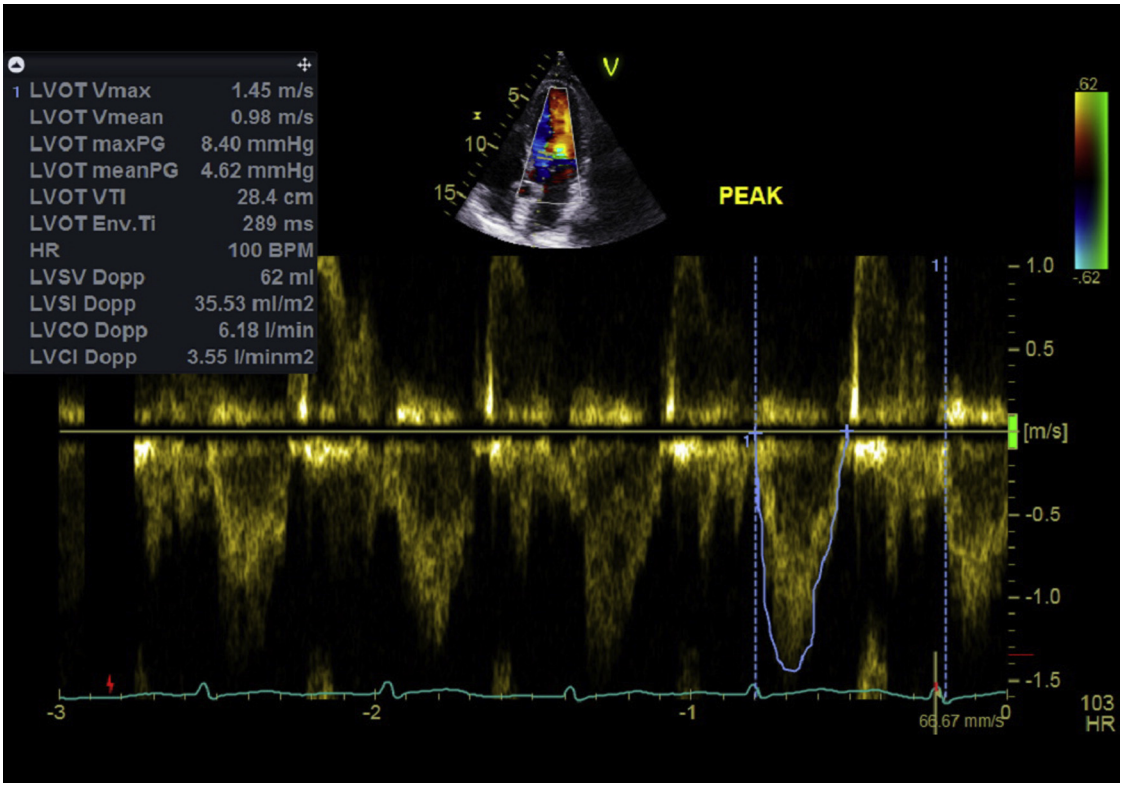
Supplemental Figure 8 CHD. Tricuspid regurgitation maximal velocity at rest.



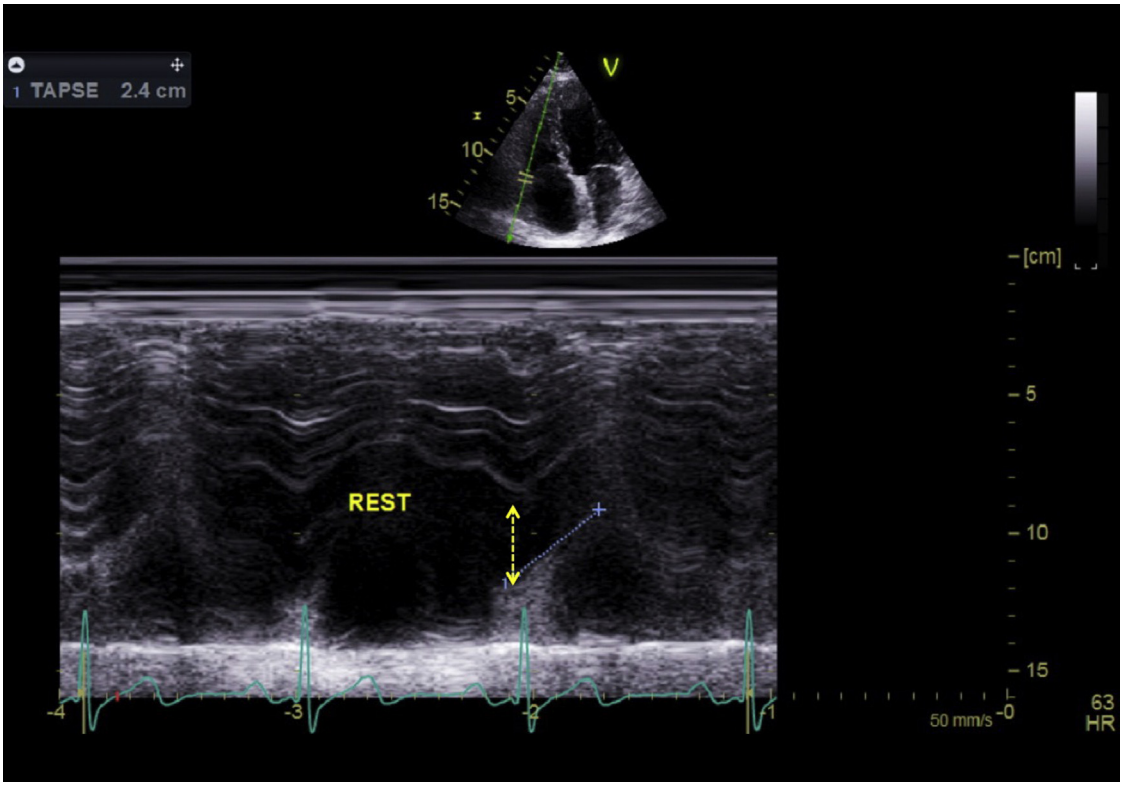
Supplemental Figure 9 CHD. Tricuspid regurgitation maximal velocity at peak stress.



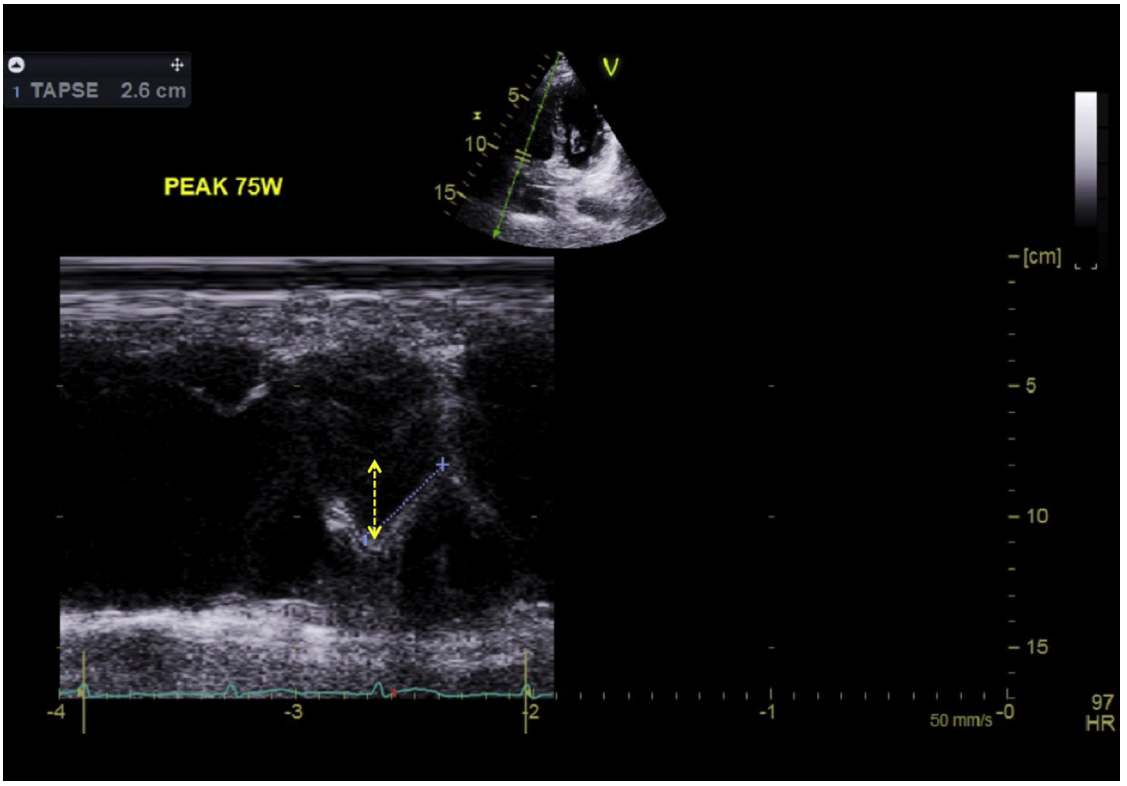
Supplemental Figure 10 CHD. Velocity-time integral Doppler spectrum at rest (to calculate CO).



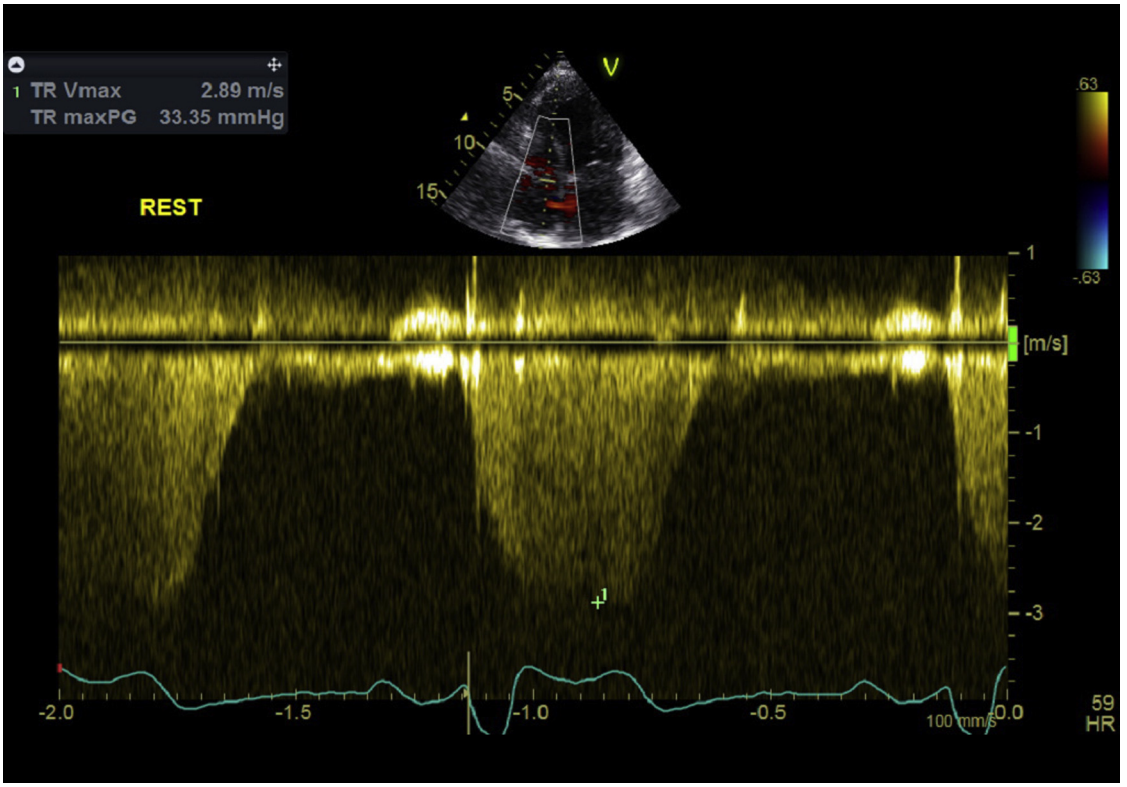
Supplemental Figure 11 CHD. Velocity-time integral Doppler spectrum at peak stress (to calculate CO).



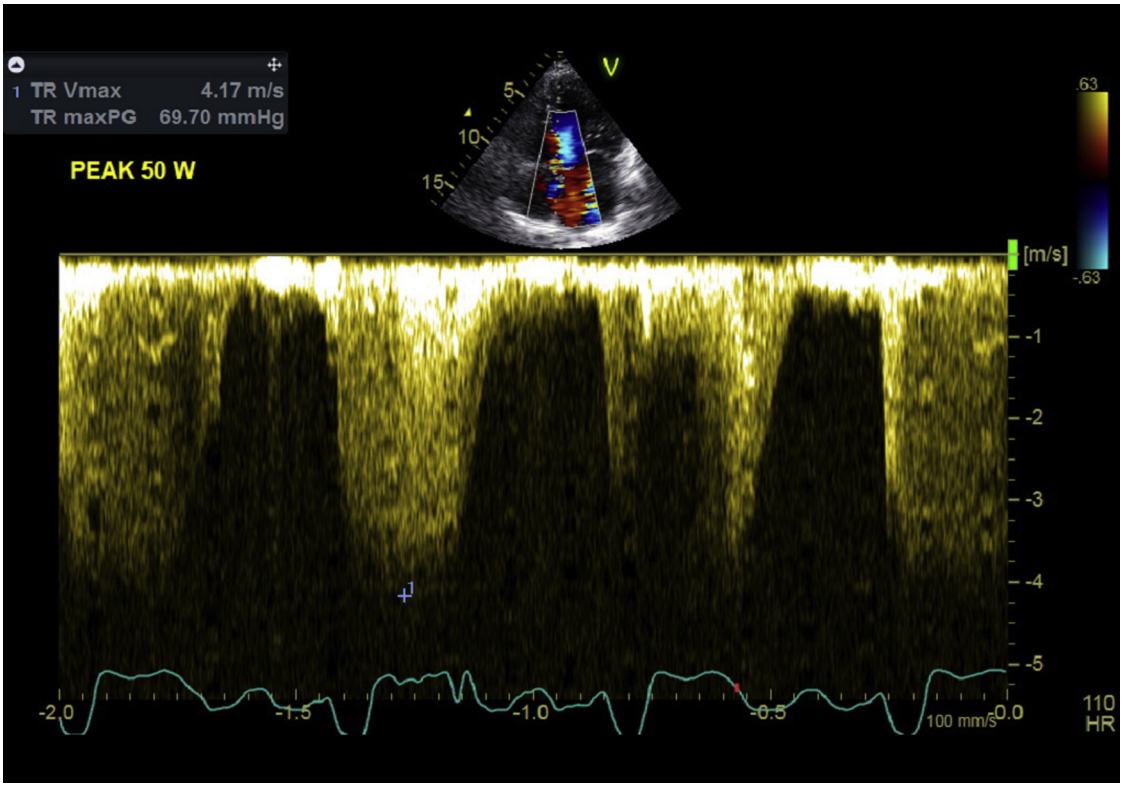
Supplemental Figure 12 CHD. TAPSE at rest.



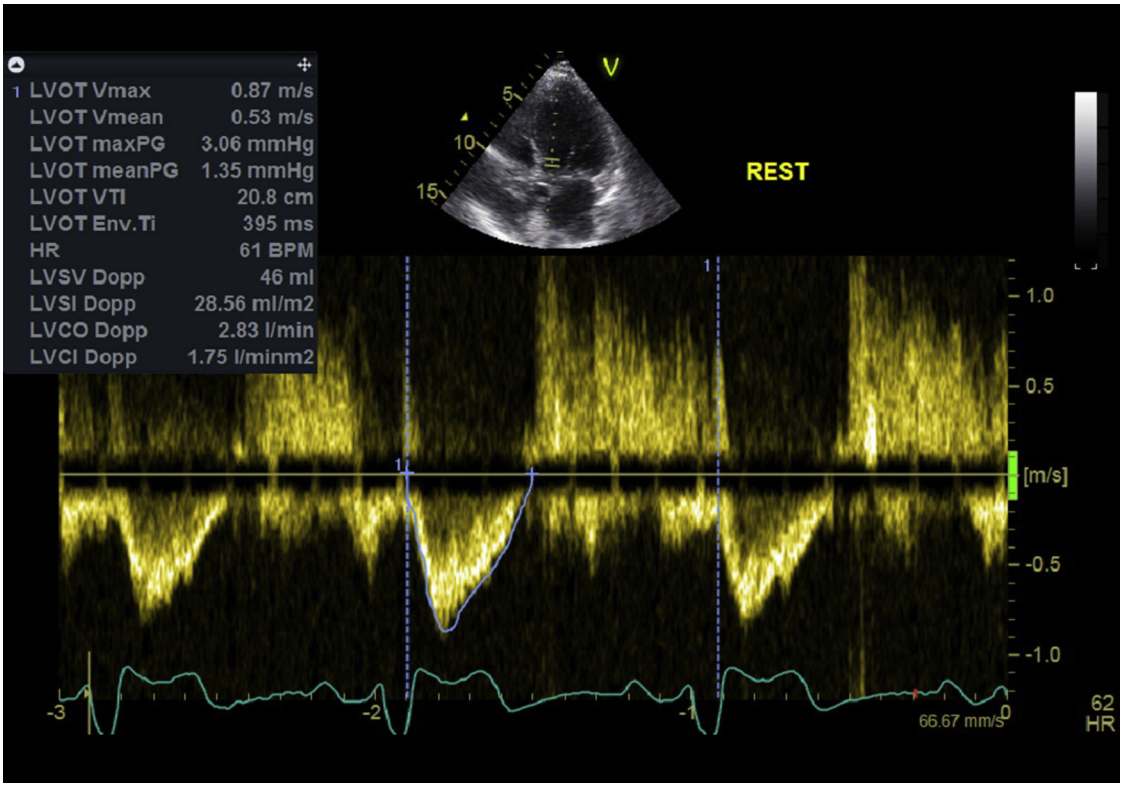
Supplemental Figure 13 CHD TAPSE peak. TAPSE at peak stress.



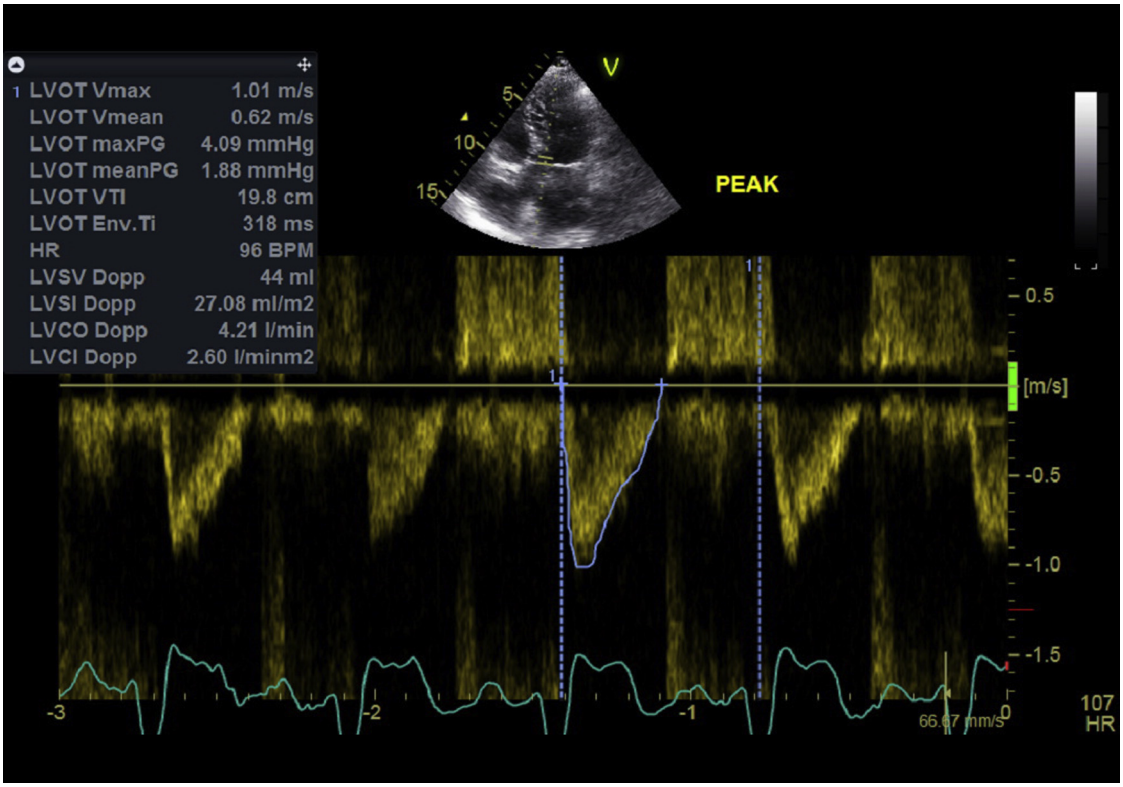
Supplemental Figure 14 HF. Tricuspid regurgitation maximal velocity at rest.



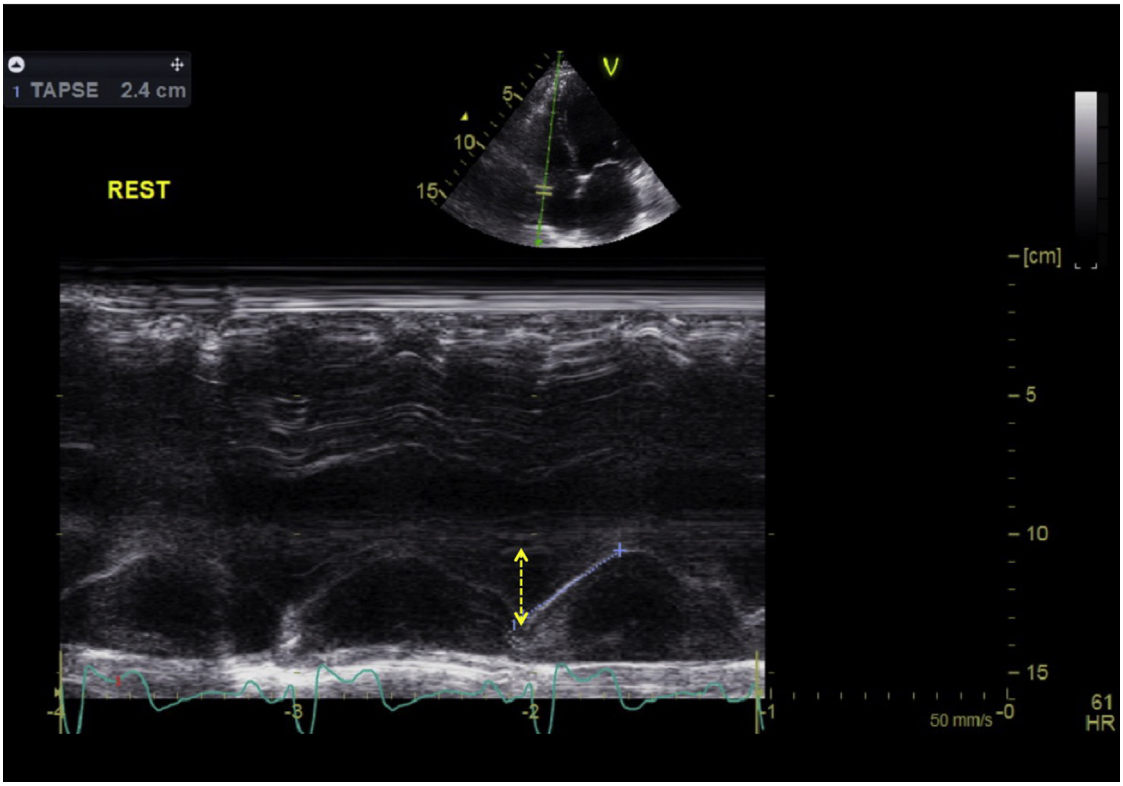
Supplemental Figure 15 HF. Tricuspid regurgitation maximal velocity at peak stress.



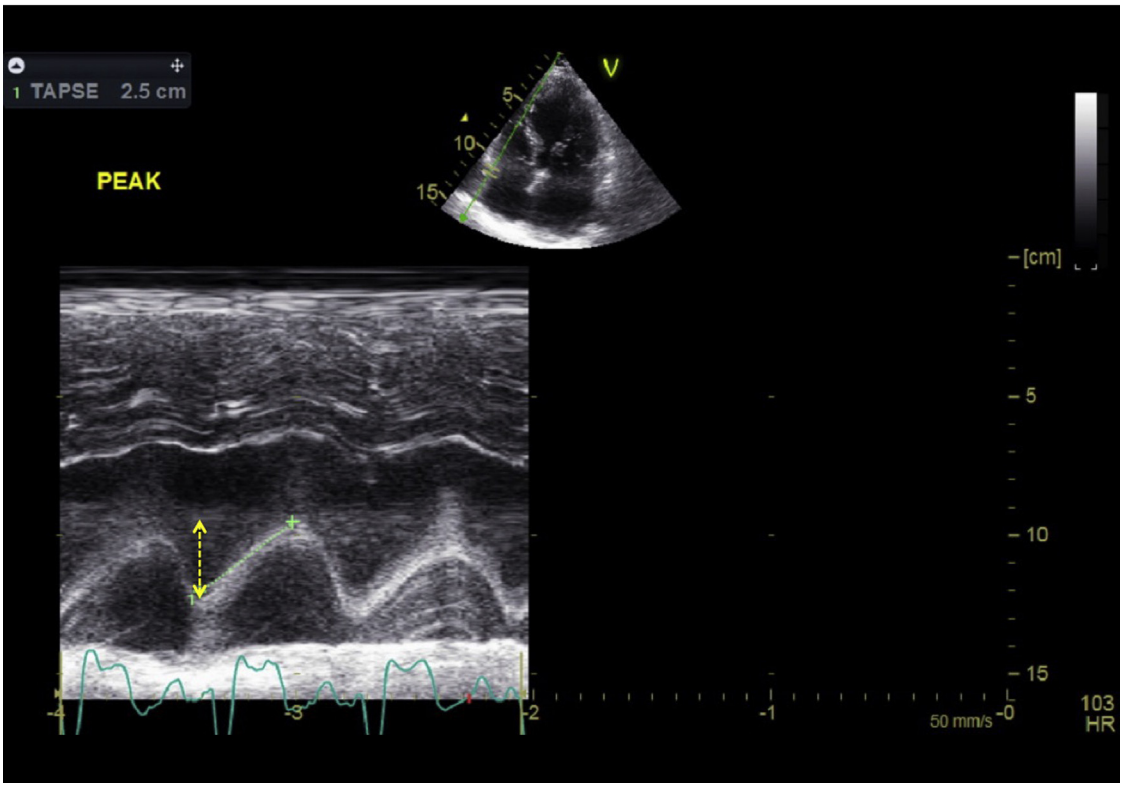
Supplemental Figure 16 HF. Velocity-time integral Doppler spectrum at rest (to calculate CO).



Supplemental Figure 17 HF. Velocity-time integral Doppler spectrum at peak stress (to calculate CO).



Supplemental Figure 18 HF. TAPSE at rest.



Supplemental Figure 19 HF. TAPSE at peak stress.