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PULMONARY HYPERTENSION (JR KLINGER, SECTION EDITOR)

Assessment of Right Ventricular Function in Pulmonary Hypertension

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Abstract Right ventricular function is a major determinant of symptomatology and prognosis in severe pulmonary hypertension. The diagnosis of right heart failure rests on a clinical approach with invasive and noninvasive measurements. Magnetic resonance and echocardiographic imaging of the right ventricle is of prognostic relevance. The gold standard of right ventricular function is the ratio of end-systolic to arterial elastances determined from synchronized volume and pressure measurements. Pressure measurements can be obtained during a right heart catheterization and volume measurements by integration of Doppler pulmonary flow-velocity, magnetic resonance imaging, or, more recently, three-dimensional echocardiography. Imaging also informs about regional function and derived estimates of dyssynchrony and asynchrony. Modern imaging with 3D echocardiography and magnetic resonance aims at improved assessment of regional function and right ventriculo-arterial coupling to assist in the evaluation and prognostication of severe pulmonary hypertension.

Keywords Right ventricular function · Right ventriculo-arterial coupling · End-systolic elastance · Arterial elastance · Time constant · Afterload · Pulmonary hypertension · Magnetic resonance imaging · Echocardiography

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Introduction

Right ventricular (RV) function is a major determinant of clinical presentation and prognosis in severe pulmonary hypertension (PH) [1••]. This has been particularly well demonstrated in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH). Both are dyspnea-fatigue syndromes with clear lungs due to progressive increase in pulmonary vascular resistance (PVR), distal in PAH and mostly proximal in CTEPH, without causal left ventricular diseases (LVD) or respiratory diseases (RD) [2]. Thus, in both entities, RV failure symptomatology is not affected by abnormal lung mechanics, gas exchange, or left heart function [3]. Right ventricular function determines symptoms and survival in any type of PH but with variable impact depending on causal disease and comorbidities [3].

This review will be devoted mainly to RV function in PAH or CTEPH.

Right Ventricular Function to Predict Outcome in Severe PH

A right heart catheterization is mandatory for the diagnosis of PAH [2]. However, the procedure only allows for an indirect description of RV function with right atrial pressure (RAP) used to estimate RV end-diastolic volume (EDV) or preload and pulmonary artery pressure (PAP) or pulmonary vascular resistance (PVR) to estimate afterload and stroke volume (SV) to reflect contractility.

Imaging provides more information on RV function. By far, the most commonly used are echocardiography and magnetic resonance imaging (MRI). Both provide reliable, though sometimes unprecise, estimates of systolic, mean and diastolic PAP, left atrial pressure (LAP), and cardiac output (CO) [4] and, thus, also provide derived calculations of PVR and pulmonary arterial compliance (Ca). More importantly, both echocardiography and

MRI provide a series of indices of RV systolic function, diastolic function and filling pressures, planar estimations of dimensions and reconstruction of volumes, and quantifications of dyssynchrony (inter-regional inhomogeneity of contraction) and asynchrony (inter-ventricular inhomogeneity of contraction) and RV volumes, all of which are beyond the information derived from a right heart catheterization.

An overview of the prognostic capabilities of right heart catheterization-, echocardiography- and MRI-derived variables in severe PH is presented in Table 1. Only studies of patient populations with primary pulmonary hypertension (PPH), now referred to as pulmonary arterial hypertension (PAH) or CTEPH, or predominantly so with a small minority of PH associated with LVD or RD reporting on univariate and multivariate analyses to identify predictors of outcome were included.

Predictors of adverse outcome obtained by right heart catheterization were CO [5–8, 10], RAP [6–8, 11], PVR [9, 11], and PAP [6]. It is interesting that this procedure aimed at the diagnosis and assessment of pulmonary vascular disease

Table 1 Right ventricular function to predict outcome in severe PH

Studies	Patients	Etiology	Measurements
Right heart catheterization			
Fuster (1984) [5]	120	PPH	SvO_2
D'Alonzo (1991) [6]	194	PPH	RAP, PAP, CO
Sandoval (1994) [7]	61	PPH	RAP, CO
McLaughlin (2002) [8]	162	PPH	RAP, CO
Sitbon (2002) [9]	178	PPH	Unchanged PVR
Humbert (2010) [10]	354	IPAH	CO
Benza (2010) [11]	2716	PAH	RAP, PVR
Echocardiography			
Eysmann (1989) [3]	26	PPH	Peff
Raymond (2002) [12]	81	PPH	Peff, RAS, EI
Bustamente (2002) [13]	25	PPH	RAS, TR
Forfia (2006) [14]	63	PAH CTEPH, RD	TAPSE
Utsunomiya (2009) [15]	50	PAH	Tricuspid E/e′
Ghio (2010) [16]	59	IPAH	TAPSE, EI
Sachdev (2011) [17]	80	PAH	Strain
Brierre (2010) [18]	79	PAH CTEPH, RD	PAP, Peff, EI, TAPSE, MPI, IVC
Ghio (2011) [19]	72	PAH	RV diameter
Haeck (2012) [20]	150	PH	2D speckle LPSS
Fine (2013) [21]	575	PH	2D speckle LPSS, Peff
Ernande (2013) [22]	142	PAH, CTEPH	IVV
Ameloot (2014) [23]	78	PAH, CTEPH	TAPSE, dP/dt
Smith (2014) [24]	97	PAH, CTEPH	3D speckle, area strain
Yeo (1998) [25]	53	PPH	MPI
Grunig (2013) [26]	121	PAH, CTEPH	Stress echo Δ TRV
MRI			
Van Wolferen (2007) [27]	64	IPAH	SV, RVEDV, LVEDV
Moledina (2013) [28]	100	PAH	EF, SV
Yamada (2012) [29]	41	IPAH	RVEDV
Veerdonk vd (2011) [30]	110	PAH	EF
Swift (2014) [31]	80	IPAH	ESV
Freed (2012) [32]	58	PH	LGE

Peff pericardial effusion, *RAS* right atria surface area, *EI* eccentricity index, *TR* tricuspid regurgitation, *TAPSE* tricuspid annular plane systolic excursion, *PAP* pulmonary artery pressure, *IVC* inferior vena cava, *MPI* myocardial performance index, *IVV*, maximum velocity of isovolumic contraction, *TRV* maximum velocity of TR, *SV* stroke volume, *EDV* end-diastolic volume, *ESV* end-systolic volume, *LGE* late gadolinium enhancement, *EF* ejection fraction, *LPSS* longitudinal peak systolic strain, *PPH* primary pulmonary hypertension, *PAH* pulmonary arterial hypertension, *I* idiopathic, *CTEPH* chronic thromboembolic pulmonary hypertension, *LVD* left ventricular disease, *RD* respiratory disease

provides better prognostication from measures of RV function (SV, RAP) than from measures of pulmonary hemodynamics (PAP, PVR).

Predictors of adverse outcome obtained from echocardiography included pericardial effusion [12, 18, 21, 33], right heart dimensions [12, 13, 16, 18, 19], estimated RV diastolic pressure [15, 18], tricuspid regurgitation (TR) [13], tricuspid annular plane systolic excursion (TAPSE) [14, 16, 18, 23], maximum tissue velocity of isovolumic contraction (IVV) [22], dP/dt [23], strain evaluated by variable and evolving methodologies [20, 21, 24], a myocardial performance index, which is a ratio of the sum of isovolumic contraction and relaxation times to SV [25, 34], and RV contractile reserve defined as the exercise-induced increase in the maximum velocity of TR (TRV) [26]. Thus, echocardiography offers a lot of prognostication from measurements of systolic function (TAPSE, IVV, dP/dt, strain, MPI, contractile reserve) but also dimensions and filling pressures of the RV.

Negative prognostic indicators obtained from cardiac MRI were SV [27, 28], EDV [27, 29], ejection fraction (EF) [28, 30] end-systolic volume (ESV) [31], and late gadolinium enhancement [32]. The latter is however not confirmed [35]. Thus, MRI offers prognostication from measures of systolic function (ESV, EF) and dimensions of the right heart.

It must be underscored that some predictors such as RAP, TAPSE, EI, EF, or strain were often significantly correlated with outcome only with univariate analysis and that the independent predictors identified by multivariate analysis were not always the same. This is explained by biases related to the retrospective nature of almost all of these studies, disparities in distribution of diagnoses, small sample sizes, and different lists of imaging variables and variable combinations with catheterization and often also exercise capacity parameters. Whether variables from retrospective studies can really "predict" outcome may be a matter of debate. Only one of the studies listed in Table 1 [24] was prospective.

All these studies point at the importance of RV function in severe PH but generate a lot of numbers with no directions on how to integrate them into clinical decision making.

What is needed is large-scale multicentric prospective studies with carefully selected high-quality variables that are most likely to be pertinent and integrate those showing up as independent predictors by a multivariate analysis into a multiparametric approaches.

However, variables qualify not only by prognostic capability. For example, depression is one of the most potent predictors of outcome in heart failure but of little diagnostic relevance [36]. Measurements of the pulmonary circulation and the RV help determine the clinical probability of a specific diagnosis and a pathophysiological understanding of why the RV is failing.

What is Right Ventricular Failure?

The structural and functional characteristics of the RV allow for the accomodation of large increases in flow but are not prepared for rapid increases in afterload. However, the basic laws of the heart remain applicable, that is rapid beat-to-beat heterometric adaptations (Starling's law of the heart) and otherwise progressive structural and inotropic homeometric adaptations (Anrep's law of the heart) to changes in loading conditions [37•].

Thus, the RV adaptation to pulmonary hypertension is basically homeometric with increased contractility, eventual hypertrophy, and preserved dimensions. Failure of RV-arterial coupling requires heterometric adaptation with increased RV dimensions [1••, 37•, 38•].

Accordingly, RV failure can be defined as a dyspnea-fatigue syndrome with eventual systemic congestion caused by the insufficient adaptation of systolic function (homeometric adaptation, Anrep) to increased afterload and involvement of increased dimensions (heterometric adaptation, Starling) to maintain RV flow output adapted to metabolic demand [1••, 37•, 38•].

Right Ventricular Afterload

The evaluation of the adequacy of RV-arterial coupling requires a quantification of RV afterload. There are several equally valid estimations of RV afterload [38•]. The first is maximum wall tension, which is however unpractical because of the irregular shape of the RV and regional inhomogeneous contraction. The second is hydraulic power (W_{TOT}), calculated from the integration of pressure and flow waves, thus integrating its oscillatory component (W_{OSC}). The third is arterial elastance (Ea) or end-systolic pressure (ESP) divided by SV measured on a RV pressure-volume loop, corresponding to a measurement of afterload as it is "seen" by the ventricle.

Because of the near-constancy of the time constant of the pulmonary circulation, Ca × PVR around 0.4 to 0.6 s, W_{OSC} is stable at 23 % of W_{TOT}, or 1.3 times mean power W_{MEAN} [39].

$$W_{TOT} = 1.23 \times W_{MEAN} = 1.23 \times SV \times PAP$$

Because ESP can be approximated by PAP, Ea is estimated by a ratio of PAP to SV

$$E\mathrm{a} = PAP \Big/ SV$$

or PVR divided by heart rate.

Practically, *E*a is most relevant as a single-number definition of afterload that the RV needs to adapt its contractility to.

The RV pressure-volume loop allows the identification of a point of maximal elastance (*E*max) approximated as end-systolic elastance, *E*es, which is the gold standard measure of load-independent contractility in in vivo conditions.

$$E\mathrm{es} = \mathrm{ESP} \Big/ \mathrm{ESV}$$

Identification of maximum or end-systolic elastance on a RV pressure-volume loop makes possible the calculation of an *E*es/*E*a ratio as a measurement of the coupling of the RV to the pulmonary circulation, [1••, 37•, 38•].

Optimal mechanical RV-arterial coupling corresponds to an *E*es/*E*a of 1. Optimal efficiency of RV-arterial coupling for flow output at minimal energy cost corresponds to *E*es/*E*a of 1.5–2.

As *E*a can be approximated by PVR or PAP at a given SV and W_{TOT} is much determined by PAP, it is understandable that measurements of the pulmonary circulation emerge as prognostic markers of RV failure in severe PH [6, 8, 9, 11, 18, 26, 40, 41]. Because the ability of the RV to increase its contractility in response to an increased afterload is altered in LVD [42], Ca determined by echocardiography [43] or PAP together with decreased EF of the RV determined with dedicated thermodilution pulmonary cathetes [44] have been shown to be strong predictors of outcome in LVD patients.

Bedside Measurements of RV-Arterial Coupling

The complex geometry of the RV makes functional evaluations with measurement of instantaneous volume changes technically difficult, and the determination of *E*max by *E*es may be unreliable because of the particular shape of the RV pressure-volume loop and noncoincidence of end-ejection and end-systole. This problem is overcome by measuring pressure-volume loops at several levels of preload [45].

However, manipulating systemic venous return to alter RV preload is not practical at the bedside. Accordingly, a single-beat method has been developed allowing for the determination of *E*es and *E*a from instanteous ventricular pressure and flow output measurements [46]. The approach rests on a *P*max determined from the extrapolation of early- and late-isovolumic portions of a RV pressure curve, synchronized absolute or relative volume measurements, Ees defined by a tangent from *P*max to the pressure-volume relationship, and *E*a by a line drawn from the *E*es point to EDV (Fig. 1).

Single-beat determinations of *E*es/*E*a have been implemented in experimental animal studies to show for example that acutely administered prostacyclin has no intrinsic inotropic effect [47], and that β-blocker agents deteriorate RV-arterial coupling acutely [46] but may improve RV-arterial coupling chronically [48].

The coupling of RV function to the pulmonary circulation has been reported in PAH patients, with single-beat calculation of the *E*max/*E*a ratio from magnetic resonance imaging (MRI) and right heart catheterization [49•]. This is illustrated in Fig. 2.

As compared to controls, *E*max was almost tripled, but *E*max/*E*a was decreased, indicating insufficient homeometric adaptation and pending RV failure. These results were confirmed by *E*max/*E*a ratio measurements using conductance catheters and the Valsalva maneuver to decrease venous return [50]. In that study, *E*max/*E*a was maintained in the patients with idiopathic PAH, but decreased in systemic sclerosis-associated PAH [50]. This is in keeping with the previous report with analysis of RV-arterial coupling by plotting pressure as a function of stroke volume, or the so-called "pump function graph" [51]. Systemic sclerosis is a systemic disease that affects the myocardium and thus may alter RV function adaptation to afterload at lower PAP [50, 51].

The single-beat method was also implemented using conductance catheters in patients with CTEPH. The results again showed an increased *E*es but insufficiently to maintain *E*es/*E*a [52].

Finally, an increased *E*es, but decreased *E*es/*E*a was measured on a systemic RV in a patient with congenitally corrected transposition of the great arteries [53].

Altogether, these results agree with the notion of homeometric adaptation of RV function to afterload, even though the results do not allow the identification of critical levels of decoupling associated with onset of heterometric adaptation and congestion.

Simplified Measurements of RV-Arterial Coupling at the Bedside

The number of studies reporting RV-arterial coupling with synchronized RV pressure and volume measurements remains small, pointing at practical difficulties in integrating these measurements into bedside clinical evaluation. Simpler surrogates are needed.

Since the *E*es/*E*a ratio has ESP as a common term, it can be simplified to a ratio of volumes, easy to measure with MRI [54]:

$$E\mathrm{es} \Big/ E\mathrm{a} = \mathrm{ESP} \Big/ \mathrm{ESV} \Big/ \mathrm{ESP} \Big/ \mathrm{SV} = \mathrm{SV} \Big/ \mathrm{ESV}$$

The *E*es/*E*a ratio determined using the single-beat method can be simplified to a ratio of pressures easy to obtain during a standard right heart catheterizations [55]:

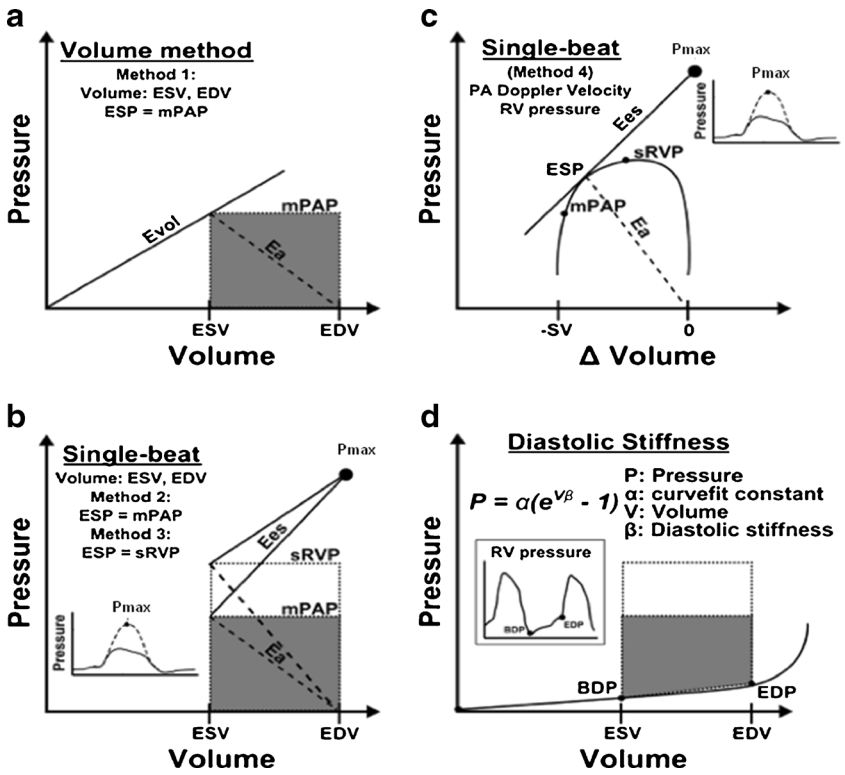

Fig. 1 Methods used to estimate right ventriculo (RV)-arterial coupling and diastolic stiffness (β). In both the volume method (**a**) and the pressure method (**b**), arterial elastance (*E*a) is calculated from the ratio of end-systolic pressure (*ESP*) to stroke volume (*SV*). End-systolic elastance (*E*es) as an approximation of maximum elastance in the volume method is estimated by the ratio of ESP to end-systolic volume (*ESV*), which results in a simplified Ees/Ea of SV/ESV. In the pressure method, *P*max is estimated from the nonlinear extrapolation of the early systolic and diastolic portions of the RV pressure curve. End-systolic elastance is then ratio of (*P*max−mPAP) divided by SV, which results in a simplified *E*es/*E*a of (*P*max/ESP−1). The single-beat method (**c**) calculates *E*es as a straight line drawn from *P*max tangent to RV pressure-relative change in volume relationship. Diastolic stiffness β is calculated by fitting the nonlinear exponential, $P=\alpha(e^{V\beta}-1)$, to pressure and volume measured at the beginning of diastole (*BDP*: beginning diastolic pressure, ESV) and the end of diastole (*EDP*: end-diastolic pressure, EDV). After reference 56, with permission

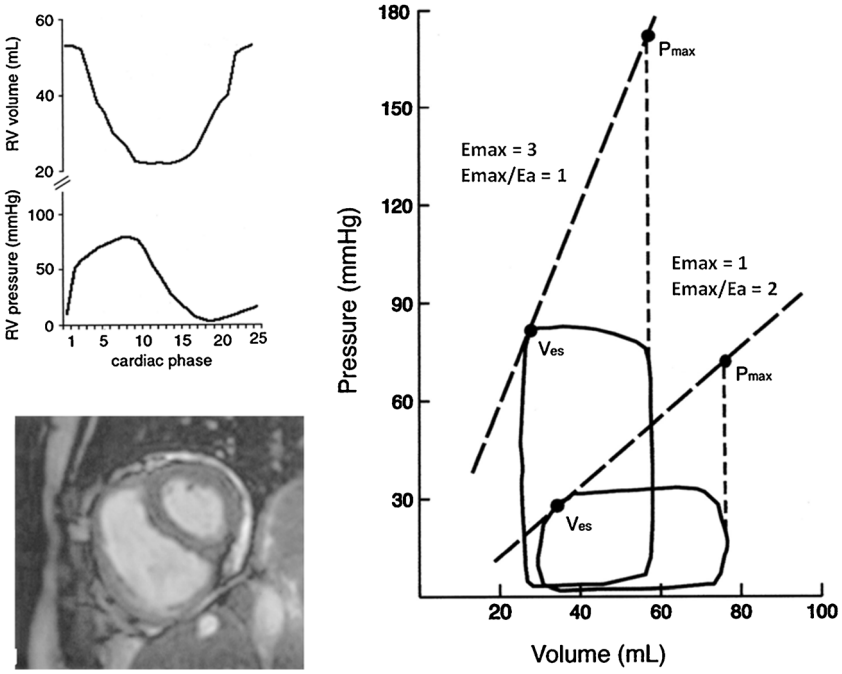

Fig. 2 Right ventricular (*RV*) pressure and volume curves with illustrative magnetic resonance imaging which was used for volume measurements (*left*) and derived maximal RV pressure (*P*max) and maximal elastance (*E*max) in a normal control subject and in a patient with severe pulmonary arterial hypertension (*PAH*) (*right*). The normal subject had an *E*max/*E*a ratio of 1. The *E*max/*E*a ratio was decreased to 1 in the PAH patients, because of insufficient increase in *E*max to match the increased *E*a. From ref 49, with permission

$$Ees/Ea = (Pmax-PES)/SV/PES/SV$$
$$= Pmax/PES-1.$$

Both volume and the pressure methods are illustrated in Fig. 1.

The volume method assumes ESP equal to PAP and *E*es elastance as a straight line crossing the origin, which is irrealistic as ventricular end-systolic elastance curves are slightly curvilinear with a positive extrapolation to the volume axis defining an unstressed volume (V_0) [37•, 55]. The pressure method requires digitized pressure curves and software for *P*max calculations and assumes ESP equal to either PAP or to peak systolic RV pressure. The latter may be in agreement with early peaking triangular shape of RV pressure curves in severe PH (Fig. 1d). The pressure methods lead to higher *E*es/*E*a and appear to better agree with the single-beat method [56]. However, RV-arterial coupling estimated by the volume method, not by the pressure methods, or EF, has been shown to be an independent predictor of outcome in patients referred for PH [56].

Diastolic Function

Coupling of RV function to afterload has an inevitable diastolic component [1••, 37•]. Diastolic function is described by a diastolic elastance curve determined by a family of pressure-volume loops at variable loading. It is curvilinear and thus, impossible to summarize as a single number. Several formulas have been proposed [30]. Most recently, RV diastolic stiffness was estimated in PAH patients by fitting a nonlinear exponential curve through the diastolic pressure-volume relationships, with the formula $P=\alpha(e^{V\beta}-1)$, where α is a curve-fitting constant and β a diastolic stiffness constant [57]. This is also illustrated in Fig. 1. The RV diastolic stiffness constant β is closely associated with disease severity [57] but also to end-systolic stiffness [56, 57] and has not been found, except in one small study, to be an independent predictor of outcome [57].

Diastolic function of the RV has not been specifically defined and explored by imaging studies. Its description is generally limited to the isovolumic relaxation time, the ratio of trans-tricuspid flow E wave to tricuspid annulus tissue Doppler imaging tricuspid e′, the deceleration of the E wave, estimated RV filling pressure from the inferior vena cava dimension and inspiratory collapse and end-diastolic area or volume. These measurements have not been systematically confronted with diastolic pressure-volume curves or, with exception of some isolated parameters (see Table 1) looked at from a prognostication point of view.

Perspectives, Alternative Approaches, and Limitations

The most flexible and accessible tool for the imaging of the RV is echocardiography. The procedure generates a large number of measurements which are currently being integrated in multi-parametric approaches during a diagnostic work-up [58, 59]. Multi-parametric approaches will hopefully be developed for prognostication. This also applies to MRI but with less rapid data accumulation as access to this procedure remains restricted to dedicated reference centers.

A rapidly evolving use of imaging is the evaluation of regional function and quantification of dyssychrony and asynchrony of RV contraction in PH. Both dyssychrony and asynchrony can be assessed by 2D or 3D speckle tracking echocardiography [24, 60, 61] or MRI [62]. A recent 3D speckle tracking echocardiography study showed area strain, but not dyssynchrony or RVEF to be of prognostic relevance in PAH [24]. This requires further evaluation.

There is also a great interest in finding simpler measurements to assess RV-arterial coupling. One such measurement, already shown to be of prognostic relevance in heart failure, is the TAPSE to TRV measured by echocardiography [63]. Further development might rely on tissue Doppler imaging of the acceleration or maximum velocity of RV isovolumic contraction [22], known to be relatively load independent [64] perhaps coupled to some measure of afterload.

Conclusion

Stressing the RV to measure its "contractile reserve" may disclose borderline or latent functional uncoupling from the pulmonary circulation. Accordingly, exercise-induced increase in systolic RV pressure estimated from a TRV has been shown to be a strong predictor of survival in patients with PAH or CTEPH [26]. The possibility to replace exercise by low-dose dobutamine, which makes imaging easier, and measure the RV contractile response by a TAPSE or tricuspid annulus S wave, is also being considered [65]. There is experimental work showing that dobutamine-induced increase in these indices of RV systolic function reflects the resting state of RV-arterial coupling [66].

Exercise capacity in PH is limited by RV flow output adaptation to peripheral demand. Accordingly, maximum oxygen uptake, workload or maximum average running or walking speed (the 6-min walk test) are determined by the state of RV-arterial coupling [67•]. Exercise capacity is an indirect measurement of RV function in PH.

The evaluation of RV function in PH using echocardiography and magnetic resonance imaging is making rapid progress in the favorable context of constant improvement in technology combined with refreshed pathophysiological understanding. Clinicians now have better noninvasive tools to help them

in the diagnosis and prognostication of right heart failure syndromes, but more research is needed in the direction of efficient multi-parametric approaches and decreased reliance on cardiac catheterization.

Compliance with Ethics Guidelines

Conflict of Interest Robert Naeije declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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