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Pulmonary Hypertension and the Heart: a Complex Interaction

Robert Naeije, MD, PhD

Department of Cardiology, Erasme University Hospital, ULB, Brussels, Belgium

ABSTRACT

Pulmonary hypertension primarily affects the heart by increasing right ventricular (RV) afterload. The initial response of the RV is an increased contractility soon followed by hypertrophy, with little or no increase in dimensions. When this "homeometric" adaptation fails, in case of rapid and/or severe increase in pulmonary artery pressure, the RV also uses a "heterometric" adaptation at the price of increased dimensions, higher filling pressures, systemic congestion and decreased exercise capacity. Dilatation of the RV impairs left ventricular (LV) filling. This diastolic interaction eventually alters systolic interaction, or contribution of LV contraction to the strength of RV contraction, which further deteriorates RV function. Too high or low lung volumes may increase pulmonary vascular resistance. Excessive decrease in pleural pressures be a cause of LV failure and worsening of pulmonary hypertension by upstream transmission of filling pressures. The complexity of heart-lung interactions in pulmonary hypertension needs understanding to optimize treatment strategies.

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Corresponding author: Robert Naeije, rnaeije@ulb.ac.be

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Correspondence to:
Robert Naeije
Department of Pathophysiology
Erasme Campus of the Univerrsité Libre de Bruxelles
808 Lennik road, B-1070 Brussels, Belgium
E-mail: rnaeije@ulb.ac.be

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INTRODUCTION

Pulmonary hypertension (PH), defined by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg is a common complication of cardiac and respiratory diseases, but may sometimes present as an intrinsic pulmonary vascular disease without identifiable aetiology called pulmonary arterial hypertension (PAH)[1]. Symptomatology, functional state, exercise capacity and outcome in PH are essentially to be accounted for by an altered right ventricular (RV) function adaptation to afterload[2]. This review will focus on the mechanisms of adaptation and failure of RV failure in PH, with consideration of RV-arterial coupling, ventricular interdependence and heart-lung interactions.

RIGHT VENTRICULAR FAILURE

The normal RV is thin-walled and crescent-shape flow generator, which is vulnerable to any acute rise in wall stress[3]. A brisk increase in pulmonary vascular resistance (PVR) induces acute dilatation and pump failure of the RV. However, a gradual increase in PVR allows for RV adaptation and remodelling. Beat-to-beat changes in preload or afterload are accompanied by a heterometric dimension adaptation following Starling's law of the heart[4]. Sustained changes in load are associated with a homeometric contractility adaptation following Anrep's law of the heart after the initial observation by Gleb von Anrep[5] in 1912 of rapid increase in LV contractility in response to an aortic constriction. Failure of homeometric adaptation results in heterometric adaptation to maintain stroke volume (SV) but at the price of increased RV end-systolic volume (ESV) and end-diastolic volume (EDV)[2,6].

The so-called "laws of the heart" equally apply to the RV and to the LV, but in different proportions[6].

It is therefore possible to define RV failure as a dyspnoea-fatigue syndrome with eventual systemic venous congestion, caused by the inability of the RV to maintain flow output in response to metabolic demand without heterometric adaptation resulting in increased filling pressures and volumes?[2].

RIGHT VENTRICULAR AFTERLOAD

When PVR is normal, around 1 Wood unit (WU) or less, the RV functions as a low pressure volume generator with minimal work at rest or at moderate levels of exercise[3,6]. A good quality of life is even possible without a RV, as shown by near-normal life expectancy with only mild to moderate exercise intolerance after a "Fontan operation", or cavo-pulmonary anastomosis used as palliative intervention in infants with some congenital cardiac abnormalities[7]. However, as soon as PVR starts to increase, the pump function of the RV is needed to accommodate systemic venous return and preserve LV pre-loading. Thus, afterload matters considerably to the RV.

There are several equally valid estimations of RV afterload[8]. The first is maximum wall tension, but which is difficult to measure because of the irregular shape of the RV and regional inhomogeneous of contraction. The second is hydraulic power (W_{TOT}), calculated from the integration of pressure and flow waves, thus encompassing oscillatory and steady-flow components (W_{OSC} and W_{ST}). The third is arterial elastance (Ea), or end-systolic

pressure, ESP divided by SV measured on a RV pressure-volume loop. Ea corresponds to afterload perceived by the RV.

Because of the near-constancy of the time constant of the pulmonary circulation, or pulmonary arterial compliance x PVR, around 0.4 to 0.8 seconds, W_{OSC} is stable at 23% of W_{TOT}, and is estimated by 1.3 times mean power W_{ST}[9]:

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

As RV end-systolic pressure (ESP) is approximated by mPAP, Ea is estimated by a ratio of mPAP to SV:

$$Ea = mPAP/SV$$

or PVR divided by heart rate.

Practically, Ea is most relevant as a single number definition of afterload the RV.

RIGHT VENTRICULAR SYSTOLIC FUNCTION

The homeometric adaptation relies on increased contractility. Myocardial fibre contractility is defined by an active tension-length relationship. In vivo, ventricular contractility is defined by a maximal elastance (Emax), or the maximum slope of a pressure-volume (PV) relationship measured continuously during the cardiac cycle - or PV loop[2,6,8].

Emax of the LV coincides with end-systole, and is thus equal to the ratio between ESP and ESV defining an end-systolic elastance (Ees). Left ventricular Ees is clearly identifiable at the upper left corner of a square-shaped PV loop[10].

Because of naturally low pulmonary vascular impedance, the normal RV PV loop has an oval rather than square shape and Emax occurs before the end of systole. However, a satisfactory definition of Emax can be obtained by a family of PV loops at decreasing venous return (as generated by progressive inferior vena cava balloon occlusion)[11].

Increasing impedance to pulmonary blood flow in PH changes the shape of the RV PV loop, so that Emax becomes closer to peak systolic pressure and the slope of end-systolic P-V relationship increases, indicating increased contractility[12].

Even though there has been recent progress in three-dimensional echocardiography and magnetic resonance imaging (MRI), instantaneous volume measurements of the RV are not yet possible at the bedside. Manipulations of venous return through insertion of a vena cava balloon catheter to generate families of PV loops add to the invasiveness of right heart catheterization, and are ethically problematic. A Valsalva manoeuvre to generate a family of RV PV loops at decreased venous return was recently introduced and validated[13]. The practicality and clinical relevance of this approach will require confirmation.

Since Emax is insensitive to immediate changes in preload or afterload, single beat methods have been developed, initially for the LV[14] and subsequently adapted to the RV[15]. The single beat method relies on a maximum pressure Pmax calculation from a nonlinear extrapolation of the early and late portions of a RV pressure curve, an integration of pulmonary flow and synchronization of the signals. Emax is estimated from the slope of a straight

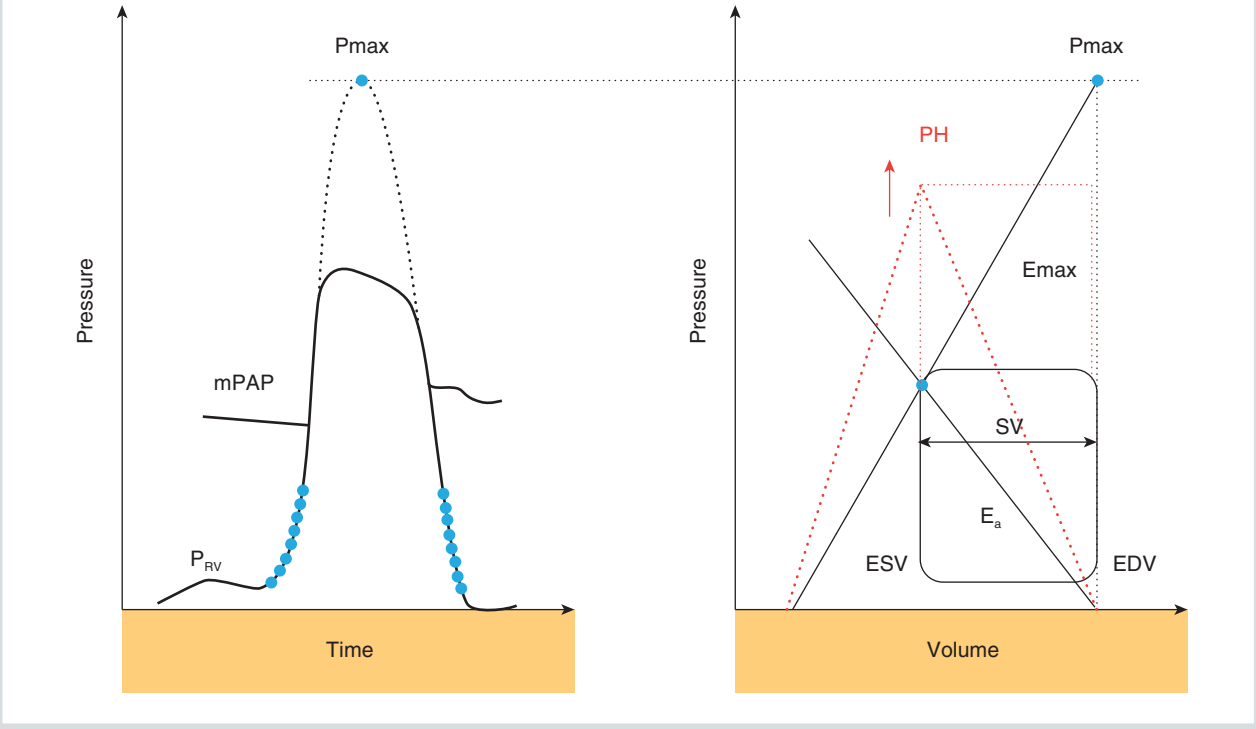

Figure 1. Simplified pressure method to calculate end-systolic elastance (Ees) and arterial elastance (Ea) based on a maximum pressure (Pmax) derived from nonlinear extrapolation of early and late portions of a right ventricular pressure curve (PRV), a measure of stroke volume (SV) and assumption that mean pulmonary artery pressure (mPAP) is a reasonable approximation of end-systolic pressure. The effects of an increase in mPAP (PH) with preserved RV-arterial coupling and no change in RV volumes is shown in red. EDV: end-diastolic volume; Emax: maximum, or end-systolic elastance; ESV: end-systolic volume; PH: pulmonary hypertension.

line tangent from Pmax to the upper left portion of the PV curve. This is illustrated in figure 1.

A Pmax corresponds to the pressure the RV would generate during a non-ejecting beat at EDV. An excellent agreement between directly measured Pmax by clamping the main pulmonary artery for one beat and calculated Pmax has been demonstrated in a large animal experimental preparation with no PH or a mild increase in PAP induced by low oxygen breathing[15]. Whether the calculated Pmax is equally valid in patients with severe PH has not been yet established with certainty.

Measurements of RV Emax with conductance catheter technology and inferior vena cava balloon obstruction have been reported in normal subjects[16]. A limited number of Emax determinations have been reported in patients with severe PH, either PAH or thrombo-embolic (CTEPH)[13,17-20] and in one patient with a systemic RV on congenitally corrected transposition of the great arteries[21]. The methods varied, with single or multiple beat approaches, fluid-filled or micro-manometer-tipped catheters to measure pressures, and conductance technology or magnetic resonance imaging to measure volumes. Emax consistently increased in response to increased Ea.

COUPLING OF RV SYSTOLIC FUNCTION TO AFTERLOAD

Ventricular adaptation to increased preloading or afterloading is initially heterometric, so that ESV and EDV are increased with preserved or increased SV but decreased ejection fraction (EF). This was established by Starling in heart-lung preparations. However, after 20 to 30 seconds, ventricular contractility increases returning volumes to pre-intervention state. This "homeometric adaptation" results in increased or preserved SV and unchanged or decreased ESV and unchanged EDV[22]. It is thus important to correct measurements of contractility for increased afterload.

Contractility corrected for afterload is best defined by a ratio of Emax to Ea. Experimental work and mathematical modelling have allowed the definition of an optimal mechanical coupling of Emax to Ea equal to one. However, the optimal condition for energy transfer from the ventricle to the arterial system occurs at a Emax/Ea ratio of 1.5-2[2,6,8].

Measurements of the Emax/Ea ratio have been reported in various models of PH[6]. RV-coupling was preserved with increased Emax to match Ea in models of hypoxic pulmonary vasoconstriction, pulmonary embolism, pulmonary artery banding, early endotoxic shock and short term (3 months) aorta-pulmonary shunting in piglets. This is schematically illustrated in figure 1. However, RV-arterial coupling was deteriorated with a decrease in the Emax/Ea ratio in late endotoxic shock, monocrotaline-induced PH, long-term (6 months) aorta-pulmonary shunting in piglets and mild PH in overpacing-induced heart failure. Deterioration of RV-arterial coupling was associated with increased EDV. There is thus compelling experimental evidence of predominant RV systolic function adaptation to increased afterload in PH, but with early RV-arterial uncoupling and increased RV volumes in the context of inflammation (endotoxemia, monocrotaline), long-term increase in PVR (systemic-to-pulmonary shunting), or heart failure.

Measurements of both Emax and Ea have been reported in a limited number of patients with PAH or CTEPH[13,17-20]. In the presence of increased Ea, Emax was always increased but with either preserved or decreased Emax/Ea. A decreased Emax/Ea was more constantly observed in patients with PAH associated with systemic sclerosis (SSc)[13,20]. Exercise decreased Emax/Ea even in those patients with a normal Emax/Ea at rest, in contrast to preserved Emax/Ea during exercise in controls without PH[19,20]. A decrease in Emax/Ea during exercise was associated with a decreased EDV[20] confirming current notion that a decrease in Emax/Ea at some point in the course of severe PH as associated with increased right heart chamber dimensions, increased central venous pressures, systemic congestion, and decreased life expectancy[2,23].

The ventricular homeometric adaptation to increased afterload is eventually but variably strengthened by a hypertrophic response. The increase in (right) ventricular wall thickness (h) in (pulmonary) hypertension is adaptative as, according to Laplace's law, it decreases the amount of wall tension (T) at any given level of volume and pressure:

$$T = P \times V/h$$

While deleterious effects of excessive ventricular hypertrophy are conceivable, imaging

studies have recently shown that concentric RV hypertrophy improves outcome in patients with severe PH[24,25].

PHARMACOLOGY OF RV-ARTERIAL COUPLING IN PULMONARY HYPERTENSION

There are no reported studies on the effects of pharmacological interventions on RV-arterial coupling in patients with severe PH. One has therefore to rely on translations from experimental animal literature.

Catecholamines are in principle not recommended in severe PH because of their potential to induce pulmonary vasoconstriction, excessive tachycardia and arrhythmia[26]. Moreover, catecholamines have been associated with increased mortality in RV failure[27]. However, the latter effect is probably due to the fact that these drugs are prescribed in the most severely ill patients. Low-dose catecholamines are often used for short periods of time in the intensive care setting to stabilize patients with acute or acute-on chronic RV failure, buying time for fluid management and treatments targeting the pulmonary circulation. In experimental PH low-dose dobutamine improved RV-arterial coupling by an inotropic effect with a slight decrease in PVR[15,28]. Low-dose norepinephrine improved RV-arterial coupling through an exclusive positive inotropic effect, which was however less pronounced than with low-dose dobutamine[28].

Quite different is the idea that β-blockers might improve RV failure like in LV failure. Heart failure, whether global or limited to the RV is associated with a neuro-humoral activation which helps initially to preserve blood pressure and glomerular filtration, but in the long term further deteriorates cardiovascular function. Experimental animal evidence is contrasted. Acute administration of propranolol reduced RV-arterial coupling through combined negative inotropy and pulmonary vasoconstriction in acute hypoxic PH[15]. However, chronic administration of bisoprolol improved RV-arterial coupling by an increased contractility in monocrotaline-induced pulmonary hypertension[29]. Chronic administration of carvedilol or metoprolol improved echocardiography of RV function in PH induced by monocrotaline injection or by administration of the vascular endothelial growth factor-receptor antagonist SU5416 combined with hypoxia[30]. Accordingly randomized controlled trials of low-dose β-blockers have been initiated in patients with PAH. The results so far have not been encouraging, with no signal of possible benefit and concerns about side effects and decreased exercise capacity and cardiac output[31].

There has been suggestion that pharmacological interventions targeting the pulmonary circulation in PAH might also have intrinsic beneficial effects on the RV[32,33]. However, the experimental evidence for such direct myocardial effects in intact animal models of PH is scarce, with some discrepant results about sildenafil. Prostacyclins decreased Emax in proportion to decreased Ea[34-36]. Sildenafil improved RV-arterial coupling in hypoxia by exclusive pulmonary vasodilating effects[37]. However, sildenafil improved RV-arterial coupling by a positive inotropic effect in monocrotaline-induced PH[38]. Bosentan had no intrinsic effect on contractility in PH induced by 3 months of aorta-pulmonary shunting[39].

SIMPLIFIED METHODS FOR THE MEASUREMENT OF RV-ARTERIAL COUPLING

The pressure method

With the calculation of a Pmax from a RV pressure curve and assuming that mPAP is a satisfactory estimate of RV pressure at the point of maximal elastance, Emax can be estimated by the ratio of the difference (Pmax – mPAP) to SV, and Ea by the ratio of mPAP to SV[40]:

$$Emax/Ea = Pmax/mPAP - 1$$

The pressure method has been implemented on digitized right heart catheterization recordings of patients with PH on left heart diseases (PH-LHD) or PAH. Emax/Ea was depressed in patients with combined pre- and post-capillary PH, not in patients with isolated post-capillary or PAH, and was related to survival[41]. In another study on patients referred for PH, Emax/Ea measured by the pressure method did not emerge as an independent predictor of outcome[42].

The volume method

The ratio of elastances Emax/Ea presents with a common pressure term, and can thus also be simplified to a ratio of volumes[43]:

$$ESP/ESV \ / \ ESP/SV = SV/ESV$$

The main inherent assumption that the end-systolic PV relationship is linear and crosses the origin[40]. Therefore, the ESP/ESV relationship under-estimates Emax[40,42].

A simple rearrangement of the EF equation EF = SV/EDV shows that SV/ESV and EF are nonlinearly related[44]:

$$SV/ESV = EF \ / \ (1 - EF)$$

The nonlinear relationship between EF and SV/ESV is illustrated in figure 2.

The SV/ESV ratio, not EF has been shown to be an independent predictor of outcome in patients referred for PH[42]. However, this was not confirmed in a study on patients with established PAH, in whom the SV/ESV and EF performed equally, even though a decrease in SV/ESV was more tightly related to poor outcome[45]. Different predictive capability of SV/ESV and EF may be related to their nonlinear relationship, with SV/ESV being more sensitive than EF to changes in RV function in less advanced disease (Fig. 2).

Right ventricular EF is a potent independent predictor of survival in PH, with a cut-off value determined by the best combination of sensitivity and specificity of 35%[46,47]. The rigorously determined cut-off value for SV/ESV is 51%[42]. A simple re-arrangement of the EF and SV/ESV equations allows to demonstrate that below these cut-off values, preservation of SV requires an increase in both ESV and EDV (Fig. 3).

It is important to note that PVR can increase considerably without decrease in RV EF[46] and that RV EF can decrease in spite of therapeutic success to decrease in PVR[47]. In both cases, outcome is predicted by EF, not PVR[44,45]. A decrease in PVR at increased cardiac output cannot unload the RV if not accompanied by a marked decrease in PVR[48].

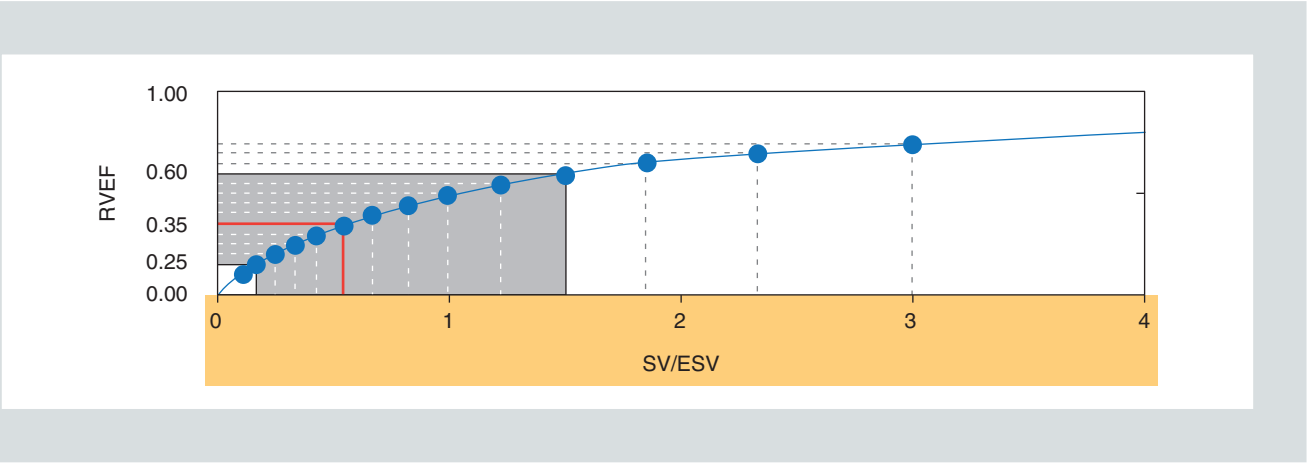

Figure 2. Curvilinear relationship between right ventricular (RV) ejection fraction (EF) and ratio of stroke volume (SV) to end-systolic volume (ESV). The grey region shows the pulmonary hypertension RVEF range (0.15-0.60) and the red line shows the RVEF and corresponding SV/ESV cut-off value that is predictive of outcomes *(reproduced with permission from Vanderpool RR et al.[44])*.

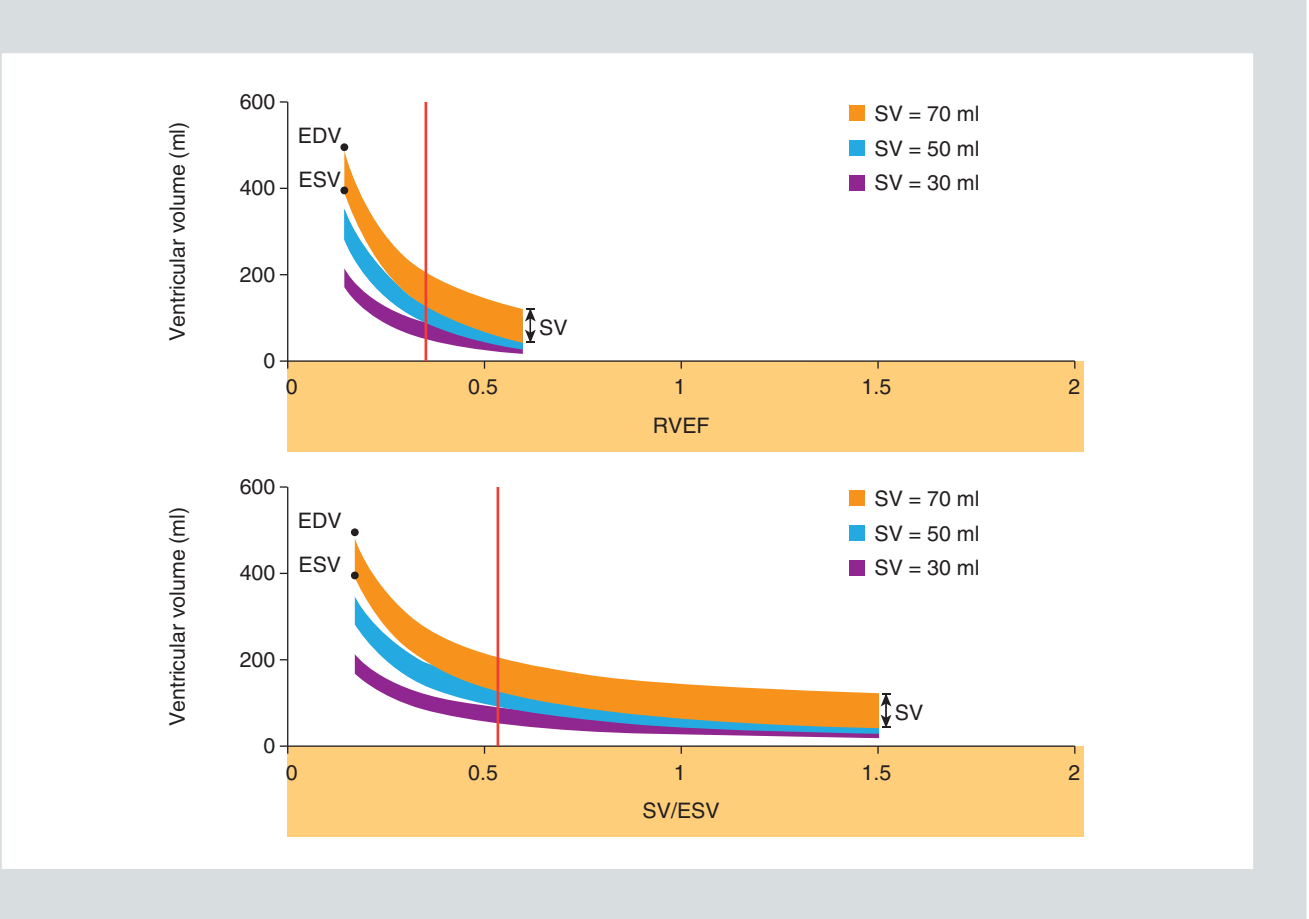

Figure 3. Non-linear relationship between right ventricular (RV) end-diastolic volume (EDV) and end-systolic volume (ESV), and respectively ejection fraction (EF) and ratio of stroke volume (SV) to ESV at a given SV. As RVEF and SV/ESV decrease, ESV and EDV have to increase to maintain SV. The red line shows the RVEF and corresponding SV/ESV cut-off value that has been shown to be predictive of outcomes *(reproduced with permission from Vanderpool RR et al.[44])*.

A hyper-dynamic state with little effect on PAP, as was sometimes reported with high doses of prostacyclins in PAH[32] can only but increase RV afterload, which is not a desirable objective.

Advances in 3-dimensional echocardiography now offer the prospect of easier bedside measurements of RV volumes[49], and thus of EF or SV/ESV for the evaluation of RV-arterial coupling.

The contractile reserve

Systolic function adaptation to afterload can also be tested dynamically to determine a contractile reserve, or the capacity to increase contractility at a given level of loading. Contractile or ventricular reserve determined using exercise or pharmacological stress tests (typically an infusion of dobutamine) has been shown to be a strong predictor of outcome in heart failure[50].

As a simple noninvasive approach to assess RV contractile reserve, Doppler echocardiography was used to measure RV systolic pressure from the maximum velocity of tricuspid regurgitation at rest and at exercise in patients with either PAH or CTEPH[51]. An exercise-induced increase in systolic RV pressure by more 30 mmHg was a strong predictor of exercise capacity and better survival. It was however subsequently shown that the increase in PAP (or systolic RV pressure) during exercise in severe PH is but loosely correlated to Emax/Ea[19] so that there is uncertainty as to whether the measurement effectively addresses the RV rather than the pulmonary circulation.

Other tentative assessments of RV contractile reserve have relied on low-dose dobutamine to increase tricuspid annular plane systolic excursion (TAPSE) or tissue Doppler tricuspid annulus S' wave[52] or exercise-induced changes in TAPSE/PAP ratio[53]. While dobutamine-induced increase in indices of RV systolic function are indeed tightly related to resting Emax/Ea[54] the optimal protocol to assess RV contractile reserve remains to be validated.

DIASTOLIC FUNCTION

Even though systolic function adaptation to afterload is central to RV failure symptomatology, diastolic function (mal)adaptation must also be taken into consideration.

Diastolic function is described by a diastolic elastance curve determined by a family of pressure-volume loops at variable loading. It is curvilinear thus impossible to summarize as a single number. Several formulas fitting two or three diastolic PV coordinates have been proposed[8]. Most recently RV diastolic stiffness was estimated in 21 patients with PAH by fitting a non-linear exponential curve with the formula $P = \alpha (e^{V\beta} - 1)$, where α is a curve fitting constant and β a diastolic stiffness constant[55]. These results were confirmed in a larger cohort of 63 patients but with diastolic function simplified as a single end-diastolic PV ratio[56].

Whether RV diastolic function however defined might be an independent predictor of outcome in PH is not always confirmed[42]. Another still unsolved issue is whether diastolic function might deteriorate independently of systolic function.

VENTRICULAR INTERACTION

RV function cannot be dissociated from LV function. Both structures have the septum and free wall myocardial fibres in common, and are constrained within a non-distensible pericardial envelope. There is thus direct interaction, or ventricular interdependence, defined as the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium, independent of neural, humoral or circulatory effects[57].

Diastolic ventricular interaction refers to the competition for space within the pericardium when the RV dilates, which alters LV filling and may be a cause of inadequate cardiac output response to metabolic demand. Right heart catheterization and imaging studies have shown that in patients with severe PH, mPAP and LV peak filling rate are altered in proportion to decreased RV EF[58].

Systolic interaction refers to positive interaction between RV and LV contractions. It can be shown experimentally that aortic constriction and associated enhanced LV contraction, markedly improve RV function in animals with pulmonary artery banding[59]. Similarly, in electrically isolated ventricular preparations in the otherwise intact dog heart, LV contraction contributes a significant amount (~30%) to both RV contraction and pulmonary flow[60]. This is explained by a mechanical entrainment effect, but also by LV systolic function determining systemic blood pressure, which is an essential determinant of RV coronary perfusion. Increased RV filling pressures and excessive decrease in blood pressure may be a cause of RV ischemia and decreased contractility in severe PH[61].

An additional cause of negative ventricular interaction disclosed by magnetic resonance imaging studies is regional and inter-ventricular asynchrony with post-systolic contraction or "shortening", which has been shown to develop in parallel to increased PAP and contributes to altered RV systolic function and LV under-filling[62]. Inter-ventricular asynchrony can be assessed by tissue Doppler imaging[63]. The RV regional inhomogeneity of contraction or dyssynchrony can now accurately be identified and quantified by speckle tracking echocardiography[64-66]. RV dyssynchrony alters systolic function and is associated with a poor survival[64-66].

In addition to direct interaction, RV and/or LV failure trigger an activation of the sympathetic nervous and renin-angiotensin-aldosterone systems which may deteriorate function of the initially unaffected ventricle and contribute to worsen symptomatology, functional state and outcome.

RESPIRATORY SYSTEM MECHANICS

High or low lung volumes increase PVR[67]. This is caused by dominant effects of compression of alveolar vessels at high lung volumes and a compression of extra-alveolar vessels at low lung volumes. PVR is minimal at functional residual capacity.

Breathing is necessarily associated with pleural pressure (Ppl) changes. The amplitude of Ppl variations is proportional to tidal volume and respiratory system compliance, and tends to be on average positive during mechanical ventilation and negative during spontaneous breathing. The heart is exposed a surrounding

pressure approximately equal to Ppl, which is on average 3-4 mmHg below atmospheric pressure. Respiratory Ppl swings do not affect trans-mural RV, pulmonary vascular and LV pressures. However, LV-arterial coupling is affected as the aorta is in open communication with the systemic arterial system. Positive intra-thoracic pressure decreases the pressure gradient needed to open the aortic valve, and thereby decreases LV afterload, in addition to a preload reduction due to a decrease in systemic venous return[68]. This carries a risk of insufficient preload adaptation to afterload in advanced PH and RV failure. Negative intra-thoracic pressure increases the pressure gradient to open the aortic valve, and thus increases LV afterload – while systemic venous return is slightly increased or maintained[69]. Markedly negative intra-thoracic pressure may be a cause of left heart failure on weaning from mechanical ventilation[70]. Negative Ppl with hyper-inflation in spontaneously breathing patients may thus cause worsening PH on upstream transmission of pulmonary artery wedge pressure (PAWP).

An additional effect of disturbed respiratory system mechanics is due to dynamic hyper-inflation in patients with obstructed airways[71]. This causes prolonged positive Ppl during expiration and is a cause of over-estimation of PAP and PAWP by reading pulmonary vascular pressure curves at end-expiration.

In the presence of excessive intra-thoracic pressure swings, with or without dynamic hyper-inflation, the reading of pulmonary vascular pressures has to be corrected for Ppl, or, as an acceptable approximation, averaged over several respiratory cycles[72]. This notion was recently incorporated in the European guidelines[1].

Lung disease can also is of course a cause of hypoxic vasoconstriction which, if globally distributed over the lungs, may aggravate PH[73].

A GLOBAL VIEW ON RV FAILURE

Thus, PH increases RV afterload requiring a homeometric adaptation with eventual hypertrophy. When this adaptation fails, the RV enlarges, decreasing LV preloading because of competition for space within the pericardium. This decreases SV and blood pressure, with negative systolic interaction as a cause of further RV-arterial uncoupling, which may be aggravated by RV ischemia from decreased coronary perfusion pressure (gradient between diastolic blood pressure and right atrial pressure).

These interactions may allow one to identify targets of interventions. The first target is increased PVR, which can be controlled by thrombolytics in severe pulmonary embolism, inhaled NO, inhaled iloprost in case of acute pulmonary vasoconstriction, prostacyclins, intravenous epoprostenol, PDE5i's and ERA's for PAH, correction of decreased or increased functional residual capacity, pH and hypoxemia all causes of increased PVR in lung diseases. The second target is RV contractility, which can be temporarily improved by intravenous dobutamine. The third target is excessive RV preload and associated negative diastolic interaction which can be controlled by high-dose intravenous diuretics and fluid restriction, or hemo-filtration in case of renal insufficiency. The fourth target is hypotension and associated negative systolic interaction and eventual RV ischemia, which can be controlled by intravenous norepinephrine.

CONCLUSIONS

The interactions between the heart and the normal or hypertensive pulmonary Circulation. are complex. Their understanding offers indispensable guidance to differential diagnosis and therapeutic options.

CONFLICT OF INTEREST

Dr. Robert Naeije has nothing to disclose.

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