REVIEW

Right ventricular pulsatile afterload and right ventriculo-arterial coupling in pulmonary hypertension

Elena Popa[1,2], Ana-Maria Daraban[2,3], Roxana Enache[1], Sorin Giușcă[1], Carmen Ginghină[1,2], Ruxandra Jurcuț[1,2]

Abstract: The right ventricle (RV) is a thin-walled structure, adapted to eject into the low-impedance, high-compliance pulmonary circulation. In chronic pressure overload, the RV initially adapts by myocardial hypertrophy, maintaining efficient RV-arterial (RVA) coupling. Later on this adaptive mechanism is overrun and RV dilation with ensuing RV failure, RVA uncoupling and eventually death occur. Pulsatile afterload is more relevant in the pulmonary circulation than in the systemic circulation, because of the high compliance of the former, both in normal physiology and in pulmonary hypertension (PH). This review studies the importance of pulsatile afterload, as assessed by pulmonary artery (PA) stiffness parameters, and of RVA coupling in the setting of PH. Assessment of these parameters adds to the physiopathological understanding and the clinical and therapeutic assessment in PH. Further studies are needed to better understand the mechanisms that lead from efficient RVA coupling to RV failure and RVA uncoupling and thus to translate these findings into efficient treatment for PH patients.
Keywords: pulsatile afterload, stiffness, right ventricular-arterial coupling, right ventricle, pulmonary hypertension

Rezumat: Ventriculul drept (VD) este o structură anatomică cu pereți subțiri, adaptată pentru ejecția în circulația pulmonară cu impedanță joasă și complianță crescută. În suprasarcina cronică de presiune, VD se adaptează inițial prin hipertrofie miocardică, păstrându-se cuplarea ventriculo-arterială (CVA) eficientă, dar mai târziu acest mecanism adaptativ este depășit și apare dilatarea de VD cu insuficiență de VD, decuplare ventriculo-arterială și în final moarte. Suprasarcina pulsatilă este mai semnificativă în circulația pulmonară decât în cea sistemică, din cauza complianței crescute a celei dintâi, atât în situații normale, cât și în hipertensiune pulmonară (HTP). În acest review sunt studiate importanța suprasarcinii pulsatile de presiune, evaluată prin parametri de rigiditate a arterei pulmonare, și a cuplării ventriculo-arteriale (CVA) drepte în contextul HTP. Evaluarea acestor parametri contribuie la înțelegerea fiziopatologiei și la evaluarea clinică și terapeutică a HTP. Studii suplimentare sunt necesare pentru a înțelege mai bine mecanismele care duc de la o CVA eficientă la insuficiență de VD și decuplare ventriculo-arterială, pentru a putea apoi transpune rezultatele în tratament eficient al pacienților cu HTP.
Cuvinte-cheie: postsarcină pulsatilă, rigiditate, cuplare ventriculo-arterială dreaptă, ventricul drept, hipertensiune pulmonară

INTRODUCTION

In pulmonary hypertension (PH), right ventricular (RV) function is correlated with functional status and is a strong predictor of survival, whereas the pulmonary artery (PA) pressures are not strongly correlated with symptoms or outcome. Even if treatment decreases pulmonary arterial resistance, this is not necessarily translated in improvement of outcome[1]. On the other hand, pressure and resistance represent only one aspect of ventricular afterload, the other one being arterial compliance, as reflected by stiffness parameters. Therefore, it is important to study the RV and the pulmonary arterial tree as a unit, with all their aspects, to further the understanding of the physiopathology of PH and to eventually improve the outcome of patients with PH.

[1] Cardiology Department, Emergency Institute for Cardiovascular Diseases "Prof. Dr. C. C. Iliescu"
[2] University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[3] Internal Medicine Department, Clinical Emergency Hospital Bucharest, Romania

Contact address:
Ruxandra Jurcut, Cardiology Department, Emergency Institute for Cardiovascular Diseases "Prof. Dr. C. C. Iliescu", Sos. Fundeni 258, Sector 2 022328 Bucuresti, Romania
e-mail: rjurcut@gmail.com

A. General aspects of right ventricular afterload

Ventricular afterload can be evaluated by several methods, for instance by the maximum ventricular wall stress or by the assessment of arterial hydraulic load. Wall stress is approximated using a transposition of the law of Laplace as follows: the maximum value of the product of volume and pressure divided by wall thickness. This transposition is problematic for the RV because it stems from Laplace's law for spheric structures, while the RV has considerable regional variations in internal radius[2]. Assessment of pulmonary arterial hydraulic load depends on the particular aspects of the pulmonary circulation.

The major anatomical differences between the systemic and pulmonary circulation are represented by the intrapulmonary location of the majority of pulmonary vessels and the extensive branching of the pulmonary vasculature. While the proximal great arteries share an intrathoracic course, thus being both subject to intrathoracic pressure variations, the pulmonary arterial tree is also subject to gravitational and radial distribution of interstitial and perivascular pressure. Moreover, the pulmonary arterial tree consists of a relatively short elastic proximal PA, with a complex pattern of vascular division, with important consequences on pulse wave transmission and wave reflection[3].

Functionally, ventricular afterload has two components: the "steady-flow" component, which represents the opposition that the ventricle faces in maintaining a forward flow with the observed mean flow rate, and the "pulsatile" component, which is added by the pulsatile nature of flow and dependent on the compliance of the arterial system and on wave reflections. While the first component is quantified as vascular resistance and is a part of clinical practice, the pulsatile afterload is often ignored, since it requires complex investigations of stiffness parameters. Nevertheless, the pulsatile afterload is especially important in the pulmonary circulation, given its low resistance-high compliance nature, as is emphasized by the pulsatile ratio of hydraulic power used by the ventricles to maintain flow: in the systemic circulation, approximately 10% of the hydraulic power generated by the left ventricle (LV) is used for the pulsatile component of flow[4], whereas in the pulmonary circulation, the RV spends approximately 25%-30% of its power for the same purpose[5,6]. On the other hand, pulsatile power fraction increases in systemic hypertension[7,8], while it remains constant in PH[6].

The amount of hydraulic power spent to overcome the steady component is consumed at the level of arterioles and capillaries for both the systemic and pulmonary circulation, while the pulsatile component depends on the significantly different distribution of compliance in the two arterial systems. As mentioned before, extensive branching of the pulmonary circulation leads to a larger number of peripheral vessels, up to 8-10 times more in the pulmonary than in the systemic arterial tree. In the systemic arterial tree, 80% of total compliance is based in the thoracic-abdominal aorta[9], while in the pulmonary circulation at least half of pulmonary arterial compliance is distal to the proximal large arteries[9,10]. Thus, the pulsatile component of ventricular hydraulic power is spent mostly at the level of the aorta in the systemic circulation and along the entire pulmonary arterial tree in the lesser circulation. This anatomical difference between the 2 major arterial systems leads to a constant product of resistance and compliance (τ, the arterial time-constant, expressed in seconds) in the pulmonary circulation, parameter that characterizes the decay of pressure in diastole. Graphically, this means that resistance (R) and compliance (C) are inversely related by a hyperbola, because of the inverse exponential relationship between the 2 parameters (Fig. 1). The RC-time remains constant in healthy individuals, in patients with PH and even after treatment of PH[11,12]. This means that in the early stage of PH, a small increase in pulmonary vascular resistance (PVR) leads to a large decrease in compliance, whereas in later stages, larger increases in PVR lead to only modest decreases in compliance, probably because at a certain level of PA pressure and dilation the PA approaches its elastic limit. From a clinical perspective, this implies that in early stages of PH the decrease in compliance may be more easily detected than the rise in PVR; conversely, in early stages, the same reduction in resistance leads to more significant increases in compliance than in later stages of PH. On the other hand, the level of PAP after which rises in pressure lead to insignificant decreases in compliance are approximately 40 mmHg for mean PAP or 60 mmHg for systolic PAP[13,14].

Another consequence of the constant RC-time in pulmonary circulation is the proportionality between systolic, mean and diastolic PAP in healthy individuals and in PH, while in the systemic circulation, where the RC-product varies with aortic pressure, there is no proportional relationship of systemic arterial pressures. On the contrary, in old age hypertension, systemic systolic pressure rise is frequently accompanied by a decrease in diastolic pressure, with a significant increase in pulse pressure (PP). On the other hand, the

PP in the aorta is approximately 40% of mean pressure, while in the pulmonary circulation, the PP is approximately equal to mean pressure.

Another difference between the systemic and the pulmonary circulation is the much larger range of pressure and compliance changes in the pulmonary arterial tree than in the systemic circulation. In systemic hypertension, resistance increases by one-fifth and compliance decreases 3-fold, while in PH, resistance and compliance can increase, respectively decrease approximately 20-times[9]. Thus, the load imposed on the RV in PH is proportionally much larger and the adaptation of the RV to increased afterload is more difficult than for the LV.

B. Evaluation of right ventricular pulsatile afterload

B.1. Pulmonary artery dilation in pulmonary hypertension

Pulmonary artery dilation is one of the consequences of PH and has been used as a non-invasive sign of PH. Good correlation has been shown between CT measurements of the main pulmonary vessels and the level of mean PAP; the dimensions of main PA and its main branches have been proposed for diagnosing PH and even for estimating the level of pressure overload[15,16]. Later similar findings were reported using MR imaging[17,18]. The most used parameter is the ratio between the diameter of main PA and the diameter of ascending aorta; if over 1, the sensitivity and specificity of identifying mean PAP over 20 mmHg are 70% and 92% respectively, independently of body surface area and sex[19].

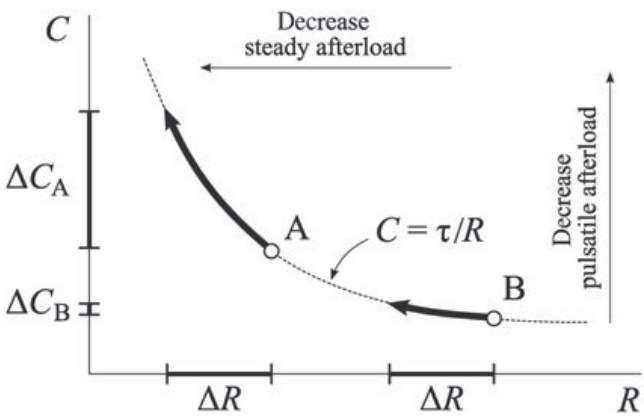

Figure 1. The inverse exponential relationship between C (compliance) and R (resistance). The same decrease in resistance (ΔR) leads to different decreases in compliance (ΔC), depending on the absolute levels of resistance. For high resistance values, the amplitude of compliance decrease is much smaller than for low resistance values. (reproduced with permission from 12: Lankhaar JW, Westerhof N, Faes TJ, Gan CT, Marques KM, Boonstra A, et al. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. Eur Heart J 2008;29(13):1688-95.).

Although PAP is considered the main cause of PA dilation, the influence of other factors, such as time and flow, is less known. A recent study has shown that in patients treated for PH, the PA has continued to dilate, irrespective of changes in mean PAP, even in patients whose PAP has decreased with treatment[20]. Thus, PA dimensions are useful for screening for PH, but cannot be used for assessing the evolution of the disease or the therapeutic response.

The causes for this behaviour of PA dilation during the course of PH are not completely understood. Histologic studies have shown significant remodeling of the proximal PA wall in PH, with extracellular matrix changes in collagen and elastin content, with significant increases in PA stiffness[21,22]. These structural changes might eventually become a cause of continued PA dilation, independent of changes in pressure and flow.

B. 2. Pulmonary artery input impedance

The ventricular afterload can be represented by the relationship between arterial pressure and flow, which can be expressed in the frequency or in the time domain. The most complete characterization is represented by the input impedance spectrum, a frequency-domain analysis of the arterial circulation, which describes the relationship between arterial pressure and flow over an entire cardiac cycle, including both mean and pulsatile data.

Initially, pulmonary impedance spectra were measured only in research laboratories using main PA catheterization, by simultaneously evaluating pulmonary arterial pressure and flow using high-fidelity, manometer-tipped catheters and flowmeters. More recently, another approach has been validated, using instantaneous PAP measurements during right heart catheterization (RHC), combined with PA blood flow measurements using Doppler transthoracic echocardiography. Consequently, Fourier analysis of pressure and flow data and computation of impedance are made using dedicated software[23,24].

The results of this analysis are expressed as an impedance spectrum, consisting of a pressure to flow ratio and a phase angle, expressed as a function of frequency[25]. The PA input impedance spectrum depends mainly on the first 5 orders of bifurcation from the main PA and includes: a measure of total PVR (Z0 - 0 frequency impedance); indices of wave reflection (the first minimum of the ratio of pressure and flow

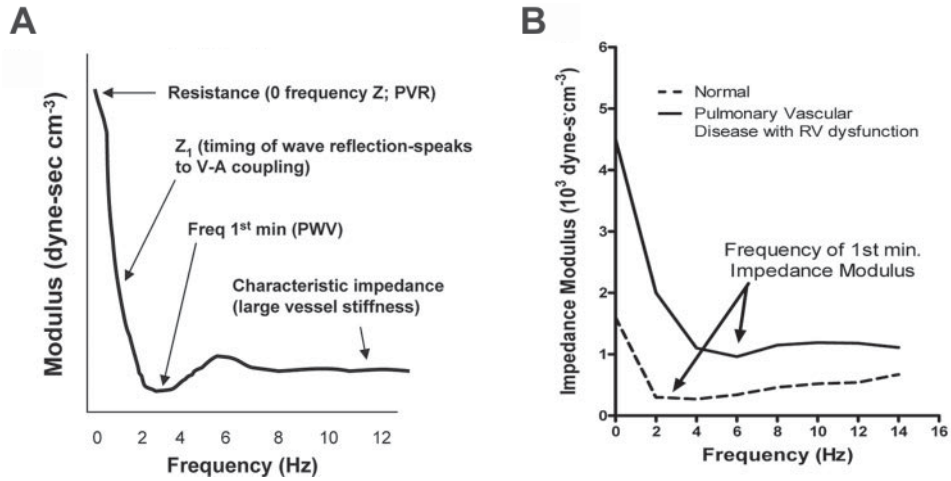

Figure 2. A. PA impedance spectrum in a normal subject. **B.** PA impedance spectra of a patient with PH and RV dysfunction (solid line) and normal subject (dashed line). Of note, the spectrum of the PH patient is shifted to higher than normal pressures and frequencies. (reproduced with permission from 26: Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. Circulation 2009;120(11):992-1007).

or low-frequency phase angle, which also correspond to optimal ventricular-arterial coupling); characteristic impedance (Zc), which corresponds to the ratio of inertance to compliance; hydraulic load, as assessed by low-frequency impedance and the amplitude of impedance oscillations[26] (Fig. 2). In patients with PH, the impedance spectrum in shifted to higher than normal pressures and frequencies, with higher Z0, reflecting higher PVR; a shift to higher frequencies of the point in which impedance declines to its first minimum, reflecting increased pulse wave velocity and increased wave reflection; higher Zc, a measure of higher characteristic impedance; signs of increased mean and total hydraulic power output (3). In clinical practice, pulmonary impedance data have been shown in a pediatric population to better predict outcome in PH than PVR alone[24].

Although impedance spectra offer a wealth of data regarding arterial load, they are complex to interpret. Thus, other measures of pulsatile afterload have been defined, that can be more easily used in clinical practice.

B. 3. Time-domain analysis of pulmonary artery pressure waveforms

Time-domain analysis of pulmonary arterial pressure waveform provides important data on pulsatile arterial load and may be a surrogate for the full assessment of RV input impedance. This analysis can be performed using RHC.

Pressure waveform analysis reveals the timing and extent of wave reflection in the arterial circulation and the magnitude of pulse pressure (PP)[27]. Pulmonary artery pulse wave velocity (PWV) is around 1.7 m/s at normal pressures[5], which is almost half of the velocity measured in the aorta at around 4 m/s[28,29]. The reflected pressure wave arrives back in both the aorta and the PA of normal subjects during the early diastolic period, because the shorter path length in the pulmonary arterial tree compensates for the lower pulse wave velocity[27,30].

When the forward pressure wave from the ventricle collides with the reflected backward pressure wave from the bifurcations, pressure increases and flow decreases[26]. Pressure and flow curves are more similar in the normal pulmonary arterial tree than in the systemic circulation, because of less wave reflection. When reflection increases, because of pharmacological or pathological increases in arterial resistance, the resemblance of pressure and flow waves decreases[30]. The characteristics of the reflected wave depend on the physical properties of the arterial tree (stiffness and branching), PWV and the distance to the reflecting sites[31].

In patients with PH, the PWV in the PA is higher, at about 4.4 m/s[5,32], thus the reflected wave reaches the PA in systole, increasing the systolic pressure. The relative increase in pressure amplitude (ΔP) is a measure of the magnitude of the reflected pressure wave (Fig. 3). The ratio ΔP/PP defines the augmentation index (AI), which normalizes the pressure rise due to wave reflection for PP. Another important parameter is the time between the beginning of systole and the beginning of the reflected wave (Δt). One study

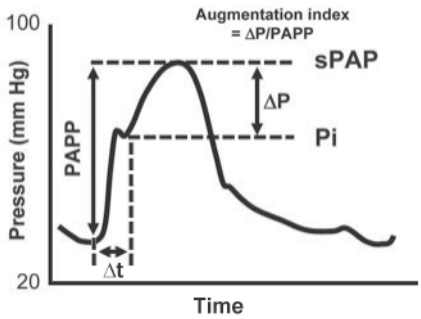

Figure 3. The pressure waveform of the PA in PH. PAPP=pulmonary artery pulse pressure; sPAP = systolic pulmonary artery pressure; Pi=pulmonary artery pressure at the inflection point (at the beginning of the reflected wave); ΔP=sPAP-Pi (the relative increase in pressure due to wave reflection); Δt= time between the beginning of systole and the beginning of the reflected wave. (reproduced with permission from 26: Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. Circulation 2009;120(11):992-1007).

showed that in patients with chronic thromboembolic pulmonary hypertension (CTEPH) wave reflection is earlier and enhanced compared with patients with idiopathic PAH (iPAH), since CTEPH involves predominantly proximal arteries, while in iPAH, the pathological lesions are mainly located in distal arteries. This finding was expressed by a shorter Δt and a higher AI in patients with CTEPH[33]. Moreover, the extent and timing of wave reflection could have an unfavourable effect on ventricular-arterial coupling, loading the still-ejecting ventricle.

B. 4. Pulmonary artery stiffness parameters

Several parameters for evaluating pulmonary artery stiffness have been defined and measured (Table 1 and 2).

Capacitance is a measure of the ability of arterial vessels to expand during systole and to recoil during diastole. A high capacitance arterial tree lowers the systolic pressure by storing blood during systole and increases diastolic pressure by recoiling during diastole, with 2 effects: damping the pressure variations of the ventricle and supplying constant peripheral blood flow during the entire cardiac cycle[9].

Most methods of estimating arterial compliance are based on the arterial windkessel method. Parameter optimizations of two- and three-element windkessel models have been developed for this purpose. The three-element windkessel model, which comprises total peripheral resistance, characteristic impedance and total arterial compliance, leads to significant overestimation of arterial compliance. Moreover, this method is unreliable when wave reflections are small[34]. The two-element windkessel model, consisting only of total peripheral resistance and total arterial compliance, has lead to three methods of calculating arterial compliance. Two of them, the diastolic decay method and the area method, require measurement of pressure curves and can be applied only when there is no flow in diastole, thus being unsuited for patients with pulmonary hypertension, that present in a vast majority of cases with pulmonary regurgitation[35]. The third method based on the two-element windkessel model is the pulse pressure (PP) method, which is a reliable method for calculating total arterial compliance in the systemic[36] and pulmonary arterial tree[34] and does not require detailed pressure curves or no reverse diastolic flow, being applicable for patients with pulmonary hypertension. On the other hand, this method requires the measurement of flow curves, vascular resistance and PP[35].

Since a compliant arterial system dampens ventricular pressure variations, it has been shown that the higher the compliance, the lower the PP is both in the systemic[37] and in the pulmonary circulation[14]. Because PP is mainly determined by stroke volume (SV) and arterial compliance, another method of estimating arterial compliance is the ratio of SV to PP, reflecting total rather than local arterial compliance. This method is also known to overestimate total compliance, since it does not consider outflow from the arterial tree during the ejection phase. Nevertheless, this equation has been shown to have a good correlation with the PP method[34] and it has been validated in the systemic[38] and pulmonary circulation[34].

Although in one study compliance has been shown to be altered in patients with exercise-induced PH without overt PAP changes at rest[13], it remains unclear if these findings predict the development of PH at rest, especially since the diagnosis of exercise-induced PH is still a matter of controversy[39]. Moreover, the causal relationship between stiffness and pressure is still unknown; it is unclear if stiffness increases only secondary to increased arterial pressure or due to pressure independent changes of the arterial wall or both. Still, the finding of altered compliance in the absence of PH at rest and moreover, the fact that higher distending pressures do not fully account for the increased stiffness as evaluated by the stiffness index β, may suggest a role of altered intrinsic elastic properties of the PA in the early stages of PH and thus worsening PA stiffness among the first physiopathological manifestations of PH[13].

Table 1. Parameters of arterial stiffness

Parameter	Units	Formula	Definition
Pulsatility	%	ΔA/min A x 100	Relative area change
Distensibility	%/mmHg	Pulsatility/PP	Relative area change for a pressure increment
Compliance	mm^2/mmHg	ΔA /PP	Absolute area change for a pressure increment
Capacitance	mm^3/mmHg	SV/PP	Absolute volume change for a pressure increment
Elastic modulus	mmHg	PP x min A/ΔA	Pressure change driving a relative increase in area
Stiffness index β	nondimensional	ln(syst. P/diast. P)/[ΔA /min A]	Slope of the function between distending arterial pressure and arterial distension
Characteristic impedance	mm Hg/cm/s	PP/v	Relationship between pressure change and flow velocity (in the absence of wave reflections)

ΔA = maximal lumen area – minimal lumen area; min A = minimal lumen area; PP = pulse pressure; SV = stroke volume; syst. P = systolic arterial pressure; diast. P = diastolic arterial pressure; v = blood flow velocity

Table 2. Reference values of parameters of arterial stiffness for the pulmonary artery

Parameter	Normal value	PH value	Reference
Pulsatility (%)	55.2	17.2	Sanz et al.[13]
		14.6	Rodés-Cabau et al.[42]
	58	20	Gan et al.[44]
Compliance (mm^2/Hg)	4.49×10^{-2}	1.5×10^{-2}	Lau et al.[45]
Capacitance (mL/Hg)	2.87	0.7	Reuben et al.[14]
	7.87	1.25	Gan et al.[44]
	4	1	Lankhaar et al.[11]
Distensibility (%/mmHg)	3.1	0.4	Sanz et al.[13]
	3.69	0.46	Gan et al.[44]
	1.18	0.32	Lau et al.[45]
Elastic modulus (mmHg)	32.6	246.9	Sanz et al.[13]
		449	Rodés-Cabau et al.[42]
	198	720	Lau et al.[45]; formula used: (PP x min D/ΔD)
Stiffness index b (-)	1.8	5.2	Sanz et al.[13]
	11	15	Lau et al.[45]; formula used: (ln(sPAP/dPAP)/[ΔD /min D]

ΔD = maximal lumen diameter – minimal lumen diameter; min D = minimal lumen diameter; PP = pulse pressure; sPAP = systolic pulmonary artery pressure; dPAP = diastolic pulmonary artery pressure

From a clinical perspective, PA stiffness may contribute to the disconnect between the severity of hemodynamic abnormalities and treatment response to vasodilator drugs[40]. Furthermore, PA distensibility has been shown to predict functional capacity in patients with PAH, as assessed by the 6-minute walk test[41]. Moreover, several indices of pulmonary stiffness have been shown to have prognostic value in PH. In one study, decreased pulsatility and increased elastic modulus of distal pulmonary arteries in patients with PAH were associated with mortality at follow-up[42]. In another study of patients with PAH, pulmonary capacitance, as assessed by the ratio of SV/PP, was a better predictor of mortality than PVR, right atrial pressure, cardiac index, 6-minute walk distance and National Institutes of Health 4-year predicted survival equation[43]. Another study showed that PA pulsatility was a better marker of death than PVR, right atrial pressure, or 6-minute walk distance[44].

C. General aspects of right ventricular-arterial coupling in pulmonary hypertension

RV function is a major determinant of clinical presentation and prognosis in PH, with RV failure being the main cause of death[46]. The RV is thin-walled compared to the LV, with approximately one-fourth of LV mass[47], but due to the low impedance and high compliance of pulmonary circulation it pumps the same volume of blood at the same rate as the LV. Therefore, the RV is especially challenged when it has to adapt to up to 4-5 fold increased chronic afterload, while RV volume overload is better tolerated[48]. In RV pressure overload, initially adaptive mechanisms come into play, with myocardial hypertrophy preserving RV systolic function and normalising wall stress and with preserved RVA coupling. Over time however RV dilation and systolic dysfunction occur, with RVA uncoupling, RV failure and eventually death[48].

RVA coupling is best quantified by the relationship between end-systolic or maximal ventricular elastance

(Ees or Emax) and effective arterial elastance (Ea), both expressed in the time domain using pressure-volume curves.

Ees, the slope of the end-systolic pressure (ESP) - volume relationship, initially characterized for the LV[49,50] and afterwards for the RV[51], is a measure of ventricular contractile state, being nearly independent of changes in preload, afterload, and heart rate (Fig. 4). Moreover, Ees integrates besides intrinsic ventricular contractility the modulating effects of geometric and biochemical properties of the ventricle[52]. Ees can be calculated as ESP/[end-systolic volume (ESV)-V_0], where V_0 is the volume corresponding to the x-axis intercept of the ESP-V linear relationship and represents the theoretical volume of the unloaded ventricle[49,53]. A common assumption is that V_0 is negligible compared with ESV, thus the equation becomes Ees = ESP/ESV[54].

On the other hand, Ea is an integrative index of arterial load, encompassing its principal elements: peripheral resistance, total arterial compliance, characteristic impedance and systolic and diastolic time intervals[55]. Despite its broad spectrum, Ea is dominated by nonpulsatile load[56]. This parameter is determined from pressure-volume loops as the negative slope of the line between the end-diastolic volume (EDV) and ESP points and can be approximated by the ratio of ESP to SV for the LV[57], while for the RV the equation becomes Ea = [ESP-pulmonary capillary wedge pressure (PCWP)]/SV[58].

The coupling between the ventricle and the respective artery is expressed by the relation of the two elastances and calculated as Ees/Ea or Ea/Ees[54]. Effective coupling can be defined using several criteria, the most important being optimal external work and optimal energetic efficiency of the heart. Numerically, it has been predicted[57] and experimentally observed that near optimal work and efficiency are achieved when the Ea/Ees ratio is between 0.6 and 1.2 for the LV[52,59], range normally maintained in various physiological conditions. For the RV normal values at rest between 0.37 and 0.7 have been reported[60-63], with optimal mechanical coupling occurring when the ratio is 1, while the optimal energy transfer from the RV to the pulmonary arterial tree occurs at ratios of 0,67-1[2].

Technically, the use of pressure-volume curves with varying load is more challenging for the RV than for the LV. Furthermore, its crescent shape makes accurate instantaneous RV volume measurements more difficult[26]. Moreover, the almost "triangular" shape of the pressure-volume curve due to the ongoing ventricular ejection despite a significant drop in pressure makes the definition of the maximal ventricular elastance more challenging, since it occurs before the end of systole in the RV[64].

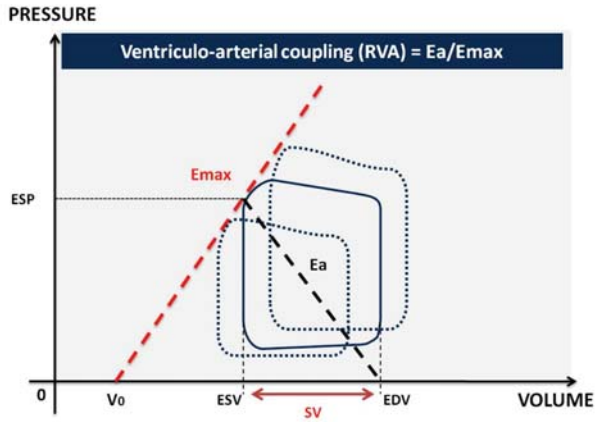

Figure 4. RV pressure-volume relationship and the method of deriving Ees (or E_{max} = maximal ventricular elastance) – the slope of the end-systolic pressure - volume relationship and Ea (=arterial elastance) – the negative slope of the line between the end-diastolic volume (EDV) and end-systolic pressure (ESP) point. V_0 is the volume corresponding to the x-axis intercept of the ESP-volume linear relationship, representing the theoretical volume of the unloaded ventricle. ESV = end-systolic volume; RVA = right ventriculo-arterial coupling.

More recently a single-beat method has been developed, which bypasses the challenging load alterations and the difficulty of measuring instantaneous RV volume *in vivo*[65] (Fig. 4). Furthermore, hybrid methods have been developed, which use invasively measured pressures and non-invasively determined volumes, either with MRI[61] or with 3D real-time echocardiography[66]. Recently, a completely non-invasive method of assessing RV-arterial (RVA) coupling using MRI has been described, with excellent correlation and good agreement with invasively determined coupling, albeit with a systematical overestimation, but with equivalent patterns of progression across disease stages in PH. In this study a simplified formula has been used, by assuming V_0 negligible in the equation for Ees and PCWP negligible in the equation for Ea and as such Ea/Ees = ESP/SV/ESP/ESV = ESV/SV[62].

In an animal model of PH induced by acute pulmonary embolism with gradual PAP increases, Ea increased progressively, while Ees increased initially, but failed to increase any further. As a result, Ea/Ees initially increased to values associated with optimal stroke work, suggesting that RV contractile reserve had been recruited to a point of optimal coupling, but submaximal efficiency, whereas in later stages the ratio increased further, suggesting RVA uncoupling and RV failure[67]. These findings were confirmed in a larger human study

of patients with PH of several etiologies, where Ea increased linearly with advancing severity of PH, while Ees increased initially, but failed to increase further and tended even to decrease in more advanced stages. Thus, RVA coupling ratio was relatively maintained in earlier stages of PH, but increased markedly from about 0.35 till 2.85 across quartiles of PVR index[62].

In another study, patients with CTEPH and patients with chronic thromboembolic disease without PH (CTED) were analyzed using conductance catheter-derived pressure-volume loops with the single-beat method. Similarly to the previous study, patients with CTEPH had higher Ees compared to CTED and controls, but with Ea/Ees suggesting RVA uncoupling, with increased values at 1.67 compared to 0.69 in controls and 0.79 in CTED[63]. In a small subset of a study that included patients with systemic sclerosis-associated PAH (SSPAH) and patients with iPAH, RV pressure-volume loops were measured and Ees, Ea and Ea/Ees were derived. Patients with SSPAH and with iPAH had similar steady and pulsatile afterload, with similar PVR and PA compliance, but with decreased Ees and increased Ea/Ees ratio for patients with SSPAH compared with iPAH, suggesting that the impaired prognosis in this group compared to iPAH is associated with a worse RV function and impaired RVA coupling at similar levels of afterload[68].

The impact of afterload on RV function differs between steady and pulsatile afterload, as has been shown in another study that assessed PA stiffness and its association with RV parameters. In this study, patients with PH were analyzed by RHC and MRI; PA elasticity, distensibility, capacitance and stiffness index were independently associated with RV ejection fraction, mass index, end-systolic volume index and stroke work index, after adjusting for age, sex and PVR index. Moreover, the relative contributions of these parameters of PA stiffness for RV stroke work index were 1.2 x to 18 higher than those of PVR index, suggesting that RV adaptation to chronic pressure afterload is more strongly related to pulsatile than to steady afterload[69]. Another study found similar results in a group of patients with atrial septal defect, demonstrating PA stiffness to be the best correlate of RV function as assessed by the myocardial performance index, better than invasively determined PAPs or PVR[70].

Another study showed that, despite a reduction in PVR after PAH-targeted therapy, in 25% of patients RV function deteriorates further and is associated with a poor outcome. The cause is not fully known, but it is suggested that unfavourable RVA coupling might play a role[71]. Interestingly, a recent study showed in an animal model of chronic RV pressure overload that echocardiographic indices of RV function, such as the RV myocardial performance index and the myocardial acceleration during isovolumic contraction are better correlated with RVA coupling ratio than with Ees[72].

RVA coupling measured with the Ea/Ees ratio has been assessed in several animal models of PH with and without RV failure and in models with persistent RV failure after transient pulmonary artery banding and pharmacological interventions. In summary, Ea increased in all models, while RVA coupling tended to be maintained by an adaptive increase in Ees in models such as hypoxic exposure[73,74], in early sepsis[75], in acute embolism[74], in PA banding[74] or a few months of aorto-pulmonary shunting[76] associated with only a moderate increase in mean PAP. Prolonged mechanical stress, such as with 6 months of overcirculation in piglets[77], in late sepsis[75] or in monocrotaline-induced PH[78] may cause uncoupling of the RV from the pulmonary circulation, with insufficiently increased Ees or even decreased Ees and consequently increased Ea/Ees. A general trend in the mentioned studies is that increased pulmonary arterial obstruction (for instance pulmonary stenosis (PS) or pulmonary artery banding) allows for longer preservation of RVA coupling when compared to situations where the PVR is increased because of pulmonary vascular diseases[2,79]. Superior RV function in this setting has been confirmed in a human study that included patients with PS and with PAH at the same level of RV pressure overload and found better RV function parameters and less RV dilation in patients with PS[80].

D. Clinical implications of right ventricular-arterial coupling assessment

The effect of several pharmacological interventions on RVA coupling have been studied in these animal models, with beneficial or deleterious effects. Milrinone[81] and chronic administration of bisoprolol[82] have shown favourable effects on RVA coupling, because of positive inotropic effects with increased Ees and no effect on Ea, with consequent decrease in Ea/Ees ratio. Combined positive inotropy (increased Ees) and vasodilation (decreased Ea), with subsequent decrease in Ea/Ees have shown low-dose dobutamine, low-dose norepinephrine (less pronounced effects than dobutamine)[83], levosimendan[84] and sildenafil, the latter in monocrotaline-induced PH[85]. In the setting of hypoxia,

sildenafil has shown favourable effects on RVA coupling through vasodilating and no inotropic effects[86], similar to acute epoprostenol administration or inhaled nitric oxide[87]. Acute administration of propranolol had deleterious effects on RVA coupling, with negative inotropic effects and pulmonary vasoconstriction during acute hypoxia[65].

The importance of assessing RVA coupling has been recently underlined by a human study which included patients with PH, in which RVA coupling remained the only independent predictor of transplantation-free survival after controlling for right atrial pressure, mean PAP and SV[88].

Another important aspect of RVA coupling is the assessment of RV contractile reserve, which may unmask borderline or latent resting uncoupling. This topic is an emerging research area; stress testing using exercise or dobutamine have been used. In one study exercise-induced increase in systolic RV pressure, as estimated from the tricuspid regurgitant jet, has been shown to be a strong predictor of survival in patients with PH[89]. Dobutamine stress has the advantage of technically easier imaging and has been demonstrated in one study to reveal subclinical reduction in RV contractile reserve in patients with PAH and preserved RV function at rest, as assessed by the change in TAPSE and tricuspid annular systolic velocity compared to controls[90]. In an animal model resting RVA coupling has been shown to correlate with RV reserve as assessed by dobutamine stress echocardiography[91].

Assessment of RVA coupling adds to the physiopathological understanding and the clinical and therapeutic assessment in PH. Further studies are needed to better understand the mechanisms that lead from efficient RVA coupling to uncoupling and thus to translate these findings into efficient treatment for PH patients.

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