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PULMONARY HYPERTENSION (Z-C JING, SECTION EDITOR)

Physiology of the Pulmonary Circulation and the Right Heart

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Abstract The pulmonary circulation is a high-flow and low-pressure circuit. The functional state of the pulmonary circulation is defined by pulmonary vascular pressure–flow relationships conforming to distensible vessel models with a correction for hematocrit. The product of pulmonary arterial compliance and resistance is constant, but with a slight decrease as a result of increased pulsatile hydraulic load in the presence of increased venous pressure or proximal pulmonary arterial obstruction. An increase in left atrial pressure is transmitted upstream with a ratio ≥1 for mean pulmonary artery pressure and ≤1 the diastolic pulmonary pressure. Therefore, the diastolic pressure gradient is more appropriate than the transpulmonary pressure gradient to identify pulmonary vascular disease in left heart conditions. Exercise is associated with a decrease in pulmonary vascular resistance and an increase in pulmonary arterial compliance. Right ventricular function is coupled to the pulmonary circulation with an optimal ratio of end-systolic to arterial elastances of 1.5–2.

Keywords Pulmonary circulation · Pulmonary hypertrension · Exercise · Pulmonary vascular resistance · Pulmonary vascular impedance · Pulmonary capillary pressure · Viscosity · Left atrial pressure · Cardiac output · Right ventricular function · Right ventriculo-arterial coupling · End-systolic elastance · Arterial elastance · Time constant

Introduction

The pulmonary circulation, as a separate high-flow, low-pressure system, is the end result of an evolutionary process aimed at the optimization of gas exchange of endothermic birds and mammals [1••]. Evolution from ancestors of fishes to amphibians, reptiles and finally birds and mammals has led to progressively greater oxygen consumption requiring a thinner pulmonary blood–gas barrier. Preservation of the integrity of this barrier has been made possible by the complete separation of the pulmonary from the systemic circulation. This evoluton has been accompanied by a progressive unloading and reshaping of the right ventricle (RV) as a thin-walled flow generator unable to adapt to brisk increases in afterload.

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Pulmonary Vascular Pressures and Resistance

Pulmonary Artery Pressures and Blood Flow

The pulmonary circulation is characterized by an inflow pressure, or pulmonary artery pressure (*Ppa*), an outflow pressure, or left atrial pressure (*Pla*) and a pulmonary blood flow (Q) approximately equal to systemic cardiac output. Pulmonary vascular pressures and flows are pulsatile. However, a simple and clinically useful description of the functional state of the pulmonary circulation may be provided by a calculation of pulmonary vascular resistance (*PVR*) from mean values of *Ppa* (*mPpa*), *Pla* and Q.

$$PVR = (mPpa - Pla)/Q$$

Measurements of pulmonary vascular pressures and cardiac output are usually performed during a catheterization of the right heart with a fluid-filled balloon-tipped thermodilution catheter [2]. This procedure allows for the estimation of *Pla* from a balloon-occluded (*Ppao*) or wedged (*Ppw*) *Ppa* and Q by thermodilution.

Fluid-filled catheters measure vascular pressures with a zero-levelled external manometer. The best reference is the

hydrostatic indifferent point, at the level of the tricuspid valve, where pressure is independent of body position. This is midchest or 5 cm below the sternal angle in the supine position, with mid-axillary intersection at the two inferior fourths of the rib cage to consider when measurements are in the upright position. Zero leveling at the catheterization table is associated with an overestimation of *Ppa* and *Ppw*.

Measurements are generally performed at end-expiration, when the lungs are at functional residual capacity. Lung volumes below or above are associated with increased *PVR*, because of predominant increased in alveolar vessel resistance at high lung volumes, and increased extra-alveolar vessel resistance at lower lung volumes [3]. Thus patients with obstructed airways as a cause of increased functional residual capacity may present with an increased *PVR*. Furthermore, these patients have important intathoracic pressure swings, which are predominantly positive during expiration [4•]. Measurements at end-expiration may then overestimate *Ppa* and *Ppw*.

Sometimes a measurement of *Pla* or *Ppao* cannot be obtained, and a *total PVR* (*TPVR*) is calculated as

$$TPVR = mPpa/Q$$

This is may be an acceptable approximation as long as *Pla* is low, but in all circumstances, *TPVR* compared to *PVR* overestimates the extent of pulmonary vascular disease. On the other hand, *TPVR* is a better estimate of RV afterload than *PVR* because the RV is exposed to *mPpa*, not the difference between *mPpa* and *Pla*.

Pulmonary Capillary Pressure

Wedged or occluded *Ppa* measurements (*Ppw*) are acceptable estimates of *Pla*, with an average gradient of 3 mmHg between the *Ppw* and left-ventricular end-diastolic pressure [5]. Micropuncture studies have shown that pulmonary capillary pressure (*Ppc*) is higher than *Ppw*, about halfway between arterial and venous pressures [6]. Thus wedged or occluded *Ppa* should not be called "capillary" or "capillary-wedge" pressure. Estimates of *Ppc* can be obtained from the analysis of *Ppa* decay curves after single arterial balloon occlusion [7]. These curves present with an initial fast portion, corresponding to the interruption of flow through the arterial resistance, and a subsequent slow portion corresponding to the emptying of the capillary venous resistance. The intersection of the fast and slow portions identifies *Ppc*.

The normal longitudinal distribution of resistances is 60 % arterial and 40 % capillary + venous resistance [7]. *Ppc* can thus be estimated from an equation initially proposed by Gaar [8]:

$$Ppc = Pla + 0.4 \times (mPpa - Pla)$$

The site of most pulmonary vascular diseases is at the resistive arterioles. Accordingly, the longitudinal disdtribution of resistances remains unchanged and the Gaar equation generally applicable. An important exception is proximal chronic thromboembolic pulmonary hypertension (CTEPH) [9]. In these patients, an increased steep initial portion of the *Ppa* decay curve after single occlusion may help to identify predominantly proximal lesions that are amenable to surgical desobstruction [10, 11•].

The Calculation of PVR

A vascular resistance calculation is an extrapolation to a vascular system of a physical law defining laminar flows of Newtonian fluids through non-distensible, straight cylindric tubes, originally proposed by Poiseuille and mathematically formulated by Hagen. The Hagen–Poiseuille law states that resistance R to flow of a single tube is equal to the product of the length l of the tube and viscosity η and a constant 8 divided by the product of π and the fourth power of the internal radius r. More generally, R can be calculated as a pressure drop ΔP to flow Q ratio:

$$R = (l \cdot \eta \cdot 8)/(\pi \cdot r^4) = \Delta P/Q$$

The ratio of pressure drop to flow through an entire vascular bed accounts for the resistances in series and in parallel of the individual vessels. The fact that r in the equation is to the fourth power explains why resistance is exquisitely sensitive to small changes in caliber of these small vessels. For example, a 10 % change in radius results in almost 50 % change in resistance. Accordingly, *PVR* is a good indicator of the state of constriction or dilatation of pulmonary resistive vessels and is useful for detecting changes in arteriolar vessel caliber due to changes in tone and/or structure.

Effects of Age, Sex and Body Position

The limits of normal of resting pulmonary vascular pressures and flows as derived from invasive measurements in 60 resting supine young adult healthy volunteers [12–15] are shown in Table 1.

In that study population, cardiac output was lower in women, who are smaller than men, and thus PVR in women was higher. However, there were no sex differences in pulmonary hemodynamics after correction for body dimensions. These data have been confirmed by a recent review of invasive measurements reported in a total of 1,187 individuals, of whom 225 were identified as women and 717 as men [16].

Aging is associated with an increase in *PVR*. This is due to a slight increase in *mPpa* and a more important decrease in cardiac output leading to a doubling of *PVR* over a a period of five decades of life [17, 18]. However, measurements in healthy old individuals are few, so that the exact limits of normal of the pulmonary circulation as a function of age are not exactly known [16].

Table 1 Limits of normal of pulmonary vascular pressures and pulmonary blood flow at rest

Variables	Mean	Limits of normal
Q L/min	6.4	4.5–8.5
Heart rate, bpm	67	40–100
Ppa systolic, mmHg	19	13–26
Ppa diastolic, mmHg	10	6–16
Ppa, mean, mmHg	13	8–20
Ppw, mmHg	9	5–12
Ppc, mmHg	10	8–12
Pra, mmHg	5	1–8
PVR, dyne·s·cm^{-5}	55	12–100

Abbreviations: see text

Body position affects *PVR* through associated changes in systemic venous return. In the upright position, *Pla*, right atrial pressure (*Pra*) and cardiac output are lower than in the supine position. Because of pulmonary vascular de-recruitment, *mPpa* remains essentially the same. Accordingly, *PVR* is increased. This difference in upright vs. supine *PVR* is important to keep in mind when examining *PVR* changes during exercise performed upright as compared to supine [19••].

Effects of Pulmonary Blood Flow

The inherent assumption in a *PVR* calculation is that the *mPpa*–flow relationship is constant and crosses the pressure axis at a value equal to *Pla*. Accordingly, *PVR* is assumed to be constant, independent of the absolute pressure or flow.

The relationship between ($mPpa - Pla$) and Q has been shown to be reasonably well described by a linear approximation over a limited "physiological" range of flows, with a zero extrapolated pressure intercept in well oxygenated supine lungs. However, cardiac and respiratory diseases and hypoxia may increase both the slope and the extrapolated intercepts of multipoint $mPpa - Q$ plots. This is explained by a combination of changes in incremental resistance and vascular recruitment in a "waterfall" model made of parallel collapsible vessels with a distribution of closing pressures initially proposed by Permutt [20]. The waterfall analogy refers to the fact that the flow rate (Q) over a waterfall is independent of its height (the pressure difference between upstream and downstream). A typical characteristic of the waterfall model is a functional dissociation between inflow and outflow pressure as long as the latter varies within a range of values that are below a mean "closing pressure". This is a feature of de-recruited upright upper lung zone I described by West [21], and has been reported in pulmonary hypertension on acute lung injury [22, 23] and in occasional cases of pulmonary hypertension on terminal heart failure, after cardiac transplantation [24].

However the waterfall model ignores the natural distensibility if the pulmonary arterioles, which accounts for the slight curvilinearity seen on multi-point $mPpa - Q$ plots, and wrongly predicts an increased closing pressure from the linear fit of multiple $mPpa - Q$ coordinates in the presence of pulmonary embolism or increased hematocrit [25].

The distensibility of pulmonary resistive vessels has been shown to be of 2 % of diameter change per millimetre of mercury of distending pressure over a wide range of vascular segments and animal species [26]. Linehan integrated resistive vessel distensibility in a simple model allowing for more realistc prediction of pulmonary vascular pressures over a wide range of flows and hematocrits [24]. In this model *PVR* at a normal hematocrit is calculated as:

$$PVR = \left[(1 + \alpha \cdot Ppa)^5 - (1 + \alpha \cdot Pla)^5\right] / 5 \cdot \alpha \cdot Q$$

The coefficient α is the distensibility factor expressed in % increase in diameter D_0 per millimetre of mercury increase in pressure:

$$D = D_0 + \alpha \cdot P$$

An interesting application of this approach is that the distensibility coefficient α can be recalculated from given sets of *Ppa*, *Pla* and Q measurements.

Reeves used reported pulmonary hemodynamic data at rest and during exercise, in healthy volunteers to recalculate α, and found it equal to 2±0.2 %/mmHg in normoxia, a value strikingly similar to that of previous in vitro measurements on isolated vessel segments [27]. Even though the individual data available to him for analysis was limited, he was able to show that α tends to decrease with aging, or with chronic but not acute hypoxic exposure.

Similar values of α have been calculated in a series of noninvasive exercise stress Doppler echocardiographic studies of the normal pulmonary circulation [28–31] and recently confirmed by invasive measurements [32••]. This data has allowed for an improved definition of the limits of normal of the pulmonary circulation at exercise [32••]. Furthermore, α was shown to be lower in men compared to pre-menopausal women [29]. The same noninvasive approach has confirmed Reeves' observation of a decrease of α with aging [29] and with chronic hypoxic exposure [32••]. There is a suggestion that a decrease in α calculated from noninvasive multiple $mPpa - Q$ coordinates could be sensitive to early pulmonary vascular disease, such as in healthy carriers of the BMPR-2 mutation, which predisposes to pulmonary arterial hypertension (PAH) [33].

The distansibility model of Linehan can also be used to estimate the effects of pulmonary vascular obstruction on *mPpa* over a wide range of cardiac outputs. The results of this modeling, shown in Fig. 1, agree with previous predictions using an alternative modified viscoelastic model and

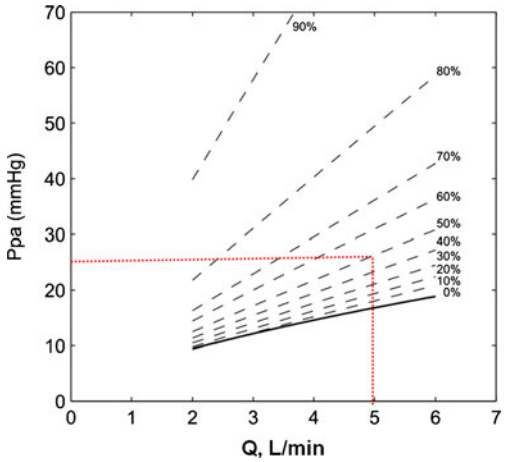

Fig 1 Mean pulmonary artery pressure (*Ppa*) − cardiac output (*Q*) relationships predicted by the distensibility model of Linehan at increasing levels of obstruction. An increase in mean *Ppa* above 25 mmHg corresponding to the definition of pulmonary hypertension occurs after approximately 50 % obstruction of the pulmonary vascular bed. A mean *Ppa* of 50 mmHg as seen in severe pulmonary hypertension corresponds to 80 % obstruction. These estimates are for a *Q* of 5 L/min

comparison with angiographic obstruction in a canine model of pulmonary embolism [34]. Thus *mPpa* reaches 25 mmHg at 50 % obstruction of the pulmonary circulation at a cardiac output of 5 L/min. The current definition of pulmonary hypertension based on a *mPpa*>25 mmHg identifies patients with already advanced pulmonary vascular disease [35].

Viscosity

In the Poiseuille–Hagen equation, resistance is directly proportional to viscosity. The viscosity of the blood is mainly determined by the hematocrit.

The most often used reference equation to estimate the impact of blood viscosity on resistance was reported by Whittaker and Winston based on studies on hindlimb vessels [36]. The equation relates linearly resistance to hematocrit, and allows to re-calculate resistance at a normal reference value of hematocrit of 45 %:

$$R_0(45\%) = R_0(HCT)\frac{1-\phi^{1/3}}{0.234}$$

where R_0 is resistance at a hematocrit (*HCT*) of 45 % and φ the measured hematocrit.

Linehan integrated an exponential relationship in his distensible model of the pulmonary circulation to fit isolated perfused lung measurements at variable levels of hemodilution or concentration [25]:

$$R_0(45\%) = R_0(HCT)\frac{1}{\exp(2(\phi-0.45))}$$

Both equations allow for similar adjustments of *PVR* in patients with abnormally high or low hematocrits, and thus provide more realistic estimates of the extent of pulmonary vascular disease [37]. It was recently shown that corrections for hematocrit smoothens ethnic differences in the pulmonary circulation of high-altitude Andean vs. Himalayans populations [38]. In terms of resting *PVR*, normalizing *PVR* for a hematocrit may increase *PVR* by up to 2 Wood units in severely anemic patients, for example with sickle-cell disease.

Left Atrial Pressure and the Transpulmonary Pressure Gradient

An increase in *Pla* is transmitted upstream to *mPpa*. The *PVR* equation assumes that this is in a 1/1 ratio at any given level of *Q*. A chronic increase in *Pla* may induce pulmonary vascular remodeling, and therefore lead to an "out of proportion" increase in *mPpa* [39]. For this reason, clinicians like to reason in terms of a transpulmonary pressure gradient (*TPG*) for the differential diagnosisd of purely passive increase in mPpa and increased mPpa resulting from pulmonary vascular disease [40]. The *TPG* is equal to the difference between *mPpa* and *Pla*.

$$TPG = mPpa - Pla$$

The upper limit of normmal of the *TPG* is usually assumed to be of 12 mmHg [40]. This corresponds to a *PVR* of 1.5 Wood units at a cardiac output at the upper limit of normal of 8 L/min.

However, it has been recently realized that the *TPG* is often higher than 12 mmHg in patients with left heart failure in whom purely passive upstream transmission could be demonstrated by observing an acute return of the *TPG* to <12 mmHg after active diuresis or after a cardiac transplantation [24].

In steady-flow conditions, an increase in *Pla* is transmitted upstream in a slightly less than 1/1 ratio because the pulmonary resistive vessels are distensible. In pulsatile flow conditions, an increased *Pla* increases pulse pressure, or difference between systolic and diastolic *Ppa*. Furthermore, the *TPG* increases with *Q* because an increase in flow increases *mPpa* more than *Pla*. Thus any increase in Pla or *Q* above normal increases the *TPG*. These problems are limited or even avoided by using the gradient between diastolic *Ppa* and *Pla*, or the diastolic pressure gradient (*DPG*) instead [41••]. The upper limit of normal of the *DPG* in young athletic adults is apprtoximately 5 mmHg [42]. A higher cut-off value may be more reasonable in older patients with left heart failure [43].

The *DPG* has been proposed to be at the basis of decision tree to identify pulmonary vascular disease in patients with a high *Ppw*, as illustrated in Fig. 2.

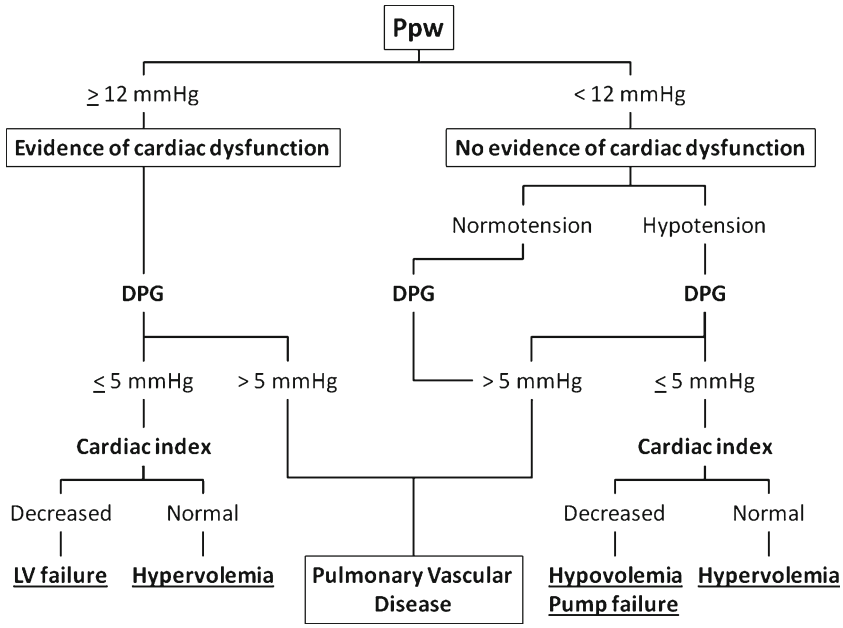

Fig. 2 Diastolic pressure–derived decision tree for the diagnosis of pulmonary vascular disease. See text for abbreviations. From Naeije et al. [41••]. Reproduced with permission of the European Respiratory Society. Eur Respir J Jan 2013 41: 217–213; doi:10.1183/09031936.00074312

Exercise

Exercise stresses the pulmonary circulation by an increase in cardiac output. The average slopes of $mPpa - Q$ relationships at exercise will be of 1 mmHg/L/min in young adults and up to 2.5 mmHg/L/min after 5 to 6 decades of life [19••, 32••, 44, 45]. An increase in *Pla* above the upper limits of normal contributes to the increase in mPpa at high cardiac outputs, in the range of 15–20 L/min/min and more [46]. Exercise-induced cardiac output is associated with a slight decrease in *PVR* which is entirely explained by resistive vessel distension [19••, 32••]. Exercise $mPpa - Q$ relationships are not affected by body position.

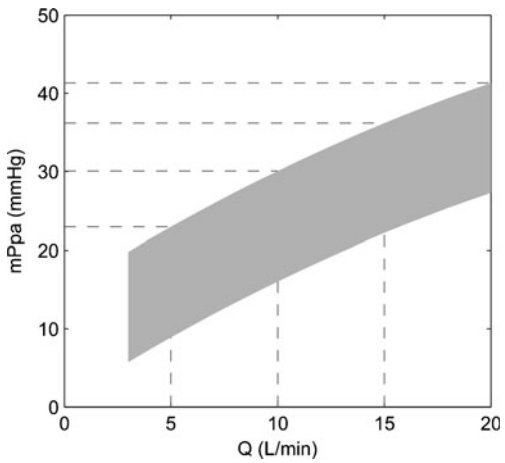

Fig. 3 Pulmonary artery pressure–flow relationships in healthy subjects, with limits of normal indicated by the shaded area. See text for abbreviations

The limits of normal of the pulmonary circulation at exercise are shown in Fig. 3. It can be seen that mPpa does normally exceed 30 mmHg at a cardiac output <10 L/min. Upper limits of normal can also be defined by a slope of *mPpa–Q* of 3 mmHg/L/min, or a *TPVR* at maximum exercise of 3 Wood unit [32••].

After exercise, *mPpa* and *Q* rapidly return to resting values [28]. This decreases the relevance of post-exercise measurements as a reflection of exercise-induced changes. On the other hand, the workload–*Q* relationship varies considerably from one subject to another [29]. It is therefore preferable to express *mPpa* at exercise as a function of cardiac output rather than of workload to define the functional state of the pulmonary circulation.

It must be underscored that abnormal exercise pulmonary vascular responses may be due to either increased *PVR* or *Pla*. Therefore, the identification of a *mPpa–Q* relationship >3 mmHg/L/min requires a differential diagnostic work-up [32••].

Pulsatile Flow Pulmonary Hemodynamics

The study of the pulmonary circulation as a steady-flow system is a simplification. Pulmonary pulse pressure is in the order of *mPpa*, as compared less than half of it in the systemic circulation. Instantaneous pulmonary blood flow varies from a maximum at mid-systole to around zero in diastole.

An analysis of pulsatile flow hemodynamics can be made by a spectral analysis of pressure and flow waves and a calculation of pulmonary vascular impedance (*PVZ*). *PVZ* is a ratio of pulsatile *Ppa* on pulsatile *Q*. This approach allows for the quantification of *PVR*, pulmonary arterial elastance

(*Ca*) and wave reflections to pressure and flow wave morphology, and pulmonary arterial hydraulic load as a measure of RV afterload [47, 48].

There has been recently a series of studies which showed that the product of *PVR* and *Ca*, or the time constant (RC-time) of the pulmonary circulation remains constant over a wide range of severities, etiologies and treatments of pulmonary hypertension [49–51]. This remarkable property of the pulmonary circulation, which had been previously reported but largely unnoticed [52] has two consequences. The first is that Ca becomes a more important determinant of RV afterload than *PVR* when *mPpa* and *PVR* are only modestly elevated [53]. The second is that RV oscillatory hydraulic load (*Wosc*) remains a constant fraction of total load (*Wtot*) irrespective of *Ppa* [54].

The RC-time may actually slightly decrease in left ventricular failure because the increase in venous pressure causes the pulmonary circulation to be stiffer at any level of *PVR* [55•]. Another cause of a slight decrease in the RC-time is proximal pulmonary arterial obstruction, either experimentally by pulmonary arterial banding [56] or in patients with purely proximal CTEPH [57•]. A decreased RC-time is associated with an increased *Wosc*.

The (near)-constancy of the RC-time explains the reported tight correlation between systolic, diastolic and *mPpa* in normal subjects and in patients with pulmonary hypertension of various etiologies [58]. Accordingly, *mPpa* can be calculated from *sPpa* using a simple formula:

$$mPpa = 0.6 \times sPpa + 2$$

This notion is of practical relevance as non-invasive evaluations of the pulmonary circulation in clinical practice often rely on the measurement of a maximum velocity of tricuspid regurgitation (*TR*) to calculate a $sPpa_s$ using the simplified form of the Bernouilli equation and a measurement or estimate of *Pra* [59]:

$$sPpa = \left(TR^2 + 4\right) + Pra$$

Right Ventricular Function

The RV is functionally coupled to the pulmonary circulation [60]. The structural and functional characteristics of the RV allow for the accomodation of large increases in flow, but are not adapted to 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 [61]. Thus the RV adaptation to pulmonary hypertension is homeometric with increased contractility, eventual hypertrophy and preserved dimensions. Failure of this mechanism depending on rate of onset and magnitude of increase in *Ppa* requires heterometric adaptation, with increased RV dimensions [60, 61, 62••].

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.

The evaluation of the adequacy of RV-arterial coupling requires a quantification of RV afterload. There are several equally valid estimations of RV afterload [62••]. 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, calculated from the integration of pressure and flow waves, thus integrating its oscillatory component. Because of the near-constancy of RC-time, *Wosc* can be approximated to 23 % of *Wtot*, or 1.3 times mean power in all circumstances [54]. The third is arterial elastance (*Ea*) measured on a RV pressure–volume loop, corresponding to a measurement of afterload as it is "seen" by the ventricle. The RV pressure–volume loop also allows to identify a point of maximal elastance (*Emax*), which is the gold standard measure of load-independent contractility in an intact heart, and thus the calculation of an *Emax*/*Ea* ratio as a measurement of the coupling of ventricular to arterial function.

Mathematical modeling shows that the optimal matching of systolic ventricular and arterial elastances occurs at an *Emax*/*Ea* ratio around 1.5.

However, the complex geometry of the RV makes functional evaluations with measurement of instantaneous volume changes technically difficult, and the determination of *Emax* may be unreliable because of the particular shape of the RV pressure–volume loop and non-coincidence of end-ejection and end-systole. This problem can be overcome by measuring pressure–volume loops at several levels of preload [63]. On the other hand, a single-beat method to calculate *Emax* and *Ea* from instanteous ventricular pressure and flow output measurements has been validated for the RV [64]. The approach has been implemented in experimental animal studies to show for example that acutely administered prostacyclin has no intrinsic inotropic effect [65], and that β-blocker agents which deteriorate RV-arterial coupling acutely [64] may improve RV-arterial coupling chronically because of an improvement in contractility [66].

The coupling of RV function to the pulmonary circulation has been reported in patients with pulmonary arterial hypertension (PAH) with single-beat calculation of the

Emax/*Ea* ratio from magnetic resonance imaging (MRI) volume and right heart catheter pressure measurements [67]. As compared to controls, *Emax* was almost doubled, but *Emax*/*Ea* was decreased, indicating insufficient homeometric adaptation and pending RV failure. These results were confirmed by *Emax*/*Ea* ratio measurements using conductance catheters and the Valsalva manoeuvre to decrease venous return [68•]. In that study, *Emax*/*Ea* was maintained in the patients with idiopathic PAH, but decreased in systemic sclerosis-associated PAH [68•], in keeping with previous similar conclusions reached on the basis of an analysis of RV-arterial coupling by plotting pressure as a function of stroke volume, or so-called the "pump function graph" [62••, 69].

Since *Emax*/*Ea* can be simplified to a ratio of volumes, MRI has also been recently implemented for the estimation of RV-arterial coupling estimated by the ratio of stroke volume (*SV*) to end-systolic volume (*ESV*). In a study on 139 patients referred for pulmonary hypertension, RV "*Emax*/*Ea*" estimated by the volume ratio was shown to decrease progressively with increasing severity of pulmonary hypertension [70]. The *SV*/*ESV* ratio contains the same functional information as an ejection fraction, but with less preload-dependency. The clinical relevance of the *SV*/*ESV* as measure of RV-arterial coupling is being evaluated.

A derived simplified measure of the adequacy of RV systolic function adaptation to afterload is contractile reserve, defined by the increase in RV systolic pressure during an exercise stress. Grunig recently reported that RV contractile reserve is an important predictor of survival in patients with severe pulmonary hypertension, with a cut-off value of 30 mmHg [71••].

Conclusions

Evaluation of pulmonary hypertension requires understanding of normal pulmonary vascular pressure–flow relationships and right ventriculo-arterial coupling. Recent progresses in imaging combined with gold standard physiological concepts have made possible bedside measurements of the pulmonary circulation and right ventricular function for improved detection, diagnosis, follow-up and prognostication of patients with pulmonary vascular diseases.

Compliance with Ethics Guidelines

Conflict of Interest Robert Naeije declares that he has 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 the author.

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