Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update

Anton Vonk Noordegraaf[1], Kelly Marie Chin[2], François Haddad[3], Paul M. Hassoun[4], Anna R. Hemnes[5], Susan Roberta Hopkins[6], Steven Mark Kawut[7], David Langleben[8], Joost Lumens[9,10] and Robert Naeije[11,12]

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Affiliations: [1]Amsterdam UMC, Vrije Universiteit Amsterdam, Pulmonary Medicine, Amsterdam Cardiovascular Sciences, Amsterdam, The Netherlands. [2]Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern, Dallas, TX, USA. [3]Division of Cardiovascular Medicine, Stanford University and Stanford Cardiovascular Institute, Palo Alto, CA, USA. [4]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, USA. [5]Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA. [6]Dept of Medicine, University of California, San Diego, La Jolla, CA, USA. [7]Penn Cardiovascular Institute, Dept of Medicine, and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [8]Center for Pulmonary Vascular Disease, Cardiology Division, Jewish General Hospital and McGill University, Montreal, QC, Canada. [9]Maastricht University Medical Center, CARIM School for Cardiovascular Diseases, Maastricht, The Netherlands. [10]Université de Bordeaux, LIRYC (L'Institut de Rythmologie et Modélisation Cardiaque), Bordeaux, France. [11]Dept of Cardiology, Erasme University Hospital, Brussels, Belgium. [12]Laboratory of Cardiorespiratory Exercise Physiology, Faculty of Motor Sciences, Université Libre de Bruxelles, Brussels, Belgium.

Correspondence: Anton Vonk Noordegraaf, Amsterdam UMC, Vrije Universiteit Amsterdam, Pulmonary Medicine, Amsterdam Cardiovascular Sciences, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: a.vonk@vumc.nl

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ABSTRACT The function of the right ventricle determines the fate of patients with pulmonary hypertension. Since right heart failure is the consequence of increased afterload, a full physiological description of the cardiopulmonary unit consisting of both the right ventricle and pulmonary vascular system is required to interpret clinical data correctly. Here, we provide such a description of the unit and its components, including the functional interactions between the right ventricle and its load. This physiological description is used to provide a framework for the interpretation of right heart catheterisation data as well as imaging data of the right ventricle obtained by echocardiography or magnetic resonance imaging. Finally, an update is provided on the latest insights in the pathobiology of right ventricular failure, including key pathways of molecular adaptation of the pressure overloaded right ventricle. Based on these outcomes, future directions for research are proposed.

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The cardiopulmonary unit: more than a sum of its parts

The function of the right ventricle is of great clinical importance in severe pulmonary hypertension (PH) since it determines the outcome of the disease [1, 2]. Given the fact that right heart failure in PH is the consequence of increased (arterial) afterload and not the mere consequence of a myocardial disease, a full description of the cardiopulmonary unit is required in the study of right heart failure (figure 1a and b). The cardiopulmonary unit is composed of two main functional subsystems, *i.e.* the right ventricle and the pulmonary vasculature, each having their own intrinsic characteristics (figure 1b). The ventricular pressure–volume loop analysis is central in understanding right ventricular physiology, while pressure–flow analysis is central in understanding pulmonary haemodynamics. For the right ventricle, intrinsic characteristics include contractility, chamber stiffness and, although perhaps less established, the time constant of ventricular relaxation (τ), which are all load independent; for the pulmonary vascular system, resistance and compliance provide intrinsic characteristics of the steady and pulsatile load.

The interaction between the intrinsic ventricular characteristics and load results in global function, and is commonly described by cardiac output (CO) and ejection fraction (EF), on the one hand, and pressure (mean, systolic and diastolic pressure), on the other hand. The pressure gradient over the pulmonary circulation also falls into this category. Energy transfer of right ventricular to arterial load is a special form of interaction for which we reserve the term "coupling". The concept of coupling is particularly important in physiologically describing the continuum of ventricular adaptation in pulmonary arterial hypertension (PAH): well-adapted right ventricles often have preserved ventriculo-arterial coupling, while maladapted right ventricles have varying degrees of altered ventriculo-arterial coupling (figure 2). These concepts will be discussed in more detail in the following section.

This distinction between intrinsic characteristic of a subsystem and global function or system characteristics has important physiological implications. For example, despite the decrease in right ventricular EF (RVEF) in patients with PAH, right ventricle contractility as measured by ventricular elastance (*i.e.* end-systolic elastance (E_{es})) is usually increased and not decreased [3].

Definitions

The current section presents some definitions that may help standardise important concepts relevant to the field of right ventricular adaptation and right heart failure.

- *Right heart failure* in PH can be defined as a clinical syndrome characterised by decreased right ventricular function that leads to insufficient blood flow and/or elevated filling pressures at rest or during physiologically demanding conditions, such as exercise, developmental growth or pregnancy. The cardinal symptoms of right heart failure include dyspnoea and fatigue as well as congestion. The severity of heart failure is often subcategorised according to New York Heart Association (NYHA) Functional Class and by the degree of congestion.

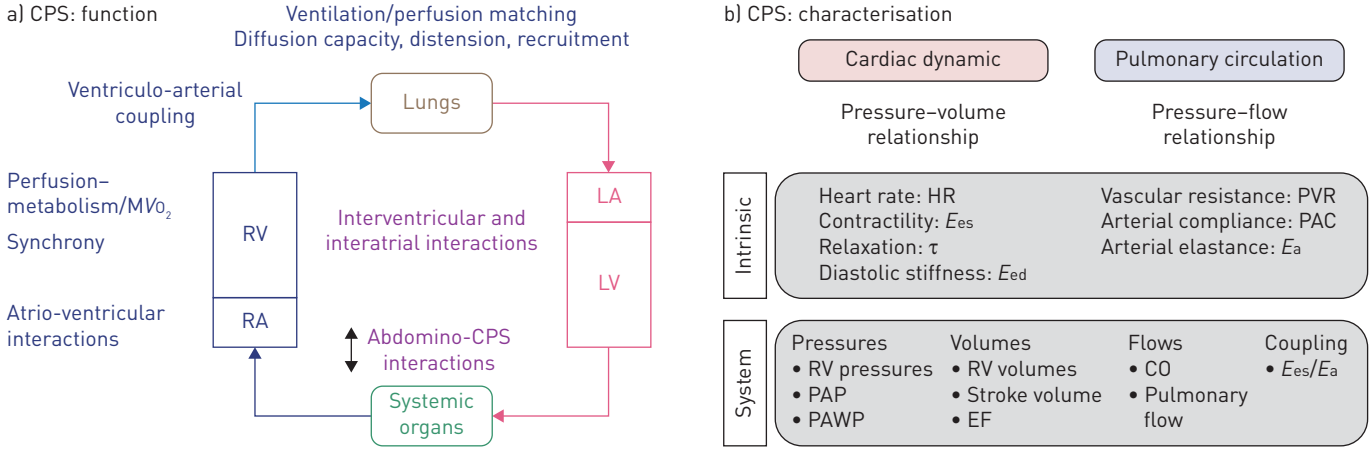

FIGURE 1 The cardiopulmonary system (CPS): a) function and b) characterisation. MV_{O_2}: myocardial oxygen consumption; RV: right ventricle; RA: right atrium; LA: left atrium; LV: left ventricle; E_{es}: end-systolic elastance; τ: time constant of ventricular relaxation; E_{ed}: end-diastolic elastance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; E_a: arterial elastance; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; EF: ejection fraction; CO: cardiac output. Subsystems (or units: heart, respectively its load) are characterised by their intrinsic function, which can be derived from the ventricular pressure–volume relationship and the pulmonary pressure–flow relationship. The system parameters result from cardiopulmonary interaction.

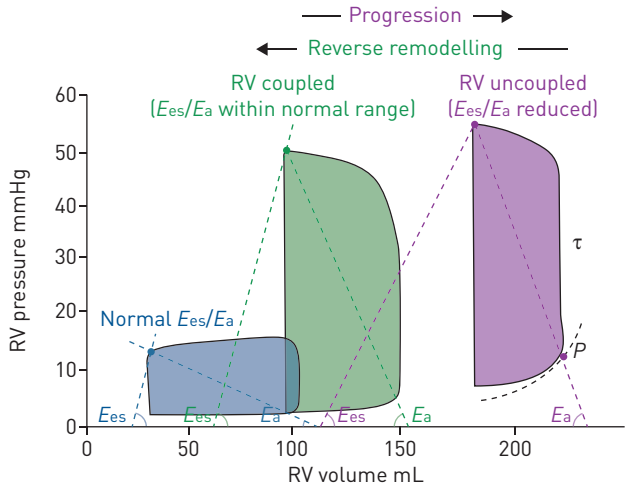

FIGURE 2 Right ventricular (RV) pressure–volume analysis. Pressure–volume loops at three different stages: normal (blue), pulmonary hypertension (green) and right ventricular failure (purple). E_{es}: end-systolic elastance; E_a: arterial elastance; τ: time constant of ventricular relaxation. $P=\alpha(e^{\beta V}-1)$ describes the diastolic pressure–volume relation. Reproduced and modified from [11] with permission.

- *Right ventricular adaptation* in PH represents a continuum with an adapted right ventricle at one end and a maladapted ventricle at the other end. An adapted right ventricle in PH is characterised by a slightly dilated right ventricle with preserved stroke volume (SV), systolic function and normal filling pressures, whereas a maladapted right ventricle is characterised by a dilated right ventricle with reduced SV, systolic function and increased filling pressures. As will be discussed in the following section, adapted ventricles usually have preserved ventriculo-arterial coupling, while maladapted ventricles usually have uncoupled ventricles (figure 2).
- *Subsystem function (intrinsic properties of the cardiac or pulmonary vascular system)*: description of the right ventricle in a load-independent manner (E_{es} and end-diastolic elastance (E_{ed})) or pulmonary vascular load in a manner independent of right ventricular function (pulmonary arterial vascular resistance (PVR), or arterial elastance (E_a), and pulmonary arterial compliance (PAC)).
- *System function* results from the interaction of the two subsystems, *i.e.* the ventricular pump and its afterload. Interaction results in SV, CO, pressure and functional imaging parameters derived by echocardiography or cardiovascular magnetic resonance imaging (CMR). Descriptions of systolic function as RVEF or SV/right ventricular end-systolic volume (ESV) are also the result of functional interaction and not surrogates for coupling.
- *Coupling*: the condition that occurs when right ventricular function is adapted to the pulmonary vascular load such that energy transfer is most efficient. This coupling is described by systolic and arterial elastance, E_{es}/E_a (figures 1b and 2).

Although this article focuses on the right ventricle, it is noteworthy that ventricular interdependency plays an important role in PH. Not only the right ventricle but also the left ventricle is involved in PH since the right ventricle and left ventricle have the septum in common, are encircled with common myocardial fibres and are within a (not acutely) distensible pericardium (figure 1a) [4, 5]. This ventricular interdependency becomes visible in PH as rapid leftward bowing of the septum during early left ventricle diastole. This typical septal motion abnormality has been shown to be a consequence of a prolonged contraction of the right ventricle free wall relative to that of the septum and the left ventricle free wall, causing interventricular relaxation dyssynchrony [6, 7]. As such, the septum acts as a whistleblower of a right–left ventricular tissue load imbalance, reflecting right ventricular tissue overload in the setting of PH. This rapid early-diastolic leftward motion of the septum is also associated with septal and left ventricular myocardial stretch during late right ventricular ejection [8], causing mechanical inefficiency of the right ventricle and contributing to left ventricular underfilling [9] and atrophy [10]. The septal curvature is a useful metric in PH, reflecting both the interventricular pressure gradient and relative interventricular size, as well as dyssynchrony of contraction [7].

Assessment of the right ventricle in a load-independent manner

Right ventricular function can be characterised by the pressure–volume relation (figure 2) [11], and measurement of right ventricular volumes and pressures are therefore useful for the assessment of the

right ventricle in PH, particularly for physiological studies. A schematic overview of an approach to right ventricle phenotyping, integrating structural imaging, haemodynamics, molecular imaging and biomarkers is given in supplementary figure S1a.

Systole

E_{es} of the ventricle is a load-independent description of the right ventricle and the current reference measure of contractility; it depends on the contractile force of the myocyte and cardiac muscle mass (hypertrophy) [12, 13].

The derivation of E_{es} is based on the pressure–volume loop (figure 2). The best method to assess E_{es} is to decrease ventricular filling, *e.g.* by partial vena cava occlusion, and analyse the series of loops that result [14]. Connection of the end-systolic pressure (P_{es})–volume points results in the P_{es}–volume relation and its slope is E_{es}. Since this approach is invasive and not widely available in the clinic, single-beat methods have been developed [13, 15]. E_{es} can be increased 5-fold in PAH patients, reflecting that the right ventricle is performing at a high contractile state [16]. In addition, the elastance response to pharmacological (usually dobutamine) or physiological stress (exercise) can be useful to assess contractile reserve. In the normal right ventricle, E_{es} usually increases significantly with exercise [3]. In the pressure overloaded right ventricle, although the baseline is higher than normal, the degree of increase is blunted with exercise or following dobutamine infusion [3, 17]. Contractile reserve at exercise is absent in more advanced disease states or might even decrease [3].

Diastole

In practice, right atrial pressure and central venous pressure are often used as surrogates for diastolic properties of the right ventricle; right atrial pressure has been consistently related to outcome in PAH starting with the original US National Institutes of Health registry study in 1991 [18]. Using load-independent metrics has the advantage of allowing a better understanding of the responsiveness to volume status or change in filling conditions. E_{ed} of the ventricle is a load-independent representation of the diastolic function and is best described by a diastolic elastance curve determined by multiple pressure–volume loops obtained by decreased loading by partial vena cave occlusion. The relation is curvilinear and the most adequate description is obtained by fitting the relation with an exponential curve through the diastolic pressure–volume points, with the formula $P=\alpha(e^{\beta V}-1)$, where α and β are curve-fitting constants (figure 2) [11, 19]. A single-beat method has been developed to determine E_{ed} [20, 21]. E_{ed} now can be calculated as $E_{ed}=\alpha\beta e^{\beta V_{ed}}$, where V_{ed} is the end-diastolic volume (EDV) [21]. The so-defined diastolic stiffness predicts outcome in PAH as well as the more complex β calculation [21].

Right ventricular diastolic function is closely associated with disease severity [20], but also with E_{es} [21, 22]. Right ventricle diastolic stiffness in severe PH is accompanied by fibrosis and specific biological alterations, such as reduced titin phosphorylation [20]. Although E_{ed} is related to E_{es}, diastolic adaptability remains variable in patients with PH and whether it may serve as a biomarker of pending right ventricle failure is not completely resolved.

Assessment of the pulmonary circulation in a heart-independent manner

Pulmonary vascular resistance

When analysing the pulmonary circulation, it is useful to distinguish a steady and pulsatile component of the load. These main components of arterial load are PVR and total PAC. In the pulmonary system these two components are inversely related (see later). PVR is calculated as PVR=(mPAP−PAWP)/CO, where mPAP is the mean pulmonary arterial pressure and PAWP is the pulmonary arterial wedge pressure. A measure of total load can also be estimated from the pressure–volume loop (figure 2) as $E_a=P_{es}/SV$. It has been proposed to use E_a∼mPAP/SV when P_{es} is not available [23]; however, this approximation should be used with caution since, especially in higher pressures ranges, P_{es} is underestimated by mPAP [24].

Pulmonary capillary flow is a dynamic process. In basal states, flow through an individual capillary is intermittent. Capillary recruitment occurs when the probability of a given capillary carrying flow increases. Capillary recruitment and distension both play a role in the lung's accommodation of pulmonary arterial blood flow. At basal or moderately increased blood flows, capillary recruitment is predominant [25, 26]. At very high regional flows or pressures, after local full recruitment, capillary distension is predominant [26–29]. The local pattern of capillary recruitment/distension may vary regionally in the lung, with gravity, arterial and post-capillary venous pressures, airway pressures, and disease states all having effects [30–34].

Examining the pulmonary circulation as a whole, since in the (healthy) pulmonary circulation the arteries and veins are distensible, the assumption that the pulmonary vascular pressure difference–flow relationship is linear and crosses the origin is inaccurate. The simple formula then no longer holds and PVR can be described using two parameters: α (the pulmonary circulatory distensibility coefficient) and R_0 (a reference resistance usually

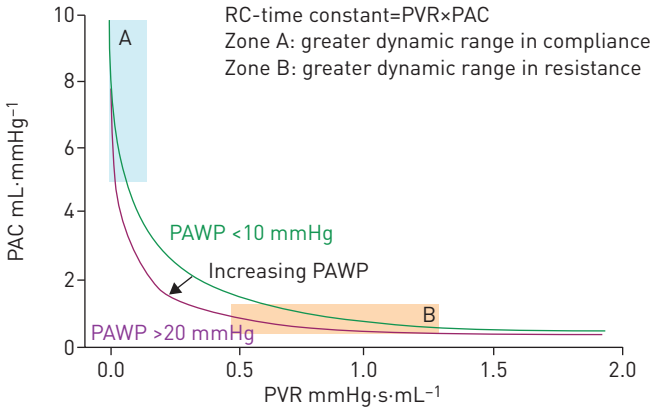

FIGURE 3 The resistance–compliance relationship: the relationship between pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAC) is characterised by a constant value of RC-time (*i.e.* the product of PVR×PAC). PAWP: pulmonary arterial wedge pressure. Reproduced and modified from [11] with permission.

assumed to be the resistance at rest) [35, 36]. While α may be relevant for the detection of early pulmonary vascular remodelling and relates to exercise capacity, right ventricular function and outcome [37], it requires accurate measurement of pulmonary vascular pressure and flow at rest and at exercise. It therefore cannot be currently recommended as part of standard haemodynamic evaluation of patients referred for PH.

Pulmonary arterial compliance

The pulsatile load of the pulmonary circulation is most often evaluated using PAC. The best method to calculate PAC is based on a two-element Windkessel model with flow waveform and resistance as inputs to estimate the compliance value that best predicts systolic and diastolic pressures, the so-called "pulse pressure" (PP) method [38]. A simpler and accepted method to derive PAC is SV/PP [39]. This ratio assumes that the SV is buffered in the large elastic arteries in systole, without any peripheral outflow. However, there is a continuous flow toward the periphery, reducing the vascular volume increase during ejection, resulting in an overestimation of the true PAC [40]. It has been shown in intact experimental animals at various severities of induced PH that SV/PP overestimates PAC by 60–80% [40, 41]. This overestimation probably depends on patient status. CMR-determined proximal arterial compliance amounts to around 20% of PAC [42], showing the greater contribution of the smaller vessels compared with the systemic arterial vasculature.

Time constant of the pulmonary circulation

In the previous sections we described the steady and pulsatile components separately; however, as already mentioned, these are closely related by an inverse relationship. The PAP decay curve in diastole is determined by PVR and PAC. The combined effect can be formulated by the product of PVR and PAC. The unit of this product is time and, therefore, is called the arterial time constant (RC-time) [43].

The inverse relationship between PVR and PAC was first reported in 1971 [44]. A series of studies showed recently that PVR and PAC are inversely related, and RC-time is constant over a wide range of severities, aetiologies and treatments of PH (figure 3) [41, 45, 46]. It is noteworthy that RC-time is decreased when PAWP increases in patients with heart failure [47, 48]. The fact that PVR takes the wedge pressure into account, whereas compliance, calculated as SV/PP, does not, gives rise to an altered RC-time in post-capillary PH.

Owing to the inverse relationship between PVR and PAC, the dynamic range in PAC will be greater in patients with mild pulmonary vascular disease (PVD) (zone A in figure 3), while the dynamic range in PVR will be greater in patients with more advanced PVD (zone B in figure 3). Therefore, PAC may be more sensitive to detect changes in PVD in the early phase of disease. Moreover, several studies using linear prediction models found that PAC is an independent predictor of outcome in PAH [49–52] over a wide range of PVR [53, 54]. Another implication of this remarkable structural characteristic of the pulmonary vasculature is that it dictates the reported tight correlation between systolic PAP (sPAP), diastolic PAP (dPAP) and mPAP in normal subjects and in patients with PH of all possible aetiologies [55, 56], independently of PAWP (figure 4) [57]:

$$\mathrm{sPAP} = 1.61 \times \mathrm{mPAP}$$

and

$$\mathrm{dPAP} = 0.62 \times \mathrm{mPAP}$$

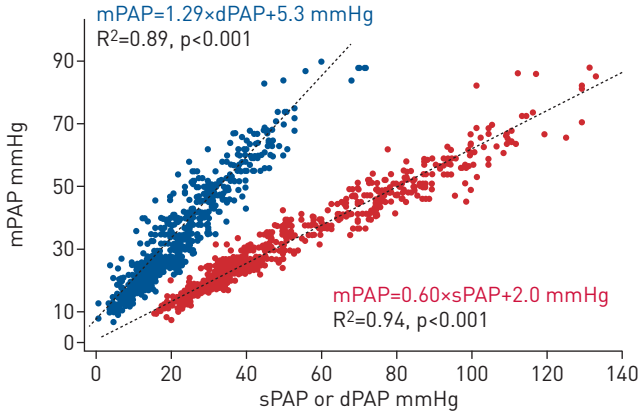

FIGURE 4 The mean, systolic and diastolic pulmonary arterial pressure (mPAP, sPAP and dPAP) relationships: relative values of pressures in the pulmonary circulation are tightly related. Reproduced and modified from [57] with permission.

The first relation implies that mPAP can be calculated from Doppler echocardiographic estimates of sPAP by the formula:

$$\text{mPAP} = 0.62 \times \text{sPAP}$$

The mPAP calculated in this way provides an estimate of mPAP in patients referred for diagnostic work-up of PH [58]. In echocardiography-based studies, different thresholds for right ventricular systolic pressure (*e.g.* 30, 35 or 40 mmHg) have been used for defining PH. According to the formula, a right ventricular systolic pressure of 40 mmHg would best approximate a mPAP of 25 mmHg assuming a mild right ventricular outflow tract gradient and an insonation angle <15°.

Assessment of the cardiopulmonary unit

Functional interaction

In the clinic, the description of right ventricular function in relation to its load is of high prognostic value. Most imaging parameters as measured by echocardiography or CMR reflect system function of the interaction of the right ventricle and the vascular load. At present no recommendations on the most relevant measurements of right ventricular function can be made. Further clinical research is needed, preferably multicentre and prospective, with an *a priori* established list of variables of interest. It should not be overlooked that adequate measurements do not only qualify based on their prognostic capability or prediction of clinical worsening; they should be reproducible and easy to assess in PH centres of expertise.

However, there is ample evidence that direct or indirect measurements of right ventricular EDV and ESV, derivation of SV, and filling pressures contain the foremost prognostic information. This can be explained by the pressure–volume loops derived from the adapted and failing right ventricle. In the adapted right ventricle, increased afterload in PH leads to hypertrophy and an increased contractility with more or less preserved dimensions and SV [2, 4, 11, 59], whereas in progressive right ventricular failure, the right ventricle progressively dilates and decreases its SV.

It should be noted that SV/ESV is inversely related to RVEF, as indicated by the formula SV/ESV=EF/(1−EF). Indeed, Vanderpool *et al.* [22] showed this inverse relation exists in patients with PH [22]. Thus, both SV/ESV and RVEF contain similar prognostic information, and should be considered as parameters of functional interaction, not coupling. RVEF and SV/ESV have been shown to be equally predictive of outcome in patients with PAH [60]. Rigorously defined cut-off values for shortened survival are 0.35 for EF [60, 61] and 0.54 for SV/ESV [22, 60]. Although theoretically RVEF and SV/ESV should have similar predictive potential, due to the hyperbolic relationship between the two, the latter may be more sensitive to early changes [62]. Then again, it is more difficult to determine ESV in an accurate manner. A large-scale head-to-head comparison of these two parameters may resolve this matter.

Coupling

Coupling implies efficiency of energy transfer from the ventricle to the arterial load and can be calculated as the ratio E_{es}/E_a. The value will be between 1 and 2 if maximal energy transfer from ventricle to load occurs (figure 2).

Coupling has been reported in PAH patients, with single-beat calculation of the E_{es}/E_a ratio from CMR measurements of right ventricular volumes and right heart catheterisation (RHC) measurements of right ventricular pressures [63]. Single-beat determinations of E_{es}/E_a have been implemented in experimental animal studies to show, for example, that acutely administered prostacyclin has no intrinsic inotropic effect [64] and that β-blocker agents may either deteriorate (acutely) [11] or improve (chronically) [64] right ventriculo–arterial coupling.

Compared with controls, in PH the E_{es}/E_a was decreased, indicating insufficient contractility adaptation ("homeometric") and impending right ventricular failure. Results have been confirmed in small cohorts of patients with either PAH or chronic thromboembolic PH, and in one case report of a patient with a systemic-like pressured right ventricle [3, 65–68]. In these studies, E_{es}/E_a was measured either by the single-beat method [3, 63, 65, 67] or using multiple pressure–volume loops obtained by decreasing venous return through a Valsalva manoeuvre [66, 68]. E_{es}/E_a was either maintained or decreased at rest, but consistently decreased at exercise. Decreased E_{es}/E_a at exercise was accompanied by an increase in right ventricular EDV [68].

Coupling is maintained at resting conditions for as long as the ventricle can adapt (figure 2). Only in the late stages of pressure overload does uncoupling occur [11, 21]. Therefore, coupling is not a sensitive parameter to identify an early disease state. Although coupling measured at exercise might contain more important clinical information, the complexity of these measurements will limit clinical use.

Practical assessment of pulmonary haemodynamics

Single variables such as PAPs, SV and CO are the result of the interaction of the right ventricle to its load. This implies that from a single variable, *e.g.* CO, no quantitative information can be obtained on either of the subsystems, *i.e.* the heart or the arterial load. For this reason, a change in PAP at exercise cannot be considered as a measure of right ventricular contractility.

Measuring the pressures correctly

Measurements of PAP and PAWP during rest and especially at exercise are technically challenging because of respiratory pressure swings. To avoid spurious increases in PAWP at end-expiration during exercise caused by dynamic hyperinflation and/or decrease in lung volume, it is preferable to average the reading of pulmonary vascular pressure curves over several respiratory cycles [69]. The 2015 European Society of Cardiology/European Respiratory Society PH guidelines recommend measurements at end-expiration at rest, as is standard procedure in most catheterisation laboratories, but allow for averaging over several respiratory cycles during exercise when respiration-related phasic changes become excessive [1, 70].

Provocation of the pulmonary circulation

Provocative testing of the pulmonary circulation with exercise or a fluid challenge has been used by some centres in clinical practice for decades, but has only recently been standardised.

Exercise

The upper limit of normal of mPAP during an incremental dynamic exercise challenge is now well established at 30 mmHg at CO <10 L·min^{-1} (figure 5), which corresponds to a total pulmonary resistance

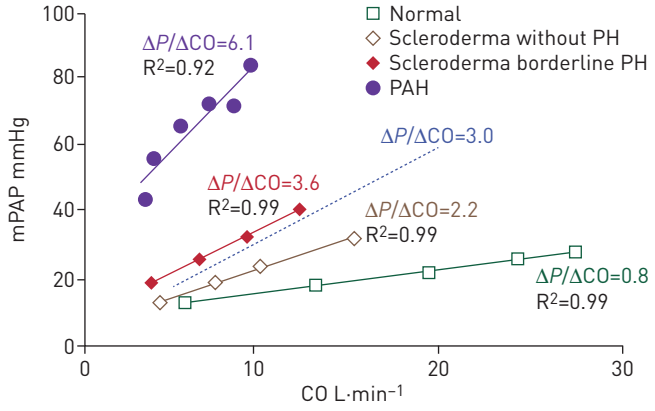

FIGURE 5 The mean pulmonary arterial pressure (mPAP)–cardiac output (CO) relationships: the ratio of $\Delta P/\Delta CO$ in health and disease. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension. Reproduced and modified from [71] with permission.

(TPR=mPAP/CO) of 3 WU [37, 71, 72]. It has been recently proposed that exercise-induced increases in mPAP >30 mmHg at CO <10 L·min^{-1} be called "exercise PH" [69].

The cause of "exercise PH" is either an upstream transmission of increased PAWP, such as in heart failure, or an increase in PVR, such as in PVD, disturbed lung mechanics or hypoxia [37, 69, 71]. This differential diagnosis relies on a clinical probability and eventual invasive measurements of PAWP and left ventricular end-diastolic pressure. The upper limit of normal of PAWP during exercise is generally thought to be between 15 and 20 mmHg, but higher values can be recorded in athletes capable of very high CO and in elderly subjects [73]. Some consider 20 mmHg as a reasonable upper limit of normal [74]. However, a higher cut-off value of 25 mmHg has been proposed for the diagnosis of heart failure [75]. As for mPAP, a flow-corrected measure may be more appropriate, but there has been no study specifically addressing this. Since TPR normally decreases by up to 30% during exercise, the PAWP/CO slope should not exceed 2 mmHg·L^{-1}·min^{-1}. Mean PAWP/CO slopes around 1 mmHg·L^{-1}·min^{-1} have been reported in control groups of studies on exercise testing in heart failure patients [71, 74, 75].

Fluid challenge

A fluid challenge will induce a rapid rise in PAWP in any condition associated with altered left ventricular diastolic compliance or mitral valvulopathy [76]. Fluid loading increases PAWP in healthy volunteers as a function of age, sex, amount infused and infusion rate [77]. There is an emerging consensus to infuse 500 mL of saline in 5–10 min as the best compromise between safety and stress efficacy, with 18 mmHg as the optimal PAWP cut-off to separate abnormal from normal [76–80]. This was recently underpinned by a report on 212 patients referred for PH who were challenged with 7 mL·kg^{-1} of saline given in <5 min (corresponding to 0.5 L for a 70-kg patient) [80]. To limit the number of healthy outliers [80], a cut-off value of 20 mmHg might be preferable. Both exercise and fluid loading increase systemic venous return, but exercise has additional effects, including sympathetic nervous system activation, intrathoracic pressure changes and mixed venous or arterial hypoxaemia. These differences probably impact on their respective efficacies for diagnosis of latent disease [81].

The emerging role of non-invasive assessment of right ventricular function

The role of right ventricular function estimated by non-invasive methods such as echocardiography (two-dimensional, three-dimensional, speckle tracking-derived echocardiography) or CMR is emerging rapidly in observational studies and has been reviewed elsewhere [82]. Speckle-derived strain technology allows measurements of regional strains by either method and demonstrates heterogeneity of right ventricular strain depending on the region (*e.g.* apical *versus* mid or basal region) and occasionally significant differences between disease aetiologies, such as idiopathic PAH (IPAH) and systemic sclerosis (SSc)-associated PAH. Recent larger studies in echocardiography have demonstrated that right ventricular longitudinal strain or indices of right ventricular end-systolic remodelling in combination with N-terminal pro-brain natriuretic peptide and NYHA Functional Class provide good discrimination of outcome in PAH [83, 84].

Imaging modalities may be incorporated into large multicentre clinical trials in PH using composite morbidity and mortality end-points, which would be ideal settings to validate potential right ventricle-based surrogate end-points. Since CMR has greater sensitivity and reproducibility than ultrasound, and can detect an efficacy signal with a small sample size in a relatively short period of time, validation of specific right ventricle surrogate CMR markers (*e.g.* RVEF, right ventricular mass, right ventricular mass index; left ventricle size and function) in the setting of smaller phase 2 trials would be useful to help identify potentially promising therapies. This could allow the creation of prediction scores constructed from a hierarchically organised series of identified independent predictors.

Recent insights in the pathobiology of right ventricular failure

Since the 5th World Symposium on Pulmonary Hypertension report in 2013 [2], there have been major advances in understanding the underlying pathobiology of right ventricular remodelling and failure. This knowledge has been derived both from animal models, reviewed elsewhere [85], and, importantly, from human tissue. Recent work has focused on several main themes and a thorough review of the complete breadth of right ventricular failure mechanisms is beyond the scope of the current article.

First, there has been an expansion of the understanding that genetic features may affect right ventricular stress responses. It is well recognised that patients with heritable forms of PAH (HPAH) have poorer survival than their IPAH counterparts, but recent work has demonstrated that this is related to more severe right ventricular failure in HPAH due to *BMPR2* (bone morphogenetic protein receptor type 2) mutation despite similar levels of afterload, suggesting a genetic contribution to right ventricular failure [86]. In a different series of investigations, *BMPR2* mutation was shown to promote lipotoxicity in the

BMPR2 mutant right ventricle in rodents, in humans and in cultured cardiomyocytes with overexpression of mutant *BMPR2* [87–89]. More recently, Potus *et al.* [90] demonstrated downregulation of miR-126 in human tissue and the monocrotaline model of right ventricular failure, with subsequent reduction in angiogenesis. Taken together, these data suggest a role for genetic regulation of right ventricular failure and may be used to develop new models of right ventricular failure.

The effect of sex hormones on the right ventricle has gained further attention. Male sex is known to be an independent risk factor for poor survival [91] and Jacobs *et al.* [92] found that despite a similar burden of PVD, male patients lack improvement in RVEF regardless of treatment, while their female counterparts improved RVEF. Frump *et al.* [93] demonstrated using the Sugen hypoxia models that oestrogen improves right ventricular function and bioenergetics, and reduces proapoptotic signalling and inflammatory cytokine expression, perhaps suggesting a protective role for oestrogen underlying the clinically recognised sex differences.

There is improved understanding of right ventricle metabolism with recent findings that right ventricular failure is characterised by reduced fatty acid oxidation in addition to increased glycolysis [87, 88, 94, 95]. Presently, it is unknown if enhanced fatty acid oxidation or improved glucose oxidation would most successfully improve right ventricular function. Finally, there is a new perception of the contribution of altered cytoskeletal function in the right ventricle. Pulmonary artery banding was used to induce right ventricular hypertrophy and dysfunction in rats, resulting in increased myocardial stiffness with increased fibrosis- and myofibril-mediated stiffness [96]. Using the monocrotaline model, Prins *et al.* [97] found abnormal t-tubule architecture associated with reduced junctophillin-2 expression. Colchicine ameliorated these findings, perhaps suggesting a new therapeutic avenue for the failing right ventricle. Taken together, these studies present new data on the role of the cytoskeleton and myocardial fibrosis in promoting right ventricular dysfunction.

Animal models of right ventricular failure related to group 2 PH should be developed and may require a "multiple-hit" rather than "single-hit" approach in order to more adequately reproduce the clinical syndrome [98].

Finally, insight into the pathophysiology of right ventricular function is also emerging from human right ventricle biopsies. Isolated cardiomyocytes thus obtained may allow for deep phenotyping and mechanistic investigations of specific pathways. Using this approach in patients with end-stage PAH undergoing heart–lung transplantation, and comparing with non-failing donors, Rain *et al.* [20] demonstrated increased fibrosis and stiffening of right ventricle sarcomeres in conjunction with decreased titin phosphorylation in PAH. A recent study by Hsu *et al.* [99], using right ventricle biopsies obtained during RHC under echocardiographic guidance, revealed that patients with SSc-PAH have depressed sarcomeric function, which is manifested by a significant decline in maximal force (F_{max}) calcium dependence compared with non-PAH patients, while the opposite (*i.e.* increased calcium-activated F_{max}) was demonstrated for patients with IPAH, in line with data obtained by Rain *et al.* [20] in (non-scleroderma) PAH patients. Collectively, these findings may explain the significant differences in outcomes and survival in these two groups of patients.

Future directions

A summary of future directions is given in supplementary figure S1b.

Our insights into the role of the right ventricle in PH have considerably improved over recent years. These insights allow for a full assessment of right ventricular function and pulmonary vascular load based on pressure and volume measurements in patients. Such an assessment permits us to test the differential effects of future drugs on the right ventricle and pulmonary vasculature. Use of CMR should be implemented in PAH clinical trials and clinical practice when possible. Molecular imaging should be used to translate from bench to bedside (and *vice versa*). Novel approaches are necessary to show the clinical value of echocardiography for predicting response and tailoring therapy.

Currently, the clinical relevance of an abnormal exercise pulmonary haemodynamic response is largely unknown and requires long-term follow-up studies. If PH is present, diuretics and atrioseptostomy are the only options available to treat the right ventricle, mainly by reducing wall tension [100].

Better characterisation of normal right ventricular function, early dysfunction and irreversible failure is needed. Growing insights into how to prevent right ventricular failure at a biological level need to be translated to the clinic *via* well-designed trials. If right ventricular failure is present, the role of inotropic agents is unknown. Based on the finding that contractile reserve of the right ventricle is absent in advanced disease, the effectiveness of inotropic drugs in end-stage right ventricular failure needs to be re-evaluated. Finally, the optimal medical care of patients in end-stage right heart failure needs to be defined.

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