REVIEW TOPIC OF THE WEEK

The Relationship Between the Right Ventricle and its Load in Pulmonary Hypertension

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ABSTRACT

In pulmonary hypertension, the right ventricle adapts to the increasing vascular load by enhancing contractility (“coupling”) to maintain flow. Ventriculoarterial coupling implies that stroke volume changes little while preserving ventricular efficiency. Ultimately, a phase develops where ventricular dilation occurs in an attempt to limit the reduction in stroke volume, with uncoupling and increased wall stress as a consequence. With pressure-volume analysis, we separately describe the changing properties of the pulmonary vascular system and the right ventricle, as well as their coupling, as important concepts for understanding the changes that occur in pulmonary hypertension.

On the basis of the unique properties of the pulmonary circulation, we show how all relevant physiological parameters can be derived using an integrative approach. Because coupling is maintained by hypertrophy until the end stage of the disease, when progressive dilation begins, right ventricular volume is the essential parameter to measure in follow-up of patients with pulmonary hypertension. (J Am Coll Cardiol 2017;69:236–43) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The pulmonary circulation and right ventricle (RV) have been undiscovered land for a long time. It is only recently that we learned to understand the unique structure and function of the pulmonary circulation, and their consequences with regard to RV load and function in pulmonary hypertension (PH). There are striking differences between the pulmonary circulation and the systemic circulation, both anatomically and functionally. The systemic arterial system consists of a large main artery with side branches, whereas the pulmonary arterial bed is more like a system of short vessels repeatedly branching into, on average, 3 daughter vessels (1,2). Not only does the anatomy differ, but functional differences also exist. One example is the response to hypoxia, with vasoconstriction in the pulmonary vasculature, but dilation in the systemic vasculature. A hemodynamic comparison between aortic and pulmonary artery pressures (PAP) with increasing vascular resistance, as in hypertension, is schematically shown in Figure 1 (3). The increased vascular load on the RV in PH and its consequences for RV function are not well understood. The difference in RV failure in PH in comparison to left ventricular (LV) failure is that the RV fails after a course of immense adaptation, with RV contractility able to increase 4- to 5-fold. Therefore, RV failure can only be understood in relation to its load, called coupling. Combining hemodynamic assessments with novel imaging techniques allows these changes to be measured over time.
The aim of this review is to summarize recent hemodynamic insights in the pulmonary circulation in PH, indicate the consequence of these findings for daily practice in the clinic, and identify the limitations and gaps in our current knowledge. All relevant physiological parameters will be discussed using an integrative approach. We will start with a description of the pulmonary vascular load and its changes in PH, and subsequently outline the response of the RV (Central Illustration).

**THE PULMONARY VASCULAR SYSTEM**

**THE ORIGIN OF PH.** The pivotal hemodynamic change in PH is the increase in resistance as the consequence of pulmonary vascular remodeling. Resistance may increase by a factor of 4 or more, rather than the 50% increase in systemic hypertension (Figure 1). Because pulmonary vascular resistance (PVR) is calculated as: \( PVR = (mPAP - PAWP)/CO \) (with \( mPAP = \) mean pulmonary artery pressure, \( PAWP = \) pulmonary arterial wedge pressure, and \( CO = \) cardiac output), it includes the resistance in capillaries and veins. The contribution of the veins to the different types of PH is unknown. Animal experiments have shown that venous resistance may contribute up to 40% of PVR (4). In addition, quantitative information on the number of vessels affected and their (average) decrease in diameter is still limited. Arterial and venous data in health and PH reported by Chazova et al. (5) suggest that changes in the veins may indeed contribute to PVR. Reid (6) has suggested that rarefaction may also play a role. Further research in this area is required to understand the structural basis of increased resistance in the pulmonary vascular bed.

**THE PRESSURES ARE PROPORTIONAL IN PH.** As a consequence of the increased resistance, PAP will increase. One of the most striking features of the pulmonary circulation in PH is that pulmonary artery systolic and diastolic pressures are proportional to \( mPAP \) (7,8). Even in left heart failure, with considerably increased PAWP, this proportionality is maintained (9).

Echocardiography or invasively measured RV systolic pressure (\( P_S \)) in patients with patent pulmonary valves allows for a reliable calculation of mean and diastolic pressures: systolic \( PAP = P_S \); diastolic \( PAP = 0.36 \times P_S \); \( mPAP = 0.6 \times P_S \); and pulse pressure (PP) = 0.6 \( P_S \) (9).

**RESISTANCE AND COMPLIANCE ARE INVERSELY RELATED.** The proportionality of the pressures follows from the unique properties of the pulmonary vascular system. Kind et al. (10) showed that it results from an inverse relationship between the 2 major components of the vascular load: PVR and total arterial compliance (TAC). Although this inverse relationship was already indicated in 1971 (11), it was Lankhaar et al. (12,13) who demonstrated that this inverse relationship holds in patients with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), as schematically represented in Figure 2. For the inverse relation, it holds that \( PVR \times TAC = \) constant and is called the arterial time constant (abbreviated as RC). In a study of Saouti et al. (14) in CTEPH patients, it was shown that the inverse relationship is valid for the left and right pulmonary artery, even though the clots were asymmetrically distributed over both lungs. This suggests that the impact of proximal or distal obstruction has a similar effect on the relationship. Whether the inverse relation also holds for central obstructions in the main pulmonary artery is debated (15,16). In a large patient cohort, the relationship was confirmed (17,18), but it was also established that the relationship shifts to the left in patients with PH due to left-sided heart failure, as illustrated in Figure 2.

It is an open question whether the decreased RC-time with increased PAWP reflects a larger stiffness (smaller compliance) of the pulmonary vascular system at a similar pressure in pre-capillary PH patients than in patients with left heart failure PH or a smaller resistance at similar compliance (Figure 2). It may also be the consequence of an over-simplification of the calculation of TAC as stroke volume (SV) divided by PP (19). The calculation of PVR contains PAWP, but TAC is calculated from SV/PP and does not contain PAWP; therefore, their product depends on PAWP. Measurement of the decay of PAP in diastole, thereby directly determining RC, could give the answer.

**CLINICAL RELEVANCE.** The clinical relevance of the proportionality of pressures is that all pressures can be derived from a single measurement.

The constant RC-time is an arterial property and is called the arterial time constant because its units are time. In the systemic circulation, where the aorta mainly determines compliance, this constant RC-time is not seen. This constant inverse relationship between PVR and TAC has 3 important implications:
Compliance can be estimated on the basis of PVR findings alone. This relationship makes PVR a reliable estimation of load in the pulmonary vascular system and a valid endpoint in study design.

- In the case of CTEPH, measurement of flow in the left and right main pulmonary arteries, for instance by cardiac magnetic resonance (CMR), suffices to calculate the PVR and the TAC ratio between the left and right lungs because the flow ratio equals the inverse PVR ratio.

- Compliance is the most variable component in the early phase of the development of PH (small PVR increase) (area A in Figure 2), whereas at high PVR the compliance changes little with PH severity (area B in Figure 2). Therefore, changes in (local) pulmonary artery distensibility, as a surrogate for pulmonary arterial compliance, might serve as an indication of the development of early pulmonary vascular disease, even before PVR is increased. Indeed, in a study by Swift et al. (20), it was suggested that a decrease in pulmonary artery compliance is an early marker of increased PVR.

**THE RIGHT HEART**

**THE COUPLING OF THE RV AND ITS LOAD.** The challenge for the RV in PH is to remain coupled to its load. A complete description of coupling can be obtained by constructing pressure-volume (P-V) loops. Ventricular contractility, determined by muscle properties and muscle hypertrophy (wall thickness), is given by the slope of the end-systolic pressure versus the end-systolic volume, and is called the end-systolic elastance (E_{es}) (21). To determine E_{es}, multiple P-V loops are required, such as can be obtained by reducing ventricular diastolic filling, by (partial) vena cava occlusion (21), or otherwise by the Valsalva maneuver (22). The so-called single-beat method to determine E_{es} without filling changes was originally proposed by Sunagawa et al. (23), extended by Senzaki et al. (24), and proven practical for the RV by Bromioille et al. (25). The method relies on extrapolation of the measured pressure to a theoretical isovolumic contraction, P_{s vol}. This P-V point, in combination with the end-systolic P-V point, is used to calculate E_{es}. It should be noted that the estimation of P_{s vol} has not been validated in patients with severe PH.

The ventricular load can be estimated from the P-V relation as arterial elastance (E_a) (area A in Figure 3), which is a measure of PVR, namely the PVR/R-R interval or PVR · heart rate (26), under the assumption that end-systolic pressure can be approximated by mPAP (27). E_a is not a measure of compliance, as the term suggests (Figure 3).

E_a is a ventricular-independent measure of arterial function, and E_{es} is a so-called load-independent measure of ventricular function, whereas pressure, CO, and SV are load and heart dependent. “Coupling” is a measure of energy transfer (discussed later) and can be assessed from the ratio between end-systolic elastance and arterial elastance E_{es}/E_a. The single-beat analysis gives E_{es}/E_a = P_{s vol}/P_{es} − 1 (with P_{es} being end-systolic pressure); as a further simplification, P_{es} is often set equal to mPAP.

The slope of the P-V relation at end-diastole, called end-diastolic elastance (E_{ed}) (area C in Figure 3), can be used to characterize diastolic stiffness (27). A single-beat analysis to obtain E_{ed} has also been worked out (27-29). Thus, RV systolic and diastolic function, together with the arterial load, can be studied using P-V information.

**THE RESPONSE OF THE RV TO INCREASED LOAD.** Figure 4 depicts the sequence of RV heart failure in PH. In the early phase of the disease, coupling is maintained by a 4- to 5-fold increase in contractility (the E_{es}) of the RV. Important mechanisms to achieve this increase in E_{es} include muscle hypertrophy leading to an increase in wall thickness, as well as changes in muscle properties per se. However, if the disease advances, the hypertrophic process will be halted and SV decreases (30). The only mechanism to
preserve SV is then RV dilation. In an attempt to maintain CO with the decreasing SV, the heart rate increases, and because $E_a = \frac{PVR}{hr}$ heart rate, the $E_a$ increases, and the ratio $E_a/E_s$ decreases. Thus, RV uncoupling will occur in advanced stages of disease (27), as well during exercise (31). Compared with LV adaptation until heart failure, the RV can remain coupled for the large increase in load.

The ventricular response to the load also affects diastolic function. The hypertrophy itself makes the ventricle stiffer, but changes in muscle properties add to this effect (29).

**CLINICAL RELEVANCE.**

- Because uncoupling will only occur in end-stage disease (27,31), the adaptational mechanisms to maintain coupling are more interesting to measure than the coupling itself.
- Consequently, volumetric measures, including measures of SV, RV end-diastolic volume, and RV end-systolic volume (RVESV), are parameters to be monitored during follow-up of patients with PH.
- Both RV ejection fraction (RVEF) and $SV/RVESV$ meet these criteria, and have been shown to be of high prognostic value. In fact, RVEF and $SV/RVESV$ are inversely related to each other: $SV/RVESV = RVEF/(1 - RVEF)$, and thus should, in principle, contain similar prognostic information.

However, sensitivities to predict outcomes (as in Figure 2) may be different: large changes can be more reliably detected in the presence of measurement noise. For instance, $SV/ESV$ may be more

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**Figure 2** Schematic Relation Between PVR and TAC

PVR and TAC have an inverse relationship that can be described as $PVR \cdot TAC = \text{constant}$. This so-called time constant is affected by PAWP. At normal and low PVR (area A), changes in PVR have a large effect on TAC. At high PVR (area B), a similar change in resistance has little effect on TAC. PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; TAC = total arterial compliance.
be interpreted as an adaptive response of the RV, rather than a negative inotropic effect of the drug (35). The load-dependent nature of RV heart failure is further demonstrated by the fact that unloading the RV in patients with PH will lead to normalization of RV function.

**THE CONSEQUENCE OF RV VOLUMETRIC ADAPTATION.** Volumetric adaptation by means of dilation and reducing SV occurs at the cost of increased wall tension (stress) and increased pressure. The consequences of these changes include increased oxygen consumption, together with deterioration of oxygen efficiency, ventricular interaction, and changes at the myocyte level that increase RV stiffness. These 3 effects will be detailed in the following sections.

**Increased oxygen consumption and decreased oxygen efficiency.** Oxygen consumption of the RV is mainly determined by wall tension and PAP (36,37). As a consequence, oxygen consumption will increase if the RV dilates and pressure increases, both augmenting wall stress. Oxygen supply, on the contrary, is limited in case of PH (38,39). Oxygen consumption of the RV can be assessed by a short-living oxygen tracer or, as a surrogate, the acetate tracer. If combined with right heart catheterization, mechanical efficiency, defined as the ratio of external power and oxygen consumption, can be calculated. In this formula, power (work per time) is calculated as $P_{\text{AP}} \cdot \dot{Q}$, and consists of a mean part ($mP_{\text{AP}} \cdot \dot{Q}$) and an oscillatory part. The oscillatory part of the power was found to be 23% of total power, both in health and in PH, allowing calculation of total power as $mP_{\text{AP}} \cdot \dot{Q}$ (40). RV efficiency is normally about 20% to 25% and decreases with progression of PH as a consequence of increased oxygen consumption despite a stable power output (37).

Because mechanical efficiency is complex to derive and requires the measurement of oxygen consumption by means of positron emission tomography, a surrogate measure might be the $E_{\text{ed}}/E_{\text{a}}$ ratio, Figure 3 (26). Sunagawa et al. (26) showed that if this ratio is between 1 and 2, RV efficiency is within normal range. A ratio above or below this range reflects decreased mechanical efficiency and loss of ventriculoarterial coupling. Altered metabolism, mitochondrial dysfunction, and inadequate contraction patterns serve as an explanation for this increased oxygen consumption (41).

The clinical consequences of these concepts are:

- Total RV power can be calculated as $1.30 \times mP_{\text{AP}} \cdot \dot{Q}$ (oscillatory power is 23% of total power, thus mean

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power is 77%, that is, total power equals 100/0.77 = 1.3 mean power).

- The best way to guarantee long-term survival and prevent RV failure in patients with PH is to reduce mPAP.
- Therapies to improve RV oxygen efficiency might be effective in PH.
- An integrated imaging and invasive approach is feasible to assess all components of pulmonary vascular load and RV function in patients (Figure 5).

**Ventricular interaction.** Although the impact of the RV on LV function is negligible under normal conditions, ventricular interdependency plays an important role in the pressure overloaded RV. Ventricular interdependency can be caused either by leftward septal bowing, hampering filling of the LV (parallel interaction), or by decreased filling of the LV due to lowered RV SV (series interaction) (42). The primary cause of leftward septal bowing is a prolonged contraction time of the RV with respect to LV contraction time (43). By using Doppler echocardiography, it has been recognized for some time that post-systolic isovolumetric time is prolonged in advanced stages of PAH (44). As a consequence of the prolonged isovolumetric contraction of the RV, early diastolic LV filling is hampered (42). The main mechanism appears to be increased wall tension: RV contraction continues while the LV is already in its diastolic phase. As a consequence of the leftward shift of the septum, the pulmonary valve will close, even though the RV is still contracting. This so-called post-systolic isovolumetric contraction of the RV contributes to mechanical inefficiency because the energy of the contraction in that phase in the cardiac cycle is not used for forward flow. The prolongation of post-systolic isovolumetric time in PAH, measured by means of Doppler echocardiography (44), thus should be considered as a sign of increased wall stress and a measure of disease severity (45).

The clinical consequences of ventricular interdependency are 4-fold:

- Measures of ventricular interdependency are clinically useful to assess disease severity because these parameters contain information on SV and wall tension. Indeed, several large studies indicate that LV volumetric parameters have important prognostic information in addition to RV function measures (46–49). Parameters that incorporate post-systolic isovolumetric time, such as the myocardial performance index (an index that incorporates both systolic and diastolic time intervals in expressing global systolic and diastolic ventricular function) are of clinical relevance (44,50).
• Underfilling of the LV will bring the myocytes in an atrophic state. Recent research showed that this state is characterized by changes in cardiac muscle properties (51). Therefore, special attention is required if the RV is unloaded, as this might induce LV failure (52).

• Restoring ventricular interdependency by means of pacing will increase mechanical efficiency. This concept has only been tested in small cohorts of patients (53).

• The importance of the LV in PH is underlined by the fact that SV is closely related to LVEDV, and not to RV end-diastolic volume (54).

Series interdependency of LV and RV in LV failure has recently been discussed in detail (54).

**Increased stiffness.** Finally, the increased wall tension reflects increased RV cardiomyocyte stress. Although it is not possible to measure cardiomyocyte stress directly, methods are available to derive local strain (shortening) by CMR (43) and strain echo (55). New techniques under development to measure fiber orientation in the ventricular wall (56) and to derive wall stiffness, such as ultrasound-based elastography (57) are promising, but have not yet been applied in the context of PH. Myocyte stress is the basis of right heart failure in PH because stress is the main driver of molecular changes in the myocyte, including neurohumoral activation, which leads to increased stiffness of the RV (29). Although right atrial pressure and volume can be considered as surrogate measures of RV stiffness, those measures are load dependent. Increased diastolic stiffness, expressed as Ees, is associated with a poor prognosis (27,31). Studies by Trip et al. (27) and Rain et al. (29) showed that diastolic stiffening occurs in the advanced disease state, and is the consequence of molecular changes in the cardiomyocyte, as well as hypertrophy.

**CONCLUSIONS**

This review shows that the need of the RV to remain coupled to its load explains the RV changes in PH. Because the load can increase by more than 5-fold in this disease, coupling can only be achieved by an almost similar increase in contractility. In the more advanced disease state, RV contractility is maintained by ventricular dilation in an attempt to limit the reduction in SV. The consequence of these adaptations is an increase of myocyte stress and leftward septal bowing, impairing LV and RV function. It is the uncoupling with high metabolic demand and reduced output that heralds the final stage.

Combining CMR (positron emission tomography, Doppler echocardiography) and hemodynamic measurements via catheterization (even single-beat analysis) offers the potential for a full assessment of pulmonary vascular load and right heart function, as required for evaluation of the hemodynamic state in patients with PH. In the stages of PH when coupling is still present, RV volume may be the most sensitive prognostic measure (47).

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