Review Article

Hemodynamic indices in pulmonary hypertension: a narrative review

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Background and Objective: Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) >20 mmHg and its presence is associated with worse outcomes. A comprehensive hemodynamic evaluation of the pulmonary circulation is essential for diagnosis, hemodynamic classification, and prognostication. A multitude of indices assess different aspects of the pulmonary circulation but there are no reviews that describe their specific value in PH.

Methods: We performed a thorough literature search of relevant articles in English from 1970–2021 using PubMed.

Key Content and Findings: In this article, we present both static and dynamic indices used for the hemodynamic assessment of PH. While some of these indices are routinely used in clinical practice, including cardiac index (CI), stroke volume (SV), and pulmonary vascular resistance (PVR); others such as pulmonary artery compliance (PAC), pulmonary effective arterial elastance (Ea), and pulmonary artery pulsatility index (PAPi) are gaining popularity by enhancing the understanding of different aspects of the pulmonary circulation. We described the advantages and pitfalls of various indices, including when to use them in the hemodynamic evaluation of patients with PH.

Conclusions: A variety of indices measuring different aspects of the right ventricle (RV)-pulmonary arteries (PA) system provide valuable information in patients with PH. However, it remains important to develop and validate indices that provide a comprehensive hemodynamic evaluation to improve outcomes in patients with PH.

Keywords: Pulmonary hypertension (PH); hemodynamic; indices

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Introduction

The pulmonary circulation starts in the right ventricle (RV), moves into the pulmonary arteries (PA), and extends through the pulmonary veins into the left atrium. It includes a network of arteries, veins, and lymphatics whose main function is gas exchange. The pulmonary circulation is a low pressure and low resistance system; however, in certain conditions the mean pulmonary artery pressure (mPAP) increases above 20 mmHg, leading to the diagnosis of pulmonary hypertension (PH). PH is divided into 5 groups based on similar pathophysiological mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic management (1). Group 1 PH or pulmonary arterial hypertension (PAH) is characterized by precapillary PH [pulmonary artery wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) ≥3 Wood units (WU)] that can lead to right heart failure and death (2). Group 2 PH or PH resulting from left heart disease (PH-LHD) is characterized by postcapillary PH (PAWP >15 mmHg) and can be divided into 2 hemodynamic subgroups, isolated postcapillary PH (IpcPH) in which the PVR is <3 WU and combined pre- and post-capillary PH (CpcPH) in which the PVR is ≥3 WU (3).

Great emphasis has been placed on risk stratifying patients to guide treatment. Commonly used tools include the French PH network registry assessment which incorporates data from up to six variables, and the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) 2.0 risk equation that includes up to 13 variables (4-6). These tools use limited hemodynamic information including right atrial pressure (RAP), cardiac index (CI), and PVR. A variety of other hemodynamic indices that provide information on different aspects of the pulmonary circulation have been explored in PH, but not yet incorporated into clinical practice.

Through this narrative review, we attempt to outline relevant hemodynamic indices studied in PH (*Figure 1*), including their description, normal values, use, and limitations as they apply to improving both the pathophysiological understanding and prognostic assessment in PH. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-244/rc).

Methods

We performed a literature search on PubMed using the MeSH terms "pulmonary hypertension" with each of the indices outlined below. Additionally, we included only articles published in the English language between 1970 through 2021. References from these articles were also reviewed. The search methodology is also described in *Table 1*. A complete list of the indices described above can be found in *Table 2*. All the indices presented can be obtained during a regular right catheterization. We chose to include PA pressure-volume loops (PV loops) since there are methods to estimate the RV-arterial coupling using the hemodynamic data acquired during right heart catheterization (e.g., single beat method that uses a nonlinear extrapolation of early and late isovolumic portions of the RV pressure curve). The impact of provocative maneuvers (i.e., exhaled nitric oxide, fluids, and exercise) on these indices is beyond the scope of the manuscript.

Indices

CI

CI is the cardiac output (CO) normalized for body size and is obtained by dividing CO by body surface area (BSA) (7). CI is reflective of the global function of the RV (in patients with normal systolic and diastolic left ventricular function) and forms an integral component to assess the functionality of the cardiopulmonary unit. As PH worsens, the CI decreases, due to failure of the RV in the setting of a higher afterload. CI is a well-known predictor of outcomes in PH and the European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines assigned CI thresholds of ≥2.5 L/min/m^2, 2–2.4 L/min/m^2, and <2.0 L/min/m^2 for patients at low (<5%), intermediate (5–10%) and high risk (>10%) of dying at 1-year (8).

Poor survival associated with a low CI (<2 L/min/m^2) was initially described in patients enrolled in the Patient Registry for the Characterization of Primary Pulmonary Hypertension (9). Several other studies identified CI as a prognostic variable in PH (6,10-12). In addition, patients who improve CI with PAH-specific therapies have better survival (12,13). In a meta-analysis of trials studying the addition of prostacyclin analogues to targeted therapy for PAH, CI, and other prognostic markers such as New

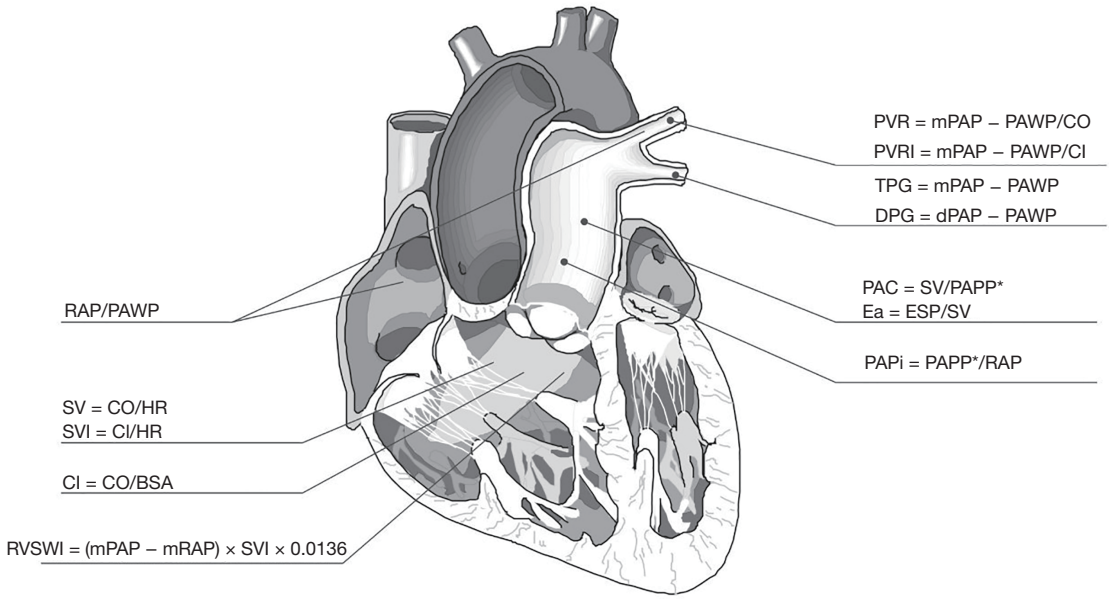

Figure 1 Hemodynamic indices in PH. *, PAPP = sPAP – dPAP. PVR, pulmonary vascular resistance; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; PVRI, pulmonary vascular resistance index; CI, cardiac index; TPG, transpulmonary gradient; DPG, diastolic pulmonary gradient; dPAP, diastolic pulmonary artery pressure; PAC, pulmonary artery compliance; SV, stroke volume; PAPP, pulmonary artery pulse pressure; Ea, pulmonary effective arterial elastance; ESP, end-systolic pressure; PAPi, pulmonary artery pulsatility index; RAP, right atrial pressure; HR, heart rate; SVI, stroke volume index; BSA, body surface area; RVSWI, right ventricular systolic work index; PH, pulmonary hypertension; sPAP, systolic pulmonary artery pressure.

Table 1 Methods

Items	Specification
Date of search	December 15th 2021
Databases and other sources searched	PubMed and references of selected articles
Search terms used	Pulmonary hypertension and each of the indices outlined in the article
Timeframe	1970–2021
Inclusion and exclusion criteria	Articles in English language and human studies
Selection process	Searched by 3 different authors independently after which a cross check was done to obtain consensus. Final check completed by faculty author

York Heart Association functional class and 6-minute walk distance (6MWD) were found to improve with the addition of prostacyclin analogues. However, no change in all-cause mortality was noted despite the improvement of CI (14). We described that mixed venous oxygen saturation was superior to thermodilution CI in predicting long-term mortality. A decrease in mixed venous oxygen saturation indicates that the CI (even if it is apparently adequate) is not sufficient to meet the tissue oxygen needs, hence there is an increase in oxygen extraction (15).

There are several limitations in using CI, particularly as it relates to the methodology used to measure it. The gold standard is the direct Fick method that requires the determination of resting oxygen consumption (VO_2) and analysis of arterial and mixed venous blood to measure the oxygen saturation and hemoglobin, which are necessary

Table 2 Indices used in the hemodynamic assessment of PH

Index	Abbreviation	Formula	Parameter measured	Use in PH
Cardiac index	CI	CO/BSA	Right ventricular function (in patients with normal systolic and diastolic left ventricular function)	• Survival prognosis • Measurement of response to targeted therapy
Stroke volume	SV	CO/HR	Right ventricular function	• Prognosis of morbidity and mortality • Increases with exercise training
Stroke volume index	SVI	CI/HR	Right ventricular function	• Survival prognosis especially in SSc-PAH • Measurement of response to targeted therapy
Transpulmonary gradient	TPG	mPAP – PAWP	Pulmonary vascular constriction/remodeling	• Survival prognosis in PH-LHD • Survival prognosis in patients undergoing trans catheter aortic valve replacement • Preoperative risk prognosticator of mortality post heart transplant
Diastolic pulmonary gradient	DPG	dPAP – PAWP	Pulmonary vascular constriction/remodeling	• Differentiate CpcPH and IpcPH in patients with PH-LHD
Pulmonary vascular resistance	PVR	(mPAP – PAWP)/CO	Pulmonary vascular disease RV afterload (static)	• Differentiating CpcPH and IpcPH in patients with PH-LHD • Survival prognosis • Measurement of response to targeted therapy
Pulmonary vascular resistance index	PVRI	(mPAP – PAWP)/CI	Pulmonary vascular disease RV afterload (static)	• Survival prognosis • Diagnosis of precapillary PH in pediatric population
Pulmonary artery compliance	PAC	SV/PAPP PAPP = sPAP – dPAP	Pulmonary artery distensibility RV afterload (dynamic)	• Early diagnosis of PH in patients with normal PVR • Survival prognosis • Predictor of mortality in PH-LHD (HFpEF and HFrEF) • Response to therapy (IV and oral prostacyclin) in PAH • Response to balloon angioplasty in CTEPH
Pulmonary effective arterial elastance	Ea	End systolic pressure/SV	RV afterload	• Prognostic marker in PH-LHD
Ratio of right atrial pressure over pulmonary artery wedge pressure	RAP/PAWP	RAP/PAWP	Right ventricular failure	• Predictor of survival in PAH
Pulmonary artery pulsatility index	PAPi	PAPP/RAP	Right ventricular function	• Survival prognosis • Predictor of RV failure in PAH
Right ventricular systolic work index	RVSWI	(mPAP – mRAP) × SVI × 0.0136	Right ventricular work	• Survival prognosis in PAH and CTEPH
PA pressure-volume loops	PV loops	End systolic elastance/Ea	RV-arterial coupling	• Early diagnosis of PAH and CTEPH • Evaluation of RV-PA coupling

PH, pulmonary hypertension; CO, cardiac output; BSA, body surface area; HR, heart rate; CI, cardiac index; SSc-PAH, systemic sclerosis associated PAH; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; LHD, left heart disease; dPAP, diastolic pulmonary artery pressure; CpcPH, combined pre- and post-capillary PH; IpcPH, isolated postcapillary PH; RV, right ventricle; SV, stroke volume; PAPP, pulmonary artery pulse pressure; sPAP, systolic pulmonary artery pressure; PVR, pulmonary vascular resistance; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; PAH, pulmonary artery hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; mRAP, mean right atrial pressure; SVI, stroke volume index; PA, pulmonary artery.

for the calculation of oxygen content. The use of pulse oxygenation and prior hemoglobin determination introduces potential sources of error (16). Thermodilution is recommended by the 6th World Symposium on Pulmonary Hypertension (WSPH) when direct Fick methodology is not available because it can provide reliable measurements even in patients with low CO and/or severe tricuspid regurgitation (3); however, the wide limits of agreement (±1.96 SD of the differences) of up to 1 L/min/m^2 between methods, impacts the risk group allocation proposed by ESC/ERS given the narrow CI band (2–2.5 L/min/m^2) (17). Indirect Fick methodology, which estimatesVO_2 based on a variety of formulae is not reliable and not recommended for routine CI determination (3,17). Current noninvasive methodologies to estimate CI, with the possible exception of acetylene and nitrous oxide rebreathing, are not precise enough to differentiate between ESC/ERS risk groups (18-23). Further technological developments are needed to precisely measure CI in a simple, non-invasive, and cost-effective manner in patients with PH (24).

Stroke volume (SV)

SV may be more accurate than CI in estimating RV function as it removes the compensatory heart rate (HR) response when CO is inappropriate to meet the body demands (SV = CO/HR). As PAH progresses the SV decreases; however, this is initially counterbalanced by an increase in HR; a compensatory mechanism that regulates the CI. Hence in the early stages, the CI may be numerically normal even when the SV is reduced.

In patients with idiopathic PAH (IPAH), SV at baseline and 1-year follow-up was a stronger predictor of mortality than CI (25). After a year of PH therapy, the increase in SV directly correlated with the 6MWD, and a 10 mL increase in SV was considered the minimal important difference (26). Treatment with epoprostenol increased the SV (41±11 mL) measured by cardiac magnetic resonance imaging with maximum improvement at 4 months after initiation of therapy, in the context of no significant changes in right ventricular end-diastolic volume and mass (27).

In patients with PAH, the SV correlates with World Health Organization functional class and its change during exercise was a predictor of morbidity and mortality (28-30). Additionally, a post hoc analysis of randomized control trials in patients with PAH and chronic thromboembolic pulmonary hypertension (CTEPH) showed that exercise training increased SV at 15 weeks by an average of 14.2 mL (31).

The accurate measurement of SV is challenging and not without pitfalls. The invasive measurement during right heart catheterization varies in accuracy depending on the methodology used (17). Fick methodology is the goal standard but requires metabolic cart determination, mixed venous and arterial blood gas oximetry (17). In addition, variations in the HR during CO determination may affect the calculation of the SV. Two-dimensional echocardiography has important limitations in assessing RV volumes because of its complex structure; a shortcoming that can be potentially overcome with continuous advances in three-dimensional echocardiography (32). Cardiac magnetic resonance imaging remains the gold standard methodology to assess SV since it can precisely determine diastolic and systolic RV volumes (25,33).

Stroke volume index (SVI)

SVI is calculated by dividing CI by HR or SV by BSA. The advantage of this index is the adjustment of SV by BSA since SV is influenced by body size, particularly fat-free body mass (34,35). SVI could allow for a more precise evaluation of the RV function in patients with PAH. In fact, an SVI, with <38 mL/m^2 at first follow-up (3–4 months after starting PAH-specific therapy) was associated with significantly higher mortality in patients with PAH at intermediate risk by ESC/ERS guidelines (5,36).

SVI during vasoreactivity testing with inhaled nitric oxide in PAH could predict outcomes since patients with an SVI >39.9 mL/m^2 had a 100% survival rate at 5 years (37). Some investigators have proposed using SVI rather than CI as a treatment target in PAH since a decrease in SVI was independently associated with death or lung transplantation (a drop of 10 mL/m^2 in SVI led to a 28% increase) at the first follow-up right heart catheterization after initiation of PAH therapies (38).

SVI is a particularly useful prognostic indicator in patients with systemic sclerosis (SSc) associated PAH (SSc-PAH), in whom traditional hemodynamic indices like RAP, CI, and PVR showed limited utility in predicting survival in one study (39). Despite these results, the 6th WSPH recommends RAP and CI for prognostication in PAH, including patients with SSc-PAH. Patients with SSc-PAH have greater RV dysfunction and lower SV than patients with IPAH despite lower PA pressures and similar CI (40,41). In fact, SVI is a strong predictor of mortality in patients with SSc-PAH, since an SVI <30 mL/m^2 carries a two-fold

increased risk of death in these patients (42,43).

Transpulmonary gradient (TPG)

The TPG is calculated by subtracting the PAWP from the mPAP and higher values reflect pulmonary vascular constriction and/or remodeling. A TPG cutoff of >12 or ≤12 mmHg was used to distinguish IpcPH from CpcPH (44,45). As with mPAP, TPG is influenced by the same hemodynamic factors, including flow, resistance, and left heart filling pressures (46). Due to these limitations, TPG was removed, in favor of PVR (TPG/CO), as a tool to establish the different hemodynamic types of PH-LHD (3,8).

An elevated TPG has been linked with worse outcomes in patients with PH-LHD. A TPG ≥12 mmHg was associated with higher mortality and cardiac hospitalization in PH-LHD with an optimal cut-off of 16 mmHg (47). Other studies found an increase in the 30-day mortality in heart failure patients undergoing evaluation for heart transplantation with elevated TPG (≥12 or 15 mmHg, depending on the study), irrespectively of the PVR (48,49). An analysis using the United Network for Organ Sharing database also revealed longer hospital length of stay and higher mortality at 5 and 10 years post-heart transplantation in patients with preoperative TPG ≥15 mmHg (50). Given the increased morbidity-mortality of a high TPG (TPG ≥15 mmHg) or PVR ≥3 WU, heart transplantation guidelines recommend regular assessment of hemodynamics with pulmonary vasodilators (e.g., intravenous nitrates or inhaled nitric oxide) and inotropic agents (e.g., milrinone), to assess reversibility of the precapillary component in patients with CpcPH (51).

In patients with PH due to valvular heart disease, a higher TPG also predicted worse outcomes. Patients with high TPG (>12 mmHg) who underwent restrictive mitral annuloplasty for severe mitral regurgitation had worse outcomes (all-cause mortality and readmission for heart failure) (52). Similarly, patients with markers of precapillary PH (including an elevated TPG and PVR) had worse survival after transcatheter aortic valve replacement (53).

Diastolic pulmonary gradient (DPG)

DPG is calculated by subtracting PAWP from the diastolic pulmonary artery pressure (dPAP). At a constant SV, an increase of PAWP has a more pronounced effect on systolic pulmonary artery pressure (sPAP) and mPAP than dPAP, which might be explained by a lower sensitivity to vessel distensibility (45,46). Based on this assumption some authors advocate DPG in favor of TPG. Recent investigations demonstrated that both DPG and TPG depend on PAWP and CO (absolute increase in DPG with CO is 62% of the TPG increase with CO), blurring the potential advantages of one calculation versus the other (46,54). The fifth WSPH included DPG ≥7 mmHg along with PVR (45,55); however, the 6th WSPH eliminated DPG and only kept PVR for differentiating IpcPH from CpcPH (3).

DPG was initially used to differentiate cardiac versus pulmonary causes of acute respiratory failure (56). Initially, DPG was proposed as a good hemodynamic indicator to differentiate IpcPH from CpcPH (46). A DPG of ≥7 mmHg showed the best combination of sensitivity and specificity to be an independent predictor of survival in patients with PH-LHD (55). In addition, patients with DPG ≥7 mmHg had worse vascular medial hypertrophy, intimal and adventitial fibrosis, and more occluded vessels (55). A metanalysis revealed that PVR, pulmonary artery compliance (PAC), and DPG are associated with survival in patients with PH-LHD (57).

Nevertheless, the prognostic value of DPG in PH-LHD remains controversial and was not associated with survival in a relatively large retrospective multicenter study of patients with PH due to heart failure with reduced ejection fraction or heart failure with preserved ejection fraction (58-64). These negative results could in part be explained by the negative numeric values of DPG observed in some studies that reflect inconsistent pressure measurements across different parts of the respiratory cycle (e.g., dPAP averaged across the respiratory cycles while PAWP measured at end-expiration), a falsely lower dPAP by including a ringing artifact, or a higher PAWP due to under/over wedging or the inclusion of V waves in the measurement (65-67).

PVR

PVR is a static hemodynamic index based on Poiseuille's law and is calculated as (mPAP – PAWP)/CO. PVR is essential for diagnosing pre-capillary PH as well as CpcPH (3). PVR has also been shown to provide prognostic information in different forms of PH and is a part of the US REVEAL 2.0 score for risk assessment (a PVR <5 WU reduces the score by one point) (6,68). A meta-regression analysis of 21 trials showed that changes in PVR were independently predictive of adverse clinical events, particularly total mortality (69).

While a PVR of ≥3 WU is currently used to define

precapillary PH, this threshold is not based on evidence regarding the upper limit of normal which is <2 WU (70). In fact, a PVR >2.2 WU was associated with all-cause mortality in patients undergoing right heart catheterization; and a PVR between 2.2 and 3 WU may represent early pulmonary vascular disease (68,70,71). Patients with SSc demonstrated reduced long-term survival when the PVR was ≥2 WU (71). Interestingly, a retrospective study from Australia and New Zealand showed improvement in the 6MWD and New York Heart Association functional class in patients with PH (mPAP ≥25 mmHg and PAWP ≤15 mmHg) without a PVR >3 WU, who received PAH therapy (72).

Pulmonary vascular resistance index (PVRI)

The PVRI differs from PVR in that it takes into account the body habitus of the patient. It is calculated as follows: PVRI = (mPAP – PAWP)/CI or PVRI = PVR × BSA. Despite potential advantages, PVRI has not been routinely adopted in the adult population. A PVRI value of ≥30 WU·m^2 (or mmHg/L/min/m^2) was a predictor of 3-year survival in patients with PAH (73). A recent study by our group showed that both PVR and PVRI were associated with disease severity in PAH, and both indices were risk factors for first PAH hospitalization and death or death or lung transplant, without any apparent superiority between them (74). Interestingly, we noted an inverse correlation between PVR and body weight which can be explained by increased CO seen in obese individuals (75,76). The current recommendations by the 6th WSPH are to use the PVR for the diagnosis of PH in adults (77). However, the guidelines for PH in pediatric patients, recommend using PVRI given the wide variations in BSA in children (78,79).

Pulmonary arterial compliance (PAC)

Unlike the static index PVR, PAC measures arterial distensibility and therefore provides information about the pulsatile load on the RV. PAC and PVR exhibit an inverse hyperbolic relationship and in the early stages of the disease, the PAC might decrease even with minimal changes in PVR (80,81). A simplified approximation of PAC uses the ratio of SV and pulmonary artery pulse pressure (PAPP) [PAC = SV/(sPAP – dPAP)]. This simplified formula can overestimate PAC since the true increase in volume in the arterial system is difficult to measure, since the actual change in volume is lower than the SV (82,83). This determination can be improved by simultaneously acquiring invasive pressure measurements and magnetic resonance flow data (82).

PAC provides prognostic information in IPAH and SSc-PAH (42,84-86). In patients with IPAH, the 4-year survival was 100% in patients with PAC of >2 mL/mmHg and <40% in those with PAC of <0.81 mL/mmHg (84). Interestingly, adding other clinical or hemodynamic variables collected in the study did not provide further prognostic value than that provided by PAC (84). In patients with systemic lupus erythematosus associated PAH, a PAC <1.39 mL/mmHg was associated with all-cause mortality and clinical worsening (87). In patients with PH-LHD, a PAC of <1.1 mL/mmHg was a better predictor of mortality than DPG, TPG, or PVR (88). Furthermore, a PAC of <2.15 mL/mmHg was an important predictor of mortality in patients with PH-LHD, both in patients with IpcPH or CpcPH (89).

Treatment for PAH with prostacyclin analogues (intravenous or inhaled) was associated with an improvement in PAC that was strongly influenced by the change in PVR (90). Treatment with the oral prostacyclin treprostinil also led to improvements in PAC in patients with PAH, as the PAC increased from 1.5 to 1.9 mL/mmHg at 24 weeks of treatment (91). Balloon pulmonary angioplasty improved PAC in patients with CTEPH from 1.03 to 1.64 mL/mmHg, a change that may have contributed to the concomitant improvement in functional capacity (92).

Pulmonary effective arterial elastance (Ea)

Ea is computed by calculating the ratio of RV end-systolic pressure (ESP) to SV. It is a comprehensive hemodynamic parameter that incorporates resistive, pulsatile, and passive components of total RV afterload. PVR and PAC do not incorporate impedance which is related to the vascular storage and blood inertia of the proximal pulmonary vessels.

In PH-LHD with heart failure with reduced ejection fraction or heart failure with preserved ejection fraction, investigators used sPAP in place of right ventricular end systolic pressure (RVESP) to calculate the elastance (93,94). The median Ea was 1.036 mmHg/mL and patients with values above the median had worse mortality. Ea and PAC were more strongly associated with RV dysfunction and were consistently better predictors of mortality than TPG and PVR in patients with PH-LHD. Interestingly, Ea and PAC remained predictive of mortality in a subgroup of patients with normal resistive

load (64).

RAP/PAWP

RAP/PAWP is another index that can serve to evaluate RV failure. As long as RV function is maintained, RAP remains lower than PAWP. When the RV starts failing, the RAP increases "out of proportion" to the PAWP, thus raising the RAP/PAWP ratio. Fluid overload and/or other organ dysfunction (left ventricular, kidney, and/or liver failure) would be expected to raise the RAP, but the RAP/PAWP ratio should remain <1 in the absence of RV failure.

In PAH, the RAP/PAWP ratio was a strong predictor of survival and performed better than RAP when not indexed for PAWP and other hemodynamic variables. A RAP/PAWP value of ≥1 provided the best combination of sensitivity and specificity (95). RAP/PAWP ratio is higher in precapillary PH and CpcPH as compared to IpcPH. A ratio of ≥1 was associated with smaller left atrial volume, decreased tricuspid annular plane systolic excursion (TAPSE), and a higher RV/left ventricle size ratio (96).

An increased RAP/PAWP ratio was associated with higher PVR, reduced RV function, and worse outcomes in patients with advanced systolic left heart failure (97). Similarly, a higher RAP/PAWP was associated with renal failure and mortality in acute decompensated systolic heart failure (98). In addition, RAP/PAWP ratio may help to identify patients at high risk of developing right ventricular failure and mortality after the implantation of a left ventricular assist device (99). RAP/PAWP ratio increased immediately following left ventricular assist device (LVAD) implantation, then decreased for a short period followed by a gradual increase in the long-term that may represent the change in the RV function over time (100).

Pulmonary artery pulsatility index (PAPi)

PAPi is an indirect measure of RV function and is defined as the ratio of PAPP to RAP [PAPi = (sPAP – dPAP)/RAP]. PAPi reflects the adaptive response of the RV to increased afterload (RV to pulmonary artery coupling) with implications for prognosis and survival (101,102). As previously described PAC = SV/(sPAP – dPAP); and by rearranging the terms, PAPP = SV/PAC. Based on this formula, the PAPP component in PAPi is affected by changes in SV and/or PVR (which has a hyperbolic relationship with PAC). In PAH, if the SV is maintained but the PVR is elevated, PAPP may not accurately reflect disease severity and hence PAPi is higher in PAH than in other conditions. As PAH progresses and the SV decreases, and RAP increases the PAPi would be lower.

PAPi was first described in 2012 in patients with acute right ventricular myocardial infarction and since then its use has expanded to advanced heart failure, cardiogenic shock, left ventricular assist device management, heart transplantation, and PAH (103-107). In PAH, a lower PAPi (<5.3) at diagnosis was associated with greater age, lower sPAP, higher mean RAP (mRAP), and higher mortality despite age stratification; an association predominantly driven by the mRAP (108). In another PAH study, patients with a lower PAPi (median 5.8) had worse survival in a multivariable model (101).

Right ventricular systolic work index (RVSWI)

RVSWI is used to quantify the amount of work required by the RV for ejecting blood in each cardiac cycle when adjusted for BSA. RVSWI is calculated as (mPAP – mRAP) × SVI × 0.0136. Hence, RVSWI takes into consideration both the pressure and SV of the RV. As the RV adapts to increased PA pressures in PH, while maintaining an adequate SVI, the RVSWI increases. In contrast, as the disease progresses, RV-arterial uncoupling occurs, and therefore the RVSWI decreases (109,110). However, a lower RVSWI may also indicate a reduction of pulmonary pressures through the effect of therapeutic agents that may lower the pulmonary pressures without pronounced increases in SVI, making the interpretation of the RVSWI challenging when used in isolation.

In patients with PAH and CTEPH, a lower RVSWI (<19.7 g·m/m^2/beat) was associated with a higher incidence of heart failure related deaths or readmissions (111). RVSWI was a predictor of mortality in patients with idiopathic or heritable PAH (111). Interestingly, RVSWI was lower in heritable PAH than IPAH, suggesting a disproportionate RV dysfunction in the former group (112). RVSWI was lower (despite similar PVR) in patients with PAH associated with connective tissue disease (mostly SSc or mixed connective tissue disease) when compared with PAH due to other etiologies (mostly idiopathic or associated with congenital heart disease) (14.5 *vs.* 20.4 g·m/m^2/beat), suggesting an intrinsic RV dysfunction in certain PAH etiologies that are linked to a lower survival (113). RVSWI of <5 g·m/m^2/beat correlated with worse outcomes (death, ventricular assist device implantation, or heart transplantation) among patients with advanced heart failure undergoing evaluation

for a heart transplant (114).

PV loops

The gold standard assessment of RV function is done by determining pressure-volume loops that allow a meticulous evaluation of the RV-pulmonary artery coupling. This procedure assesses how efficient the RV function is transferred as energy to the pulmonary vascular load (115,116). It is described by the ratio of end systolic elastance (Ees) over Ea (Ees/Ea). Ees is a measure of ventricular contractility that can be estimated by the ratio of end systolic pressure (ESP) to end systolic volume (ESV) (Ees = ESP/ESV). Pulmonary vascular load is estimated by the Ea derived from ESP divided by SV (Ea = ESP/SV). In PH, as the RV pressure rises throughout ejection with peaking at or near end-systole, the ESP is better approximated by systolic PAP and not mPAP. In the absence of direct ESP measurement, one can cautiously estimate it by the equation ESP = 1.65 × mPAP – 7.79 (117,118).

An efficient energy use or optimal RV-arterial coupling corresponds to an Ees/Ea ratio of 1.5–2 (109,119). Interestingly the shapes of the PV loops may provide information, while a rounder shape is normal, trapezoid and notched PV loops had the lowest Ees/Ea ratio (120,121). Different methods are used to determine the RV-arterial coupling including invasive methods (single beat or multiple beat measurements of Ees) as well as noninvasive methods (magnetic resonance imaging analysis) (122-125). The ratio of echocardiography-derived TAPSE and pulmonary arterial systolic pressure (PASP) may provide a noninvasive estimation of the RV-arterial coupling in PAH (126). A low TAPSE/PASP ratio (<0.19 mm/mmHg) is associated with overall mortality in patients with PAH, even when adjusted by clinical covariates and traditional echocardiographic and hemodynamic indicators (127).

Patients with PAH and CTEPH have decreased Ees/Ea ratios when compared with controls (123,124,128,129). The functional RV systolic adaptation was estimated by a simplified approach using SV/end-systolic volume ratio ("volume method") and demonstrated to be an independent predictor of survival when controlled for traditional hemodynamic determinations (RAP, mPAP, SV) (95). Interestingly, during exercise, patients with PH had an increase in Ea without changes in Ees, leading to a decreased ratio when compared to controls (29). While RV-pulmonary artery uncoupling usually occurs at the later stages of the disease; exercise may help unmask abnormalities in the RV adaptation at an earlier stage (116,130). Hence, pressure-volume loops can provide a wealth of information, the challenge however lies in the measurement.

Conclusions

The hemodynamic assessment of PH is challenging because there are many factors at play between the RV and the PA circulation. A variety of indices measuring different aspects of the RV-PA system provide valuable information in patients with PH; nevertheless, more needs to be done to identify and validate comprehensive hemodynamic indices that allow a thorough evaluation of the different types of PH with the goal of making an earlier diagnosis, understanding the specific hemodynamic compromise, assessing treatment response, and providing reliable prognostic information.

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