CHEST

Systolic and Mean Pulmonary Artery Pressures
Are They Interchangeable in Patients With Pulmonary Hypertension?

Denis Chemla, MD; Marc Humbert, MD; Olivier Sitbon, MD; David Montani, MD; and Philippe Hervé, MD

Pulmonary hypertension (PH) is a common complication of numerous diseases, including left-sided heart diseases and chronic lung diseases and/or hypoxia, where PH is associated with exercise limitation and a worse prognosis. Other forms of PH include pulmonary arterial hypertension (PAH), chronic thromboembolic PH (CTEPH), and PH with unclear multifactorial mechanisms. Over the past decade, it has been documented that systolic pulmonary artery pressure (sPAP) may help estimate mean pulmonary artery pressure (mPAP) in adults with high accuracy and reasonably good precision (mPAP = 0.61 sPAP + 2 mm Hg). This strong linear relationship between sPAP and mPAP was unexpected from a classic physiologic point of view. Consistent results have been obtained from independent teams using either high-fidelity micromanometer-tipped PA catheters or fluid-filled catheters. Overall, the strong link between sPAP and mPAP has been documented over a wide range of PAPs, heart rate, cardiac output, wedge pressure, and causes of PH, during changes in posture and activity, and irrespective of patient's sex, age, and BMI. A review of available invasive data confirms that patients with CTEPH and idiopathic PAH matched for their mPAP exhibit essentially similar sPAP. Pressure redundancy may be explained by the dependence of PA compliance upon mPAP. The 25 mm Hg threshold used to define PH accurately corresponds to an sPAP of 38 mm Hg. Although the limits of the echocardiographic estimation of sPAP are widely documented, results from invasive studies may furnish an evidence-based sPAP-derived mPAP value, potentially useful in the multiparameter echocardiographic approach currently used to diagnose and follow patients with PH.

CHEST 2015; 147(4):943-950

ABBREVIATIONS: CTEPH = chronic thromboembolic pulmonary hypertension; dPAP = diastolic pulmonary artery pressure; iPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure; Pej = pulmonary artery mean ejection pressure; PH = pulmonary hypertension; Pnotch = pulmonary artery notch pressure; sPAP = systolic pulmonary artery pressure

Pulmonary hypertension (PH) is defined on right-sided heart catheterization as resting mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg. In adults, PH is a common complication of numerous diseases, including left-sided heart diseases and chronic lung diseases and/or hypoxia, where PH is associated with exercise limitation and a worse prognosis.[1,2] Other forms of PH include pulmonary arterial hypertension (PAH), chronic thromboembolic PH (CTEPH), and PH with

Manuscript received July 17, 2014; revision accepted October 7, 2014.

AFFILIATIONS: From the Faculté de Médecine, Universite Paris-Sud, Le Kremlin Bicêtre; AP-HP, Services des Explorations Fonctionnelles et de Pneumologie, Hôpital Bicêtre, Le Kremlin Bicêtre; and Inserm UMR_S999, Centre Chirurgical Marie Lannelongue, Le Plessis-Robinson, France.

CORRESPONDENCE TO: Denis Chemla, MD, Service des Explorations Fonctionnelles, Broca 7, Hôpital de Bicêtre, 78 rue du Général Leclerc, 94 275 Le Kremlin Bicêtre, France; e-mail: denis.chemla@bct.aphp.fr

DOI: 10.1378/chest.14-1755

unclear multifactorial mechanisms.[3] Thus, there is an urgent need to noninvasively diagnose PH in the majority of patients. In this respect, the point/counterpoint editorials by Rudski[4] and Rich[5] published in *CHEST* on this topic is especially welcomed. Both Rudski[4] and Rich[5] must be congratulated for having elegantly supported the "yes" and "no" answers, respectively. Although a multiparameter echocardiographic approach has been rightly advocated by numerous authors to rule in or rule out PH diagnosis,[4-8] the accurate estimation of systolic pulmonary artery pressure (sPAP) remains at the center of the debate.[4,5]

sPAP is currently estimated from both the continuous Doppler maximum velocity of tricuspid regurgitation and the estimated right atrial pressure, assuming that sPAP and right ventricular peak systolic pressure are equal. Because PH is defined by using mPAP, Rudski[4] discussed the corresponding sPAP threshold. This appears to be a difficult task. It was first indicated that if mPAP is two-thirds diastolic pressure plus one-third systolic pressure, and if one assumes an mPAP of 25 mm Hg and a pulmonary artery diastolic pressure of 15 mm Hg, this would correlate with an sPAP of about 45 mm Hg.[4] It was acknowledged that many authors use the previously proposed upper limit of normal sPAP of >30 to 35 mm Hg.[9] Two consensus documents were also quoted, indicating that "In the absence of other potential etiologies of PH, such as left heart disease or advanced lung disease, an estimated RV systolic pressure of greater than 40 mm Hg generally warrants further evaluation in the patient with unexplained dyspnea"[6] and that "If the estimated SPAP is >35 to 40 mm Hg, stronger scrutiny may be warranted to determine if PH is present, factoring in other clinical information."[7]

The cutoff values applied to large populations must be evidence based. In this respect, this commentary has two aims: (1) to summarize the main recent findings favoring that mPAP and sPAP are strongly related and provide essentially redundant estimates of pulmonary circulation, and (2) to discuss the potential implications for PH pathophysiology and diagnosis.

mPAP and sPAP Are Strongly Related in Most Forms of PH

In 2004, our group demonstrated that mPAP and sPAP were related through a strong linear relationship in adult patients prospectively studied by using a high-fidelity micromanometer-tipped pulmonary artery (PA) catheter,[10] according to the following equation:

$$mPAP = 0.61\,sPAP + 2\ mm\,Hg$$

Results were obtained in 31 subjects, namely nine control subjects, nine subjects with PAH, seven subjects with CTEPH, and six patients with postcapillary PH. This observation has been further confirmed by using both micromanometer-tipped[11-13] and fluid-filled[14,15] PA catheters (Table 1).

A strong linear relationship between mPAP and sPAP has been documented by Syyed et al[11] in 65 subjects (of whom 47 had PH of various causes) who were retrospectively studied by micromanometer-tipped PA catheters. A high degree of accuracy was maintained following changes in posture and activity.[11] A retrospective analysis of all studies having documented pulmonary artery pressure (PAP) by using micromanometer-tipped PA catheter measurements involved a total of 166 individuals, of whom 58% had PH caused by many different conditions. It confirmed high accuracy (0 mm Hg mean bias) and reasonably good precision (3 mm Hg SD of the bias) of our empirical mPAP estimate, with sPAP explaining 98% of mPAP variance.[12] The strong linear relationship between mPAP and sPAP has also been documented in patients with precapillary PH performing moderate to vigorous supine cycling.[13]

Two large-scale studies using fluid-filled PA catheters have documented the mPAP vs sPAP empirical relationship in patients with left-sided heart disease.[14,15] The corresponding equation was identical[14] or remarkably similar[15] to ours[10] (Table 1), although signal distortions are known to be unavoidable when using conventional catheters for pulsatile pressure analysis. Overall, the strong link between mPAP and sPAP has been documented over a wide range of mPAPs, diastolic PAP (dPAP), heart rate, cardiac output, PA wedge pressure, and causes of PH and irrespective of patient's sex, age, and BMI.[10-15]

Thus, in an attempt to predict mPAP, one pressure is enough, namely sPAP (single-pressure model). Thus, one does not necessarily need to know the dPAP value and then apply either the classic rule of thumb (two-thirds dPAP + one-third sPAP) or the proposed geometric mean of sPAP and dPAP[12] (dual-pressure models). From a classic physiologic point of view, this link between the steady and the pulsatile components of PA pressure was unexpected, and such a link is less

TABLE 1] Empirical Formulas Describing the Linear Relationship Between mPAP and sPAP

mPAP Formula	No.	r^2	Mean bias ± SD, mm Hg	Sex, M/F	Age, y	PH/No PH	Diagnosis	mPAP Range, mm Hg	Reference
High-fidelity PA pressure catheters									
0.61 sPAP + 2 mm Hg	31			23/8	NA	22/9		10-78	10
Test sample	16	0.98	…				5C, 4PAH, 3 PH-HD, 4CTEPH,		
Validation sample	15	…	0 ± 2				4C, 5PAH, 3 PH-HD, 3CTEPH,		
0.65 sPAP + 0.55 mm Hg	65			28/37	59 ± 13	47/18	12C, 29 PAH, 4 PH-HD, 13 PH-LD/H, 7 CTEPH	10-82	11
Test sample	65	0.98	…						
Validation subgroup under altered hemodynamic conditions	51	…	0.5 ± 3.4						
0.61 sPAP + 2 mm Hg	166	0.98	0.0 ± 3.2	82/84	49 ± 16	96/70	44C, 54 PAH, 41 PH-HD, 13 PH-LD/H, 14 CTEPH	9-82	12
Fluid-filled PA pressure catheters									
0.61 sPAP + 1.95 mm Hg	307			168/139	58 ± 15	NA	NA (mainly HD)		14
Test sample	198	0.90	…					10-80[a]	
Validation sample	109	…	1.2 ± 2.9					…	
0.615 sPAP + 3 mm Hg	463	0.86	…	340/123	NA	337/126	126 HPREF-no PH, 337 HPREF with PH	10-75[a]	15

C = control subjects; CTEPH = chronic thromboembolism pulmonary hypertension (group 4); F = female; HPREF = chronic heart failure of reduced left ventricular ejection fraction; M = male; mPAP = mean pulmonary artery pressure; NA = not indicated or impossible to extrapolate from the subgroup data; No PH = mean pulmonary artery pressure < 25 mm Hg; PA = pulmonary artery; PAH = pulmonary arterial hypertension (group 1); PH = pulmonary hypertension (ie, mPAP ≥ 25 mm Hg); PH-HD = pulmonary hypertension due to heart diseases (group 2); PH-LD/H = pulmonary hypertension due to lung diseases/hypoxia (group 3); sPAP = systolic pulmonary artery pressure.

[a]Indicates a value estimated from the corresponding figure in the article.

marked as compared with the systemic counterpart.[10] The strong linear relationship between mPAP and sPAP may be viewed as a new property of pulmonary circulation. Before discussing the clinical and pathophysiological implications, some special patient populations must be individualized.

mPAP and sPAP in CTEPH

A fluid-filled pressure catheter study has suggested that our empirical equation applies in distal (nonoperable) CTEPH, whereas it has to be adapted in proximal (operable) CTEPH given higher sPAP than that predicted at a given mPAP.[16] However, the reanalysis of the only two previous studies having documented individual PAP values with micromanometer-tipped pressure catheters in CTEPH[10,11] does not confirm this new proposal.[17] Furthermore, if one applies our equation to the largest hemodynamic database of 1,000 patients with CTEPH undergoing pulmonary endarterectomy[18] and whose mPAP is 46.1 ± 11.4 mm Hg and sPAP is 75.7 ± 18.8 mm Hg, the mPAP is accurately predicted by the empirical equation (48.2 mm Hg), with a 2.1-mm Hg mean bias (4.5%), which seems clinically acceptable. The alternative formula proposed[16] performed less well (mean bias of 3.8 mm Hg, 8.2%). Although the possibility that some patients with markedly increased wave reflection may significantly deviate from our model cannot be excluded, especially when fluid-filled PA catheters are used,[17] it may be concluded from the above arguments that the empirical equation applies reasonably well in CTEPH. A similar conclusion was reached by Syyed et al,[11] who have compared the sPAP vs mPAP relationship between patients with and without CTEPH and concluded that "it was clear that in qualitative terms there was little difference."

Applying the same empirical formula to all forms of PH, including CTEPH, may appear at variance with the widely admitted notion that PAP pulsatility[19,20] and wave reflection[21,22] are increased in CTEPH, especially as compared with patients with idiopathic PAH (iPAH). Because the PA pressure pulsatility necessarily increases with mPAP because of the pressure-dependent decreases in PA compliance, sPAP must be compared in PH patient groups having similar mPAP. This hampers the rationale analysis of previous hemodynamic studies with marked mPAP differences between patient groups.[19,20] To our knowledge, four fluid-filled pressure catheter studies performed in patients with CTEPH and iPAH allow comparing their sPAP at similar mPAP levels.[16,23-25] The four studies have documented similar sPAP in the two groups (Table 2). The same was also confirmed by our reanalysis of the only two micromanometer-tipped PA catheter studies available (Table 2). Thus, against general belief, it may be concluded that patients with CTEPH and iPAH matched for mPAP exhibit essentially the same sPAP.

TABLE 2] Hemodynamic Data From Studies Having Used Fluid-Filled PA Catheters and High-Fidelity Pulmonary Artery Pressure Catheters in CTEPH and in iPAH

Data	CTEPH	iPAH	*P* Value
Fluid-filled PA catheters			
Tanabe et al[23]/2001			
No.	32	18	…
sPAP	83 ± 17	88 ± 20	NS
mPAP	46 ± 9	54 ± 13	NS
Ghio et al[24]/2002			
No.	11	31	…
sPAP	76.4 ± 26.2	83.4 ± 22.1	NS
mPAP	44.8 ± 15.3	52.4 ± 15.8	NS
Palecek et al[25]/2011			
No.	52	43	…
sPAP	89 ± 19	82 ± 22	NS
mPAP	55 ± 11	55 ± 15	NS
MacKenzie Ross et al[16]/2013			
No.	53	59	…
sPAP	85.2 ± 19.0	81.8 ± 21.0	NS
mPAP	48.8 ± 10.6	49.9 ± 13.6	NS
High-fidelity PA catheters			
Chemla et al[10]/2004			
No.	7	9	…
sPAP	94 ± 16	90 ± 15	NS
mPAP	59 ± 10	59 ± 9	NS
Syyed et al[11]/2008			
No.	6	9	…
sPAP	83 ± 9	93 ± 27	NS
mPAP	55 ± 6	62 ± 15	NS
All data			
No.	13	18	…
sPAP	89 ± 14	92 ± 21	NS
mPAP	57 ± 9	60 ± 12	NS

Fluid-filled PA catheter data and statistics are as published. High-fidelity PA catheter data and statistics have been calculated based on the published individual PAP values, and only patients with mPAP ≥ 25 mm Hg were included in the analysis. PAPs are mean ± SD. iPAH = idiopathic pulmonary arterial hypertension; NS = not significant. See Table 1 legend for expansion of other abbreviations.

When observed, a higher PA pulse pressure in CTEPH may be mainly explained by lower dPAP, a point that deserves further confirmatory studies.

mPAP and sPAP in Acute Pulmonary Embolism

In patients with acute pulmonary embolism, PH is often associated with a "ventricularization" of the PAP curve (ie, disproportionately low dPAP), especially in cases of massive proximal pulmonary embolism.[26,27] This is also observed in patients with pulmonary valve insufficiency. It has been suggested that differences in the dPAP level may well impact the accuracy of our empirical formula, especially when pulmonary blood flow conditions vary.[28] However, if one reanalyzes the hemodynamic database of individual sPAP and mPAP values of patients with acute massive pulmonary embolism published in the seminal article by Miller and Sutton,[29] mean bias between the mPAP predicted from sPAP (25.4 ± 4.3 mm Hg) and the mPAP measured (26.6 ± 4.7 mm Hg) was -1.2 ± 2.7 mm Hg. This suggests accurate sPAP estimation in patients with acute pulmonary embolism, a point that deserves to be confirmed in further studies.

mPAP and sPAP in Young Subjects

The strong linear link between sPAP and mPAP has been confirmed in young subjects with congenital heart diseases studied by using fluid-filled pressure catheters.[30,31] Although the empirical formula was accurate (mean bias = 0 mm Hg), its low precision (SD of the bias = 6 mm Hg) favors the use of empirical formulas relying on sPAP and dPAP (two-pressure model) in children with congenital heart diseases.[31]

Implication for the Noninvasive Estimation of mPAP

Overall, what can be inferred from these observations? To quote the French philosopher and scientist Blaise Pascal (1623-1662): "When we do not know the truth of a thing, it is of advantage that there should exist a common error which determines the mind of man."

Up to now, in Doppler studies, the sPAP threshold used as an estimate of an mPAP of 25 mm Hg is variable, as discussed in the introduction. Because the cutoff values applied to large populations must be evidence based, results from invasive studies performed over the past decade may be helpful. Using our empirical equation,[10] and the slightly modified equation proposed by Syyed et al[11] as well, an mPAP of 25 mm Hg corresponds to an sPAP of 38 mm Hg with 0 mm Hg mean bias, as previously discussed.[10,32]

Our results must be carefully used to rule in or rule out PH diagnosis with Doppler echocardiography, as a fixed sPAP threshold with a "yes" or "no" answer certainly does not apply.[4,5] It is outside the scope of the present article to comment on the other aspects of sPAP Doppler calculation, advantages, and drawbacks.[4,5] The accuracy of the sPAP-derived mPAP estimate will mathematically depend on the accuracy of the sPAP estimate, and we share the various remarks made by Rudski[4] and Rich[5] concerning the widely documented limits and uncertainty of echocardiographic sPAP estimates. A multiparameter echocardiographic approach must be favored,[4-8] which includes sPAP/mPAP estimation, the analysis of RV wall thickness, cavity dimension and fractional area change, tricuspid annulus plane systolic excursion, curvature of the interventricular septum, and mean velocity and acceleration time of PA flow, among others.

Finally, the redundancy between sPAP and mPAP has been shown useful to cross-check the Doppler PAP database and to improve the estimation of pulmonary vascular resistance in adults.[33,34] The mPAP has been estimated from Doppler-derived sPAP obtained both at rest and on exercise.[35]

Pathophysiologic Hypotheses

The mPAP reflects the steady component of the circuit and the functional status of the distal (resistive) pulmonary vasculature.[36-38] On the other hand, for a given mPAP, sPAP relates to the pulsatile component of the circuit, which includes the characteristics of right ventricular ejection and the characteristics of the proximal (elastic) pulmonary arteries and wave reflections.[21,38,39] Therefore, the fact that mPAP and sPAP may be used interchangeably to study pulmonary circulation is not intuitive. From a phenomenological point of view, it has been proposed that the PAP curve may slightly deviate from a perfect parabolic pressure curve, where mean pressure value is 0.67 peak value.[12] As far as physiologic modeling is concerned, it is admitted that the steady and pulsatile components of PA load are necessarily coupled, as PA compliance (1/PAstiffness) decreases when the mPAP increases.[21,36,40] In chronically pulmonary hypertensive calves, major changes in elasticity and right ventricular pulsatile load are primarily due to an increase in mPAP, whereas the increases in PA wall thickness do not separately produce any measurable changes in arterial distensibility.[40] This may suggest that the prevailing mPAP has a greater influence on PA compliance/stiffness than the disease-related changes in vascular wall properties.[10,11,22]

Pulmonary circulation may be characterized using a two-element windkessel model composed of pulmonary vascular resistance (R) and total pulmonary arterial compliance (C) disposed in parallel, with C being most often estimated by using the stroke volume over PA pulse pressure ratio.[39] It has been suggested that the time constant of the pulmonary arterial windkessel (RC = R × C product) was constant in health and diseases.[39] It has been hypothesized that the empirical equation relating sPAP and mPAP may result from the RC constancy.[39,41,42] However, studies have challenged the RC constancy paradigm.[43-46] Patients with high PA wedge pressure exhibit shorted RC values.[43,44] Because our empirical equation is observed irrespective of PA wedge pressure,[10-14] this may well imply that it applies irrespective of the RC value. Further studies are needed to solve this issue.

Implications for Pulmonary Circulation

Mean PAP is a flow-dependent variable. Despite well-known limitations of the model,[36-38,47] the mPAP-cardiac output linear relationship is the most popular way to describe pulmonary circulation. Studies from our group have documented major redundancy between mPAP on the one hand and sPAP,[10,12] PA mean ejection pressure (Pej = 1.25 mPAP),[48] and PA end-ejection pressure or notch pressure (Pnotch = mPAP)[49] on the other hand. Such pressure redundancy has been also documented on exercise[11,13,48] and during the Valsalva maneuver.[49] Thus, it may be hypothesized that a single pressure-powered function is reflected in any of these four pressures (mPAP, sPAP, Pej, Pnotch), all reflecting the steady component of arterial load. As a result, it may be kept in mind that there exists a family of pressure-flow relationships using any of these four pressures. Conceptually, each representation is similar, in that the abscissa is mean cardiac output and the ordinate is some representative measure of the steady pressure component opposing to flow (mPAP, sPAP, Pej, Pnotch). This approach may be useful to describe the steady-state, time-independent coupling between the ventricle and its load.[50] Both dPAP and PA pulse are also linearly related to mPAP,[10-13] with mPAP explaining approximately 90% of variance of the two pressures. However, the linear relationship appears slightly less strong, such that the small remaining part of dPAP and PA pulse pressure variance may be explained by mechanisms related to the pulsatile component of PA load.

Remaining Issues

Right-sided heart catheter is the gold standard technique for measuring mPAP and confirming PH.[51] However, it must be kept in mind that mPAP may change spontaneously, with the amount of variation (coefficient of variation) in mPAP averaging 8% over 6 h in patients with PH.[52] A small number of patients may deviate from our model, and thus there is also a need to increase the precision of the sPAP-derived mPAP estimate (ie, to decrease the SD of the bias). In this respect, it must be noted that both sPAP and mPAP values slightly depend upon the patient's age,[9,53,54] and the role of BMI has also been discussed.[9,54] Although the accuracy of our empirical equation has been documented irrespective of taking into account patient's clinical characteristics,[10-14] further studies are needed to test the hypothesis that refined empirical equations taking into account patient's age and BMI may increase the precision of the mPAP estimate. Finally, the sPAP vs mPAP relationship remains to be documented in patients with PH with unclear multifactorial mechanisms (group 5).[3]

Conclusions

The current recommendations mandate that confirmation of PH be made by right-sided heart catheterization. Over the past decade, numerous invasive studies have documented that sPAP and mPAP may be used interchangeably to study pulmonary circulation in adults (mPAP = 0.61 sPAP + 2 mm Hg), with high accuracy and reasonably good precision in patients with PH, including CTEPH (Table 3). Physiologic hypotheses to explain this relationship may involve the major

TABLE 3] Salient Points

Point
There is a strong linear relationship between sPAP and mPAP.
The relationship has been documented in adults over a wide range of mPAP, dPAP, heart rate, cardiac output, PA wedge pressure, and causes of PH, and irrespective of patient's sex, age, and BMI.
An accurate and precise estimate of mPAP may be obtained (mPAP = 0.61 sPAP + 2 mm Hg).
sPAP mainly reflects the steady component of pulmonary arterial load.
Patients with CTEPH and iPAH matched for mPAP exhibit essentially the same sPAP.
The prevailing mPAP has a greater influence on PA compliance than the disease-related changes in vascular wall properties.
The 25 mm Hg threshold used to define PH corresponds to an sPAP of 38 mm Hg.
Further invasive studies are needed to improve the precision of the sPAP-derived mPAP estimate.

dPAP = diastolic pulmonary artery pressure. See Table 1 and 2 legends for expansion of other abbreviations.

dependence of PA compliance upon mPAP. The 25 mm Hg threshold used to define PH corresponds to an sPAP of 38 mm Hg. Further invasive studies are needed to improve the precision of the sPAP-derived mPAP estimate.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1. Vachiéry JL, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol*. 2013;62(suppl 25): D100-D108.
2. Seeger W, Adir Y, Barberà JA, et al. Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol*. 2013;62(suppl 25): D109-D116.
3. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(suppl 25):D34-D41.
4. Rudski LG. Point: can echocardiographic estimates of pulmonary systolic pressures be relied upon to accurately make the diagnosis of pulmonary hypertension? Yes. *Chest*. 2013;143(6):1533-1536.
5. Rich JD. Counterpoint: can echocardiographic estimates of pulmonary systolic pressures be relied upon to accurately make the diagnosis of pulmonary hypertension? No. *Chest*. 2013;143(6): 1536-1539.
6. McLaughlin VV, Archer SL, Badesch DB, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53(17):1573-1619.
7. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685-713.
8. Bech-Hanssen O, Karason K, Rundqvist B, Bollano E, Lindgren F, Selimovic N. Can pulmonary hypertension and increased pulmonary vascular resistance be ruled in and ruled out by echocardiography? *J Am Soc Echocardiogr*. 2013;26(5):469-478.
9. Lam CS, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-associated increases in pulmonary artery systolic pressure in the general population. *Circulation*. 2009;119(20):2663-2670.
10. Chemla D, Castelain V, Humbert M, et al. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest*. 2004;126(4):1313-1317.
11. Syyed R, Reeves JT, Welsh D, Raeside D, Johnson MK, Peacock AJ. The relationship between the components of pulmonary artery pressure remains constant under all conditions in both health and disease. *Chest*. 2008;133(3):633-639.
12. Chemla D, Castelain V, Provencher S, Humbert M, Simonneau G, Hervé P. Evaluation of various empirical formulas for estimating mean pulmonary artery pressure by using systolic pulmonary artery pressure in adults. *Chest*. 2009;135(3):760-768.
13. Chemla D, Castelain V, Hoette S, et al. Strong linear relationship between heart rate and mean pulmonary artery pressure in exercising patients with severe precapillary pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2013;305(5):H769-H777.
14. Steckelberg RC, Tseng AS, Nishimura R, Ommen S, Sorajja P. Derivation of mean pulmonary artery pressure from noninvasive parameters. *J Am Soc Echocardiogr*. 2013;26(5):464-468.
15. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail*. 2013;1(4):290-299.
16. MacKenzie Ross RV, Toshner MR, Soon E, Naeije R, Pepke-Zaba J. Decreased time constant of the pulmonary circulation in chronic thromboembolic pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2013;305(2):H259-H264.
17. Chemla D, Castelain V, Herve P. Letter to the editor: "Pulsatile pulmonary artery pressure: are fluid-filled catheters accurate in pulmonary hypertension?" *Am J Physiol Heart Circ Physiol*. 2013;305(11):H1680-H1681.
18. Madani MM, Auger WR, Pretorius V, et al. Pulmonary endarterectomy: recent changes in a single institution's experience of more than 2,700 patients. *Ann Thorac Surg*. 2012;94(1):97-103.
19. Nakayama Y, Nakanishi N, Sugimachi M, et al. Characteristics of pulmonary artery pressure waveform for differential diagnosis of chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol*. 1997;29(6):1311-1316.
20. Nakayama Y, Nakanishi N, Hayashi T, et al. Pulmonary artery reflection for differentially diagnosing primary pulmonary hypertension and chronic pulmonary thromboembolism. *J Am Coll Cardiol*. 2001;38(1):214-218.
21. Castelain V, Hervé P, Lecarpentier Y, Duroux P, Simonneau G, Chemla D. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol*. 2001;37(4):1085-1092.
22. Naeije R, Huez S. Reflections on wave reflections in chronic thromboembolic pulmonary hypertension. *Eur Heart J*. 2007;28(7):785-787.
23. Tanabe N, Okada O, Abe Y, Masuda M, Nakajima N, Kuriyama T. The influence of fractional pulse pressure on the outcome of pulmonary thromboendarterectomy. *Eur Respir J*. 2001;17(4):653-659.
24. Ghio S, Raineri C, Scelsi L, et al. Usefulness and limits of transthoracic echocardiography in the evaluation of patients with primary and chronic thromboembolic pulmonary hypertension. *J Am Soc Echocardiogr*. 2002;15(11):1374-1380.
25. Palecek T, Jansa P, Ambroz D, et al. Are pulmonary artery pulsatility indexes able to differentiate chronic pulmonary thromboembolism from pulmonary arterial hypertension? An echocardiographic and catheterization study. *Heart Vessels*. 2011;26(2):176-182.
26. Agustsson MH, Arcilla RA, Gasul BM, Bicoff JP, Nassif SI, Lendrum BL. The diagnosis of bilateral stenosis of the primary pulmonary artery branches based on characteristic pulmonary trunk pressure curves. A hemodynamic and angiocardiographic study. *Circulation*. 1962;26:421-427.
27. Morpurgo M, Marzegalli M, Casazza F. "Ventricularization" of the pulmonary artery pressure curve: a hemodynamic sign of proximal pulmonary embolism. *Cardiologia*. 1998;43(7):745-748.
28. Kothari SS. Estimating mean pulmonary artery pressure from systolic pressure: a caveat? *Chest*. 2008;134(5):1108.
29. Miller GA, Sutton GC. Acute massive pulmonary embolism. Clinical and haemodynamic findings in 23 patients studied by cardiac catheterization and pulmonary arteriography. *Br Heart J*. 1970;32(4):518-523.
30. Friedberg MK, Feinstein JA, Rosenthal DN. A novel echocardiographic Doppler method for estimation of pulmonary arterial pressures. *J Am Soc Echocardiogr*. 2006;19(5):559-562.
31. Chemla D, Lambert V, Losay J. Mean pulmonary artery pressure estimated from systolic and diastolic pulmonary artery pressure in children with congenital heart disease: an invasive study. *Pediatr Cardiol*. 2009;30(8):1137-1142.
32. Chemla D, Herve P. Derivation of mean pulmonary artery pressure from systolic pressure: implications for the diagnosis of pulmonary hypertension. *J Am Soc Echocardiogr*. 2014;27(1):107.
33. Aduen JF, Castello R, Daniels JT, et al. Accuracy and precision of three echocardiographic methods for estimating mean pulmonary artery pressure. *Chest*. 2011;139(2):347-352.
34. Bech-Hanssen O, Selimovic N, Rundqvist B, Wallentin J. Doppler echocardiography can provide a comprehensive assessment of right ventricular afterload. *J Am Soc Echocardiogr*. 2009;22(12): 1360-1367.

35. Naeije R, Huez S, Lamotte M, et al. Pulmonary artery pressure limits exercise capacity at high altitude. *Eur Respir J*. 2010;36(5): 1049-1055.

36. Milnor WR. *Hemodynamics*. Baltimore, MD: Williams & Wilkins; 1982.

37. Naeije R, Lipski A, Abramowicz M, et al. Nature of pulmonary hypertension in congestive heart failure. Effects of cardiac transplantation. *Am J Respir Crit Care Med*. 1994;149(4 pt 1):881-887.

38. Chemla D, Castelain V, Hervé P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. *Eur Respir J*. 2002;20(5):1314-1331.

39. Saouti N, Westerhof N, Postmus PE, Vonk-Noordegraaf A. The arterial load in pulmonary hypertension. *Eur Respir Rev*. 2010;19(117):197-203.

40. Zuckerman BD, Orton EC, Stenmark KR, et al. Alteration of the pulsatile load in the high-altitude calf model of pulmonary hypertension. *J Appl Physiol (1985)*. 1991;70(2):859-868.

41. Kind T, Faes TJC, Vonk-Noordegraaf A, Westerhof N. Proportional relations between systolic, diastolic and mean pulmonary artery pressure are explained by vascular properties. *Cardiovasc Eng Technol*. 2011;2(1):15-23.

42. Saouti N, Westerhof N, Helderman F, et al. Right ventricular oscillatory power is a constant fraction of total power irrespective of pulmonary artery pressure. *Am J Respir Crit Care Med*. 2010; 182(10):1315-1320.

43. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation*. 2012;125(2):289-297.

44. Tedford RJ. Determinants of right ventricular afterload (2013 Grover Conference series). *Pulm Circ*. 2014;4(2):211-219.

45. Chemla D, Creuzé N, Hoette S, et al. Relationship between the pulsatile and steady component of right ventricular aftertload in patients with precapillary pulmonary hypertension. A1899. Paper presented at: American Thoracic Society International Conference; May 16-21, 2014; San Diego, CA.

46. Hadinnapola C, Pepke-Zaba J, Toshner M. The time constant of the pulmonary circulation is not so constant. A4717. Paper presented at: American Thoracic Society International Conference; 2014; May 16-21, San Diego, CA.

47. Naeije R. Pulmonary vascular resistance. A meaningless variable? *Intensive Care Med*. 2003;29(4):526-529.

48. Chemla D, Castelain V, Zhu K, et al. Estimating right ventricular stroke work and the pulsatile work fraction in pulmonary hypertension. *Chest*. 2013;143(5):1343-1350.

49. Chemla D, Hébert JL, Coirault C, Salmeron S, Zamani K, Lecarpentier Y. Matching dicrotic notch and mean pulmonary artery pressures: implications for effective arterial elastance. *Am J Physiol*. 1996;271(4 pt 2):H1287-H1295.

50. Schroff SG, Weber KT, Janicki JS. Coupling of the left ventricle with the systemic arterial circulation. In: Nichols WW, O'Rourke MF, eds. *McDonald's Blood Flow in Arteries*. London, England: Arnold; 1990:343-359.

51. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013; 62(suppl 25):D42-D50.

52. Rich S, D'Alonzo GE, Dantzker DR, Levy PS. Magnitude and implications of spontaneous hemodynamic variability in primary pulmonary hypertension. *Am J Cardiol*. 1985;55(1):159-163.

53. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34(4):888-894.

54. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation*. 2001;104(23):2797-2802.