Effect of Acute Arteriolar Vasodilation on Capacitance and Resistance in Pulmonary Arterial Hypertension

John H. Newman, MD; Evan L. Brittain, MD; Ivan M. Robbins, MD; and Anna R. Hemnes, MD

BACKGROUND: Pulmonary vascular capacitance (PVC) is reduced in pulmonary arterial hypertension (PAH). In normal lung, PVC is largely a function of vascular compliance. In PAH, increased pulmonary vascular resistance (PVR) arises from the arterioles. PVR and PVC share pressure and volume variables. The dependency between the two qualities of the vascular bed is unclear in a state of intense vasoconstriction.

METHODS: We compared PVC and PVR before and during nitric oxide (NO) inhalation during right-sided heart catheterization in eight NO-responsive patients with PAH. NO only directly affects tone in parenchymal vessels.

RESULTS: During NO inhalation, pulmonary arterial systolic pressure decreased, 80 ± 20 SD to 48 ± 20 mm Hg, and stroke volume increased, 62 ± 19 mL to 86 ± 24 mL ($P < .01$). PVR dropped from 10 ± 4.4 Wood units to 4.7 ± 2.2 Wood units ($P < .012$), and PVC increased from 1.4 ± 1.1 mL/mm Hg to 3.2 ± 1.8 mL/mm Hg ($P < .018$). The magnitude of PVR drop was $57\% \pm 6\%$ and the decrease in $1/\text{PVC}$ was $54\% \pm 14\%$ ($P = \text{not significant}$).

CONCLUSIONS: In vasoresponsive PAH, PVC is a function of the pressure response of the vasoconstricted arterioles to stroke volume. Immediately upon vasodilation, the capacitance increases markedly. The compliance vessels are, thus, the same as the resistance vessels. The immediate reduction in pulmonary arterial pressure during NO inhalation suggests that large vessel remodeling is not a major contributor to systolic pressure in these patients.

CHEST 2015; 147(4):1080-1085

Manuscript received June 16, 2014; revision accepted September 29, 2014; originally published Online First October 23, 2014.

ABBREVIATIONS: CO = cardiac output; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; NO = nitric oxide; PA = pulmonary arterial; PAH = pulmonary arterial hypertension; PVC = pulmonary vascular capacitance; PVR = pulmonary vascular resistance; RC = product of resistance $\times$ capacitance; RV = right ventricular; SV = stroke volume

AFFILIATIONS: From the Pulmonary Circulation Center, Divisions of Pulmonary and Critical Care Medicine and Cardiology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.

FUNDING/SUPPORT: This work was supported by the Elsa S. Hanigan Fund; National Institutes of Health (NIH) National Heart, Lung, and

Blood Institute (NHLBI)[PO1 108800-01] (Drs Newman, Robbins, and Hemnes); and American Heart Association Fellow to Faculty Award [13FTF16070002] (Dr Brittain).

CORRESPONDENCE TO: John H. Newman, MD, Vanderbilt Medical Center, T 1219 Medical Center N, Nashville, TN 37232-2650; e-mail: john.newman@vanderbilt.edu

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-1461

Because flow is continuous in the pulmonary arteries throughout systole and most of diastole, the calculation of pulmonary vascular capacitance (PVC) is necessarily influenced by vascular resistance.¹⁻⁴ PVC is calculated as stroke volume (SV) divided by pulse pressure (pulmonary arterial systolic pressure [Pa sys] – pulmonary arterial diastolic pressure [Pa dias]), but the pulmonary arterial (PA) pressures are a function of both pulmonary vascular resistance (PVR), flow, and vascular compliance. The term “pulmonary vascular capacitance” is frequently used interchangeably with compliance. The most accurate assessment of capacitance in any elastic system requires stop-flow conditions, which are possible in vivo in airway measurements but not in the pulmonary arteries.^{5,6} In normal lung, where PVR is very low, calculated capacitance is a close approximation of intrinsic compliance, but in PA hypertension (PAH), the PVR (mean PA pressure [Pa mean] – wedge pressure [P wedge]/cardiac output [CO], and CO = SV × heart rate) may rise to 10-fold to 20-fold greater than normal.⁷⁻⁹ In PAH, both PA systolic and diastolic pressures rise, and are shared in calculation of PVC. Thus, although the calculation of PVC is used to infer pulsatile arterial compliance in pulmonary hypertension,¹⁰⁻¹⁴ it is not clear what the contribution of resistance is to the calculation.

Inhaled nitric oxide (NO) offers a method to determine the effects of rapid resistance changes on capacitance

because the vasodilator effects of inhaled NO are strictly limited to small arterioles into which alveolar gas diffuses. The purpose of this study was to use the unique effect of NO on vasoconstricted arterioles in severe PAH to better understand the interaction of PVR and PVC.^{15,16} The specific test was a comparison of the simultaneous changes in hemodynamic components of PVC and PVR before and during active vasodilation in patients breathing NO and to compare these changes to the product of resistance × capacitance (RC) time, the traditional measure of pressure decay in the pulmonary circulation during diastole.^{10-14,17-19}

RC time is a measure of the exponential decay in PA pressure over the time of diastole. In the pulmonary circulation, RC time is relatively constant among differing levels of PVR, pressures, and flow, suggesting structural linkage of the resistance and compliance elements.¹⁴ However, in conditions of pulmonary venous hypertension (elevated wedge pressure), the RC time curve is shifted down and to the left, probably due to passive dilation of the upstream bed.²⁰ In this situation, PVR might be lower at the same time that right ventricular (RV) stroke work is higher. In chronic thromboembolic pulmonary hypertension, RC time has been reported to be reduced compared with idiopathic PAH (IPAH), presumably due to higher pulse pressure in the pulmonary arteries proximal to the obstructive lesions.²¹ Thus, RC time is not invariable, and further delineation is warranted.

Materials and Methods

We used hemodynamic data from patients evaluated in the Vanderbilt Pulmonary Vascular Center. These data have been partially reported in other papers but this analysis has not previously been made.^{22,23} We show data on > 157 patients confirming that our results are similar to published studies.^{13,14,17} This study was approved by the institutional review board at Vanderbilt University Medical Center (institutional review board #130268). Patients underwent right-sided heart cardiac catheterization for the evaluation of pulmonary hypertension. We used published guidelines to determine the presence, severity, and etiology of pulmonary hypertension.^{8,9} Each of the patients met the diagnostic classification of PAH, with mean PA pressure > 25 mm Hg and pulmonary wedge pressure < 15 mm Hg.^{8,9} Catheterization included direct measurements of pressure in the right atrium, right ventricle, pulmonary artery, and in the balloon wedge position. Wedge pressure was measured at end-expiration. CO was measured by thermodilution or the Fick equation which assumed an oxygen consumption based on body weight. After baseline measurements at rest were stable, NO was given 40 parts per million by mask, and measurements were remade after 5 to 10 min of breathing with stable pressures. NO usually acts within seconds in vasoresponsive patients. Vasodilator response was defined as a reduction in mean PA pressure of at least 10 mm Hg to a value of 40 mm Hg or less without a decrease in CO.⁸ All tracings were reviewed and verified by one or more of the authors as a matter of our clinical practice.

Calculations

PVR was calculated as Pa mean – P wedge, divided by CO (PVR = Pa mean – P wedge/CO). PVC was calculated as SV in milliliters

(calculated as CO/heart rate [HR])/Pa sys – Pa dias. The mathematical relationship in the multiplication of PVC × PVR is known as RC time and is shown.

Pulmonary Vascular Capacitance × Pulmonary Vascular Resistance

$$\frac{\text{Stroke Volume (SV)}}{\text{Pa sys} - \text{Pa dias}} \times \frac{\text{Pa mean} - \text{P wedge}}{\text{Cardiac Output: (SV} \times \text{HR)}} \quad (1)$$

Thus, PVC × PVR = RC time

$$\frac{1}{\text{Pa sys} - \text{Pa dias}} \times \frac{\sim (0.62 \times \text{Pa sys}) - \text{P wedge}}{\text{HR (in beats/s)}} \quad (2)$$

Pa mean is PA diastolic plus one-third of the difference between Pa sys and Pa dias and is reliably about 62% of the PA systolic pressure.²⁴ Thus, except for heart rate, the two calculations are very similar and are ordinarily nearly the inverse of each other. It might be expected in the normal circulation that the product be close to one.

We compared PVC and PVR before and during NO inhalation in the eight patients who had marked acute vasodilator responses during cardiac catheterization. The responses were compared by a paired, non-parametric Wilcoxon-signed rank test. About 5% to 7% of patients with pulmonary hypertension have large responses to vasodilators.²⁵ We multiplied PVC × PVR (RC time) for each patient and plotted the products. The statistical test for this simple multiplication is a single sample, 1-tailed *t* test.

Results

To show that our hemodynamic data are the same as in previously published articles on RC time, we show the diagnostic data of the 157 patients in the parent cohort in Table 1; the hemodynamic variables of the group are shown in Table 2. This cohort is weighted toward IPAH and heritable PAH (HPAH), two entities that are clearly a consequence of pulmonary microvascular obstruction. The patients had severe PAH, with a mean pressure of 50.1 ± 11.2 mm Hg and PVR of 10.2 ± 4.4 Wood units, similar to previously published registries.⁷⁻⁹ Functional status was weighted toward severe dysfunction, with a mean of 2.8, close to a World Health Organization 3.0 which implies significant limitation in activities of daily living.^{8,9} The plot of RC time for each of the 157 patients is shown in Figure 1. The hyperbolic relationship is similar to that of previously published cohorts.^{12,13,24,26} PVC is higher when PVR is lower, and PVC is very low when PVR is very high in a curvilinear, inverse relationship.

The hemodynamic variables in eight vasodilator-responsive patients before and during NO inhalation at a single cardiac catheterization are shown in Table 3, and their positions on the RC time plot are shown as open circles in Figure 1. Pressure and volume variables responsible for RC time are graphically shown in Figure 2. Systolic PA pressure decreased from 80 ± 20 mm Hg to 48 ± 20 mm Hg, stroke volume increased from 62 ± 19 mL to 86 ± 24 mL, and heart rate decreased from 78 ± 15 beats/min to 65 ± 16 beats/min (all $P < .01$). PA pulse pressure decreased from 47 ± 13 mm Hg to

TABLE 2] Variables of 157 Patients With PAH

Variable	Data
Heart rate, beats/min	76.5 ± 14
Systolic BP	125 ± 19
Diastolic BP	80 ± 13
Right atrial pressure	7.5 ± 4.5
PA systolic pressure	80.9 ± 18
PA diastolic pressure	33.6 ± 9
PA mean pressure	50.1 ± 11.2
P wedge pressure	8.9 ± 3.4
Cardiac output, L/min	4.5 ± 1.5
Cardiac index, L/BSA/min	2.4 ± 0.8
PVR, Wood units	10.2 ± 5.0
PA Hgb saturation, %	65.6 ± 8.9

All pressures in mm Hg. Data are expressed as means ± 1 SD. BSA = body surface area; Hgb = hemoglobin; PA = pulmonary arterial; PVR = pulmonary vascular resistance in mm Hg/L/min. See Table 1 legend for expansion of other abbreviation.

31 ± 16 mm Hg. Mean PA pressure decreased 44% from mean 49.5 ± 13 mm Hg to 27.7 ± 9 mm Hg, and PVR fell 57% from 9.9 to 4.7 Wood units. The inverse of calculated capacitance (elastance) decreased $54\% \pm 14\%$. There was a significant reduction in heart rate with an increase in SV. These changes are all presumably a consequence of reduction in pulmonary arteriolar vasoconstriction. The product of PVC and PVR before and during inhalation of NO is shown in Figure 3. By nonparametric rank-sum

TABLE 1] Description of 157 Patients With PAH

Patients	Value
Female (male)	129 (28)
Age, y	51 ± 14
BMI	28.1 ± 7
IPAH/HPAH, No. (%)	67 (42)
CTEPH, No. (%)	11 (7)
CTD, No. (%)	51 (32)
CHD, No. (%)	19 (12)
Other, No. (%)	10 (6)
WHO class (n = 148)	2.8 ± 0.6
6MWD, m	319 ± 121

Data as means ± 1 SD from the mean. 6MWD = 6-min walk distance; CHD = congenital heart disease; CTD = connective tissue disease; CTEPH = chronic thromboembolic pulmonary hypertension; HPAH = heritable pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; WHO = World Health Organization.

Figure 1 – Plot of PVC vs PVR for 157 patients with pulmonary hypertension. Data were calculated from values taken at the time of a single cardiac catheterization. The inverse relationship is similar to those reported from other centers and registries. PVC = stroke volume (SV)/(pulmonary arterial systolic pressure [Pa sys] – pulmonary arterial diastolic [Pa dias]). PVR = (mean pulmonary arterial pressure [Pa mean] – wedge pressure [P wedge])/cardiac output in milliliters per second. SV in milliliters. ○ = baseline data for the eight NO vasore-sponsive patients; NO = nitric oxide; PVC = pulmonary vascular capac- itance; PVR = pulmonary vascular resistance.

TABLE 3] Hemodynamic Responses to Inhaled NO in Eight Patients

Variable	Pre-NO	Post-NO	P Value
Heart rate, beats/min	78 ± 15	65 ± 13	.012
Systolic BP	125 ± 23	122 ± 20	.293
Diastolic BP	79 ± 12	77 ± 14	.5
Right atrial pressure	5 ± 3	4 ± 3	.6
PA systolic	80 ± 21	48 ± 20	.012
PA diastolic	34 ± 11	17 ± 5	.012
PA pulse pressure	47 ± 13	31 ± 16	.012
Stroke volume	62 ± 19	86 ± 24	.012
PA mean	50 ± 13	28 ± 9	.012
Pulmonary wedge	7 ± 2	6 ± 5	.671
Cardiac output	4.6 ± 1.6	5.5 ± 2.6	.108
PVR	10 ± 4.4	4.7 ± 2.2	.012
PVC	1.4 ± 1.1	3.2 ± 1.8	.018
RC time, s	0.90 ± 0.12	0.78 ± 0.22	.04

All pressures in mm Hg, cardiac output in L/min, PVR and PVC formulae in text. Data are means ± 1 SD. NO = nitric oxide; PVC = pulmonary vascular capacitance; RC = product of resistance × capacitance. See Table 2 legend for expansion of other abbreviations.

test, there was a significant reduction in RC time. The decrease in RC time was a function of a small decrease in the ratio of (Pa mean – P wedge)/pulse pressure, both of which decreased. Heart rate decreased in all eight responders.

Discussion

The right ventricle pumps to an afterload that is composed of three main elements: the blood flow resistance, elastance of the precapillary vessels, and pressure wave reflection.^{10,14,17,27} In PAH, much of the RV work is due

Figure 2 – Plot of hemodynamic data before and during NO inhalation in eight vasoresponsive patients. PA systolic, diastolic, and pulse pressure all decreased while SV increased. The data indicate that proximal arterial stiffness was not a major feature of the high PA systolic pressure but that capacitance increased markedly as resistance decreased. PA = pulmonary arterial. See Figure 1 legend for expansion of other abbreviation.

Figure 3 – Product of PVC × PVR (product of resistance × capacitance [RC] time) for eight patients with pulmonary hypertension with extreme vasodilator responses to inhaled NO. As in Table 3, in addition to large changes in PA pressure and PVR, the NO responders also had a decrease in heart rate and increase in SV. Paired differences analyzed using Wilcoxon signed-rank test. RC time decreased. See Figure 1 legend for expansion of abbreviations.

to pressure generated by pulsatile flow into narrowed arterioles.^{10,12,28} Therefore, PVR is a reasonable (albeit imperfect) measure of the structural problem in PAH.^{28,29} PVR is just the mean relationship of pressure and volume flow per average time down the bed, whereas beat-to-beat data include pulsatile variation that includes compliance of the bed. Ideally, for the best understanding of the pulmonary bed, compliance and flow resistance should be separable characteristics.

The NO vasodilator data confirm that, in this form of severe precapillary pulmonary hypertension, PVC is dependent in magnitude on the severity of elevated PVR. Both peak PA systolic and diastolic pressures decreased markedly in NO responders during inhalation. Surprisingly, pulse pressure was not maintained, but also decreased. Pulse pressure is largely a function of compliance of the arteries in normal lung but pulse pressure is also a function of resistance to flow. Inhaled NO traverses small bronchioles and alveoli into companion arterioles and is rapidly bound to circulating hemoglobin and, therefore, has no direct effect on resistance or compliance of larger upstream arteries that are beyond contact with alveoli.^{15,16}

What inferences can be made from the dramatic PVR and PVC responses to NO? First is that the pulse pressure in the pulmonary circulation in vasoresponsive PAH is not predominantly a function of fixed compliance of conduit vessels such as main PA and lobar arteries. If it were, then Pa sys should have remained elevated during NO inhalation, especially with the increased SV. The opposite occurred, Pa sys decreased, even as SV increased by about 24 mL per beat. On the other hand, during the very high PA pressure at baseline,

the pulmonary arteries upstream to the site of vasoconstriction might be distended to a higher and stiffer point on the pressure-volume (P-V) curve. The rapid reduction in perfusion pressure might then drop the vasculature to a more compliant point on its P-V curve. The second inference is that because PVC and PVR changed to the very same magnitude and timing during NO inhalation, and because NO can only work on ventilation-responsive arterioles, then the resistance and the capacitance vessels were the same vessels. This is not in conflict with prior work, but makes the relationship of PVR and PVC more clear anatomically.

This second inference addresses the uncertainty of why pulmonary circulation RC time is relatively constant regardless of pressures or calculated resistance. In normal humans, the pulmonary circulation is approximately 500 mL in total volume, with about 200 mL estimated to be in the arterial bed. An average resting stroke volume of 70 mL is probably injected far enough down the arterial bed that the small arterioles are volume loaded in systole and, therefore, could act simultaneously as resistance and capacitance structures.³⁰ The Windkessel model of the pulmonary circulation has been extremely useful in understanding these relationships, and the NO data suggest that the resistance and compliance functions remain in parallel but are anatomically the same structures.^{10,14} A limitation of the

NO data are that it may be specific to vasoresponsive PAH. Nonetheless, all eight patients had documented severe PAH with normal wedge pressures and the mean time from symptoms to catheterization was 4.5 years, long enough to remodel the bed. The NO data open a window to explore the reasons for the relative constancy of the RC time relationship in the pulmonary circulation. The NO data also suggest that RC time is not necessarily a time constant in all conditions of pulmonary hypertension because it varies within individuals based on changes in hemodynamic inputs.

Finally, published data suggest that pulmonary capacitance may correlate better with long-term outcome than does PVR.^{18,31-33} Our data do not directly address this possibility. PVR is not an accurate measure of RV load, and it is likely that $P_{a\text{ sys}} - P_{a\text{ dias}}$ pressure more closely reflects RV stress than does $P_{a\text{ mean}} - P_{\text{wedge}}$. It is clear that PVR measurements may not be accurate if the critical opening pressure of the arterial bed is sufficiently upstream from the capillary bed.^{28,29} Thus, it seems likely that the equation $SV/P_{a\text{ sys}} - P_{a\text{ dias}}$ more closely approximates RV stress than does PVR.

In conclusion, the anatomic location of NO effects in the vasoconstricted, high-pressure, low compliance pulmonary bed suggests that much of the compliance resides in small arterioles and that the resistance and compliance vessels are the same.

Acknowledgments

Author contributions: J. H. N. is the guarantor. J. H. N. contributed to the conception of this analysis and wrote the paper; E. L. B. contributed to the thinking and analysis and performed the statistical analysis; I. M. R. contributed to the provision of patient data and analyzed vasomotor responses; A. R. H. contributed to the concept and discussion as well as the provision of patient data; and all authors contributed to the editing and writing of the paper.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Hemnes has received research support from the National Institutes of Health and United Therapeutics Corporation and has served as a consultant for United Therapeutics Corporation; Pfizer Inc; Actelion Pharmaceuticals US, Inc; and Bayer AG. Drs Newman, Brittain, and Robbins have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

- Presson RG Jr, Baumgartner WA Jr, Peterson AJ, Glenn RW, Wagner WW Jr. Pulmonary capillaries are recruited during pulsatile flow. *J Appl Physiol* (1985). 2002;92(3):1183-1190.
- Tabata T, Thomas JD, Klein AL. Pulmonary venous flow by doppler echocardiography: revisited 12 years later. *J Am Coll Cardiol*. 2003;41(8):1243-1250.
- Guntheroth WG, Gould R, Butler J, Kinnen E. Pulsatile flow in pulmonary artery, capillary, and vein in the dog. *Cardiovasc Res*. 1974;8(3):330-337.
- Reiter G, Reiter U, Kovacs G, et al. Magnetic resonance-derived 3-dimensional blood flow patterns in the main pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure. *Circ Cardiovasc Imaging*. 2008;1(1):23-30.
- Mead J. Mechanical properties of lungs. *Physiol Rev*. 1961;41:281-330.
- Rossi A, Gottfried SB, Zocchi L, et al. Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation. The effect of intrinsic positive end-expiratory pressure. *Am Rev Respir Dis*. 1985;131(5):672-677.
- Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med*. 1987;107(2):216-223.
- 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.
- Humbert M, Sitbon O, Yaïci A, et al; French Pulmonary Arterial Hypertension Network. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. *Eur Respir J*. 2010;36(3):549-555.
- Lammers S, Scott D, Hunter K, Tan W, Shandas R, Stenmark KR. Mechanics and function of the pulmonary vasculature: implications for pulmonary vascular disease and right ventricular function. *Compr Physiol*. 2012;2:295-319.
- Sanz J, Kariisa M, Dellegrottaglie S, et al. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. *JACC Cardiovasc Imaging*. 2009;2(3):286-295.
- Hunter KS, Lee PF, Lanning CJ, et al. Pulmonary vascular input impedance is a combined measure of pulmonary vascular resistance and stiffness and predicts clinical outcomes better than pulmonary vascular resistance alone in pediatric patients with pulmonary hypertension. *Am Heart J*. 2008;155(1):166-174.
- Lankhaar JW, Westerhof N, Faes TJ, et al. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. *Eur Heart J*. 2008;29(13):1688-1695.
- Saouti N, Westerhof N, Postmus PE, Vonk-Noordegraaf A. The arterial load in pulmonary hypertension. *Eur Respir Rev*. 2010;19(117):197-203.
- Griffiths MJD, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med*. 2005;353(25):2683-2695.
- Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet*. 1991;338(8776):1173-1174.
- Champion HC, Michelakis ED, Hassoun PM. Comprehensive invasive and non-invasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. *Circulation*. 2009;120(11):992-1007.
- Gan CT, Lankhaar JW, Westerhof N, et al. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. *Chest*. 2007;132(6):1906-1912.
- Huez S, Brimiouille S, Naeije R, Vachiéry JL. Feasibility of routine pulmonary arterial impedance measurements in pulmonary hypertension. *Chest*. 2004;125(6):2121-2128.
- Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation*. 2012;125(2):289-297.
- 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.
- Robbins IM, Hemnes AR, Pugh ME, Brittain E, Zhao DX, Piana RN, Fong PP, Newman JH. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Heart Fail*. 2014;7(1):116-122.
- Brittain EL, Pugh ME, Wheeler LA, et al. Prostanoids but not oral therapies improve right ventricular function in pulmonary arterial hypertension. *JACC Heart Fail*. 2013;1(4):300-307.
- 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.
- Sitbon O, Humbert M, Jaïs X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111(23):3105-3111.
- Tedford RJ, Mudd JO, Girgis RE, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. *Circ Heart Fail*. 2013;6(5):953-963.
- Milnor WR, Conti CR, Lewis KB, O'Rourke MF. Pulmonary arterial pulse wave velocity and impedance in man. *Circ Res*. 1969;25(6):637-649.
- Naeije R, Vachiéry JL, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. *Eur Respir J*. 2013;41(1):217-223.
- Naeije R. Pulmonary vascular resistance. A meaningless variable? *Intensive Care Med*. 2003;29(4):526-529.
- Harris P, Heath D. The measurement of blood volume in the lungs. In: *Human Pulmonary Circulation*. 2nd ed. London, England: Churchill Livingstone; 1977; 104-117.
- Blyth KG, Syed R, Chalmers J, et al. Pulmonary arterial pulse pressure and mortality in pulmonary arterial hypertension. *Respir Med*. 2007;101(12):2495-2501.
- Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol*. 2006;47(4):799-803.
- Tian L, Chesler NC. In vivo and in vitro measurements of pulmonary arterial stiffness: A brief review. *Pulm Circ*. 2012;2(4):505-517.