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ORIGINAL RESEARCH

# Quantifying the Influence of Wedge Pressure, Age, and Heart Rate on the Systolic Thresholds for Detection of Pulmonary Hypertension

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**BACKGROUND:** The strong linear relation between mean (MPAP) and systolic (SPAP) pulmonary arterial pressure (eg, SPAP=1.62×MPAP) has been mainly reported in precapillary pulmonary hypertension. This study sought to quantify the influence of pulmonary arterial wedge pressure (PAWP), heart rate, and age on the MPAP-SPAP relation.

**METHODS AND RESULTS:** An allometric equation relating invasive MPAP and SPAP was developed in 1135 patients with pulmonary arterial hypertension, advanced lung disease, chronic thromboembolic pulmonary hypertension, or left heart failure. The equation was validated in 60 885 patients from the United Network for Organ Sharing (UNOS) database referred for heart and/or lung transplant. The MPAP/SPAP longitudinal stability was assessed in pulmonary arterial hypertension with repeated right heart catheterization. The equation obtained was $SPAP=1.39\times MPAP\times PAWP^{-0.07}\times(60/\text{heart rate})^{0.12}\times age^{0.08}$ ($P<0.001$). It was validated in the UNOS cohort ($R^2=0.93$, $P<0.001$), regardless of the type of organ(s) patients were listed for (mean bias [–1.96 SD; 1.96 SD] was 0.94 [–8.00; 9.88] for heart, 1.34 [–7.81; 10.49] for lung and 0.25 [–16.74; 17.24] mm Hg for heart-lung recipients). Thresholds of SPAP for MPAP=25 and 20 mm Hg were lower in patients with higher PAWP (37.2 and 29.8 mm Hg) than in those with pulmonary arterial hypertension (40.1 and 32.0 mm Hg). In 186 patients with pulmonary arterial hypertension, the predicted MPAP/SPAP was stable over time (0.63±0.03 at baseline and follow-up catheterization, $P=0.43$).

**CONCLUSIONS:** This study quantifies the impact of PAWP, and to a lesser extent heart rate and age, on the MPAP-SPAP relation, supporting lower SPAP thresholds for pulmonary hypertension diagnosis in patients with higher PAWP for echocardiography-based epidemiological studies.

**Key Words:** aging ■ cardiovascular disease ■ physiology ■ pulmonary hypertension

Pulmonary hypertension (PH) is defined as an invasive mean pulmonary arterial pressure (MPAP) >20 mm Hg.[1] Although PH definitions rely on the gold standard right heart catheterization, echocardiography plays a central role in detecting PH. Doppler echocardiography enables systolic pulmonary arterial pressure (SPAP) estimation by measuring right ventricular systolic pressure (RVSP) from the continuous Doppler tricuspid regurgitation gradient and estimated right atrial pressure, assuming a negligible right ventricular outflow tract gradient.[2,3] The use of SPAP (or RVSP) instead of MPAP for PH detection is supported by the close linear relation between systolic and mean pulmonary pressures. First reported by Chemla

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## CLINICAL PERSPECTIVE

### What Is New?

- The strong linear relation between mean and systolic pulmonary arterial pressure (eg, systolic pulmonary artery pressure=1.62×mean pulmonary artery pressure) has been previously reported in precapillary pulmonary hypertension.
- The present study, conducted in patients with pre- and postcapillary pulmonary hypertension from Stanford University (n=1135) and the United Network for Organ Sharing database (n=60 885), demonstrates the influence of pulmonary artery wedge pressure, heart rate, and age on the linear relation between the mean pulmonary artery pressure and the systolic pulmonary arterial pressure.
- Thresholds of systolic pulmonary arterial pressure for mean pulmonary artery pressure=25 and 20 mm Hg are lower in patients with higher pulmonary artery wedge pressure (37.2 and 29.8 mm Hg) than in those with precapillary pulmonary hypertension (40.1 and 32.0 mm Hg).

### What Are the Clinical Implications?

- This invasive study supports lower systolic pulmonary arterial pressure thresholds for pulmonary hypertension diagnosis in patients with higher pulmonary artery wedge pressure for echocardiography-based epidemiological studies.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **HR** | heart rate |
| **MPAP** | mean pulmonary artery pressure |
| **PAH** | pulmonary arterial hypertension |
| **PAWP** | pulmonary artery wedge pressure |
| **PH** | pulmonary hypertension |
| **RVSP** | right ventricular systolic pressure |
| **SPAP** | systolic pulmonary artery pressure |
| **T** | heart period (60/heart rate) |
| **UNOS** | United Network for Organ Sharing |

et al in 2004 and later validated in patients with precapillary PH and healthy subjects,[4–6] the SPAP/MPAP ratio approximates the "golden ratio" (Phi, Φ=1.618, a proportion found in several cardiovascular features) as follows: SPAP=1.62×MPAP.[7]

However, this equation does not take into account the potential influence of pulmonary arterial wedge pressure (PAWP) or stroke volume on the pulmonary pressure components, which was first suggested in 1971 by Harvey et al.[8] Other factors such as heart rate (HR) or aging of the pulmonary vascular system may also influence the linear relation between pulmonary pressure components.[9–12] We hypothesize that whereas an increase in PAWP and HR decreases the SPAP/MPAP ratio, an increase in age increases SPAP/MPAP. Developing and validating an equation relating systolic and mean pulmonary pressure that take into account PAWP, HR (or heart period defined by 60/HR), and age may allow to define more appropriate threshold of RVSP across World Health Organization Pulmonary Hypertension Groups. To date, echocardiographic-based epidemiological studies in PH have been using variable RVSP thresholds ranging from 30 to 45 mm Hg corresponding to the previous MPAP threshold of 25 mm Hg.[4,5,13–16]

Therefore, the first objective was to derive and validate an equation relating SPAP and MPAP, taking into account the influence of PAWP, heart rate, and age. The equation was first derived in a well-curated database at Stanford and then externally validated in the United Network of Organ Sharing (UNOS) data set. The second objective was to derive the implications of our novel equation on the determination of systolic thresholds for detection of PH (ie, MPAP of 25 or 20 mm Hg) across the World Health Organization spectrum. The third objective was to assess the stability of a predicted MPAP/SPAP ratio for longitudinal studies in pulmonary arterial hypertension (PAH), as if proven stable this ratio may have a role in assessing the reliability of longitudinal hemodynamic data in PAH.

## METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Stanford University at mamsalle@stanford.edu.

### Derivation Cohort

Adults with confirmed or suspected PH and complete right heart catheterization data were retrospectively included (Data S1). Patients were selected to represent the spectrum of World Health Organization groups: PAH (n=307), heart failure with reduced ejection fraction referred for heart transplant or left ventricular assist device implantation (n=332), pressure-overloaded left heart disease secondary to aortic stenosis (n=86), advanced lung disease referred for prelung transplant evaluation (n=349), and proximal chronic thromboembolic PH prior to pulmonary endarterectomy (n=61). Stanford Institutional Review Board (#25673), Marie Lannelongue Hospital Institutional Review Board, and the French local ethics committee (CPP Ile-de-France, Le Kremlin Bicêtre: #C0-09-015) approved the study, which was

conducted in agreement with the amended Declaration of Helsinki. All patients gave written informed consent.

Right heart catheterization methods are detailed in Data S1. Briefly, resting supine HR, mean right atrial pressure, SPAP, MPAP, and PAWP were measured at the end of expiration. The MPAP values were computer generated (Mac-Lab*, GE Healthcare, Boston, MA) from integration of pressure curves, averaged for several cardiac cycles, then verified by an experienced physician. Cardiac output was calculated using indirect Fick and/or thermodilution method. The resistance-compliance time product was calculated as the product of pulmonary vascular resistance and compliance (in seconds).

## UNOS Validation Cohort

Adults listed for heart and/or lung transplant included in the UNOS thoracic database from 1987 to 2017 were included. Patients were excluded if hemodynamic data were not available or considered "potential outliers" (ie, MPAP/SPAP ratio lower than the first percentile [1.194] or higher than the 99th percentile [2.083] of the derivation cohort, in order to exclude patients supported with extracorporeal membrane oxygenation or those with congenital disease such as Fontan circulation). As HR at the time of catheterization was not available, a value of 80/min was attributed to all patients.

## Longitudinal Data

Data from 186 patients with PAH who underwent repeated surveillance right heart catheterization were collected.

## Statistical Analysis

Continuous variables were presented as mean±SD, and categorical variables as number and percentage. Continuous variables were compared using Student *t* test or 1-way ANOVA if more than 2 groups. Coefficients of variation were defined as standard deviation/mean ratio. Variances were compared using F test. Linear regression coefficients were presented as $R^2$ and their *P* values, and partial correlation coefficients of each variable are presented along with their 95% confidence interval (95% CI) and *P* value.

A multivariate linear weighted regression model was constructed to identify independent correlates of SPAP among MPAP, PAWP, pulmonary vascular resistance, stroke volume, cardiac index, heart period (T, defined as 60/HR), age, sex, and body surface area. As not all variables followed a normal distribution, dependent and independent continuous variable were log transformed using the natural logarithm. Variables were retained in the final model using backward selection. The presence of significant interaction between variables was ruled out using interaction terms if *P* value was >0.05. Weighted least square regression was used to correct for heteroscedasticity as needed. The performance of the model was internally validated via a bootstrapping approach by creating 10 000 resamples with replacement from the entire data set. B coefficients obtained using the bootstrapping method for each retained variable were used to build the equation. The equation was then transformed into a multiplicative allometric equation, presenting the option to easily rearrange the equation variables. Comparisons between predicted and observed SPAP were performed by linear regression analysis and compared using Bland-Altman plots of the difference between predicted and observed SPAP (with 95% limits of agreement defined as ±1.96 SD of the difference). Statistical analyses were performed using IBM® SPSS® Statistics software version 25. Gradient density plots were constructed using Matlab® 2017. $P<0.05$ were considered statistically significant.

# RESULTS

## Derivation Cohort

Table summarizes the characteristics of the derivation cohort (n=1135). SPAP and MPAP were strongly related ($R^2=0.93$, $P<0.001$, Figure 1A). A strong relationship was also noted between MPAP and diastolic pulmonary arterial pressure ($R^2=0.88$) and to a lesser extent with pulmonary pulse pressure ($R^2=0.67$), both $P<0.001$, as shown in Figure S1A. The equation between SPAP and MPAP varied according to the disease etiology (Figure 1B and 1C and Figure S1B), with a lower slope noted in patients with elevated PAWP (1.514) than in those with low PAPW (1.617), $P<0.001$.

Using multivariate regression modeling for ln(SPAP), 4 factors were retained in the model ($R^2=0.95$, $P<0.0001$): MPAP (B coefficient=1.00 [0.99; 1.02], semi-partial coefficient=0.96), PAWP (–0.07 [–0.08; –0.06], –0.10), heart period T (0.12 [0.09; 0.15], 0.05), and age (0.08 [0.06; 0.10], 0.05), all $P<0.0001$. Female sex, body surface area, resistance, and stroke volume were not retained in the model. There was no significant interaction between pulmonary vascular resistance higher than 3 and ln(PAWP), ln(age) or ln(T) in the model.

The equation can be expressed as follows (Figure 2A):

$$\ln(\mathrm{SPAP}) = 1.00\times\ln(\mathrm{MPAP}) - 0.07\times\ln(\mathrm{PAWP}) + 0.12\times\ln(\mathrm{T}) + 0.08\times\ln(\mathrm{age}) + 0.33$$

$$<=> \mathrm{SPAP} = 1.39\times\mathrm{MPAP}\times\mathrm{PAWP}^{-0.07}\times\mathrm{T}^{0.12}\times\mathrm{age}^{0.08}$$

The regression line relating the predicted and observed SPAP differed little from the line of identity (Figure 2B) and there was no heteroscedasticity

**Table. Hemodynamic Characteristics According to Disease Etiology of the Derivation Cohorts**

| | PAH | CTEPH | ALD | Left Heart Disease | | *P* Value |
|---|---|---|---|---|---|---|
| | n=307 | n=61 | n=349 | HFrEF (n=332) | Aortic Stenosis (n=86) | |
| Age, y | 48.0 [38.0; 56.6] | 67.0 [56.0; 72.0] | 55.0 [44.2; 61.8] | 55.7 [45.7; 64.0] | 82.0 [73.3; 87.5] | <0.001 |
| Female sex | 240 (78) | 32 (52) | 185 (53) | 83 (25) | 33 (38) | <0.001 |
| Heart rate, bpm | 80.0 [70.0; 89.0] | 83.0 [72.0; 94.5] | 80.0 [69.0; 91.0] | 81.0 [69.3; 97.0] | 71.0 [64.0; 80.0] | 0.19 |
| Right atrial pressure, mm Hg | 8.0 [5.0; 12.0] | 6.0 [4.0; 9.0] | 5.5 [3.0; 9.3] | 12.0 [7.0; 17.0] | 5.0 [3.0; 7.0] | <0.001 |
| SPAP, mm Hg | 83.0 [67.0; 98.0] | 38.0 [32.0; 50.0] | 38.0 [32.0; 50.0] | 52.0 [40.0; 60.0] | 38.5 [29.8; 50.0] | <0.001 |
| DPAP, mm Hg | 33.0 [25.0; 41.0] | 16.0 [12.0; 22.0] | 16.0 [12.0; 22.0] | 25.0 [19.0; 31.0] | 14.5 [10.0; 20.0] | <0.001 |
| MPAP, mm Hg | 51.0 [42.0; 60.0] | 25.0 [19.0; 34.0] | 25.0 [19.0; 34.0] | 35.0 [28.0; 42.0] | 21.5 [17.2; 29.4] | <0.001 |
| PAWP, mm Hg | 10.0 [8.0; 13.0] | 10.0 [7.0; 15.0] | 10.0 [7.0; 15.0] | 25.0 [18.0; 30.0] | 13.5 [10.0; 20.3] | <0.001 |
| Cardiac output, L/min | 3.5 [2.9; 4.2] | 4.8 [4.1; 5.9] | 4.8 [4.1; 5.9] | 3.6 [2.9; 4.4] | 4.4 [3.4; 5.4] | <0.001 |
| Pulmonary vascular resistance, WU | 11.0 [7.6; 16.0] | 7.8 [5.3; 9.7] | 2.7 [1.6; 4.1] | 2.8 [1.8; 4.2] | 2.1 [1.2; 2.8] | <0.001 |
| Compliance, mL/mm Hg | 0.91 [0.65; 1.31] | 2.88 [1.90; 4.02] | 2.88 [1.90; 4.02] | 1.73 [1.81; 2.54] | 2.39 [1.66; 3.86] | <0.001 |
| Resistance-compliance time product | 0.59 [0.48; 0.70] | 0.44 [0.34; 0.56] | 0.44 [0.34; 0.56] | 0.31 [0.22; 0.40] | 0.30 [0.22; 0.40] | <0.001 |
| SPAP/MPAP | 1.62 [1.54; 1.71] | 1.70 [1.60; 1.82] | 1.58 [1.44; 1.71] | 1.47 [1.37; 1.59] | 1.71 [1.57; 1.87] | <0.001 |

Data are presented as median [interquartile range] or number (percentage). The *P* values of Kruskall–Wallis or chi-square test are presented. ALD indicates advanced lung disease; CTEPH, chronic thromboembolic pulmonary hypertension; DPAP, diastolic pulmonary arterial pressure; HFrEF, heart failure with reduced ejection fraction; MPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; SPAP, systolic pulmonary arterial pressure; and WU, Wood units.

(Figure S2). One-way ANOVA performed on the residual percentage from the equation showed that the magnitude of departure from observed SPAP was not statistically significant between subgroups (*P*=0.11, Figure 2C). In contrast, Figure S3 shows that both the original equation published by Chemla et al in 2004 (SPAP=1.64×MPAP−3.28 mm Hg corresponding to MPAP=0.61×SPAP+2 mm Hg) and the one derived from the golden number (SPAP=1.62×MPAP) did not performed as well, particularly in patients with high PAWP or aortic stenosis. Figure 2D depicts the theoretical physiological effect of PAWP, age, and heart period on the pulmonary pressure waves.

The equation can be rearranged for calculation of MPAP from SPAP as follows:

$$MPAP = 0.71 \times SPAP \times PAWP^{0.07} \times T^{-0.12} \times age^{-0.08}$$

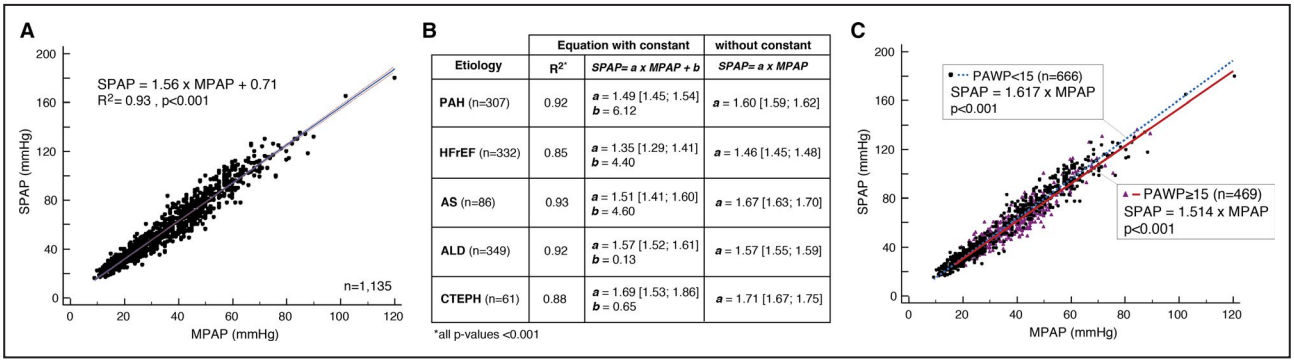


**Figure 1. Variability of the relation between systolic (SPAP) and mean pulmonary arterial pressure (MPAP).**
**A,** Linear relation between SPAP and MPAP in the total cohort. **B**, Variability of the SPAP-MPAP relation according to World Health Organization pulmonary hypertension group. Linear regressions are presented by their coefficient of determination ($R^2$), as (SPAP=slope×MPAP+constant) or without constant (SPAP=slope×MPAP). **C**, The SPAP-MPAP relation in patients with low vs high pulmonary arterial wedge pressure (PAWP). ALD indicates advanced lung disease; AS, aortic stenosis; CTEPH, chronic thromboembolic pulmonary hypertension; HFrEF, heart failure with reduced ejection fraction; and PAH, pulmonary arterial hypertension.

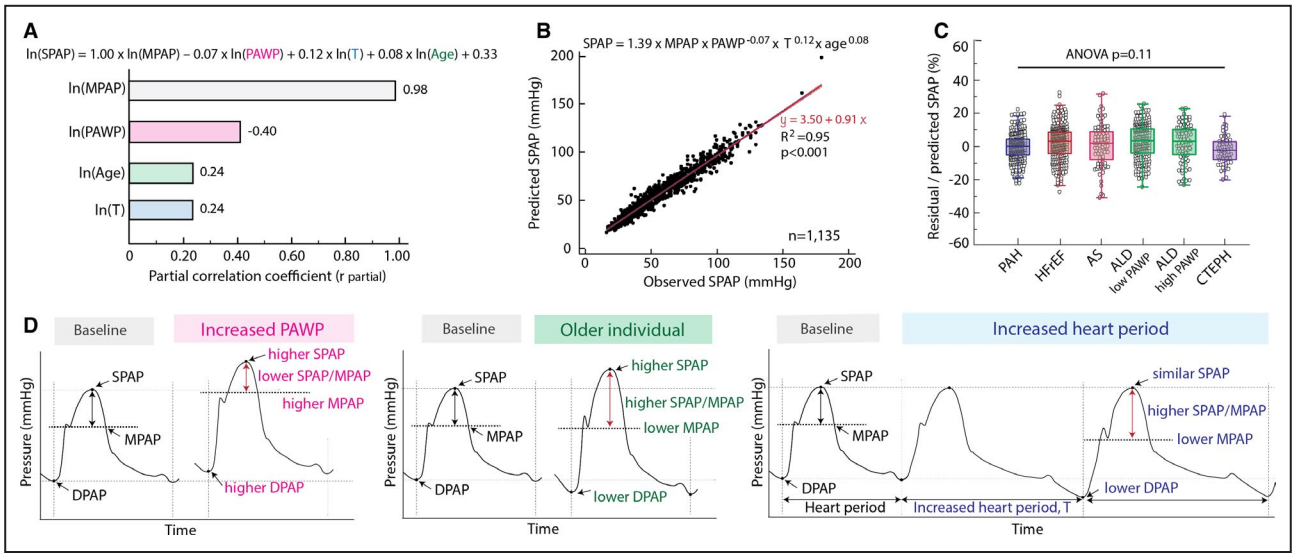


**Figure 2. Equation of estimation of the systolic pulmonary arterial pressure (SPAP) according to the mean (MPAP), pulmonary arterial wedge pressure (PAWP), age, and heart rate in the derivation cohort (n=1135).**
**A**, Contribution of each variable to the allometric model. **B**, Graphic representation of the relation between observed SPAP and predicted SPAP from the equation. **C**, Residuals of the predicted SPAP showing no statistical difference according to disease groups. **D**, Theoretical physiological effect of PAWP, age, and heart period on the pulmonary pressure waves. ALD indicates advanced lung disease; AS, aortic stenosis; CTEPH, chronic thromboembolic pulmonary hypertension; DPAP, diastolic pulmonary arterial pressure; HFrEF, heart failure with reduced ejection fraction; PAH, pulmonary arterial hypertension; T, period defined as 60/heart rate.

## UNOS Validation Cohort

The characteristics of the UNOS cohort are presented in Figure 3A and Table S1. As HR at the time of catheterization was not available in the data set, a predefined HR of 80 bpm was chosen exposing to an error (=$T^{0.12}$) ranging from –1.50 to +3.00 mm Hg

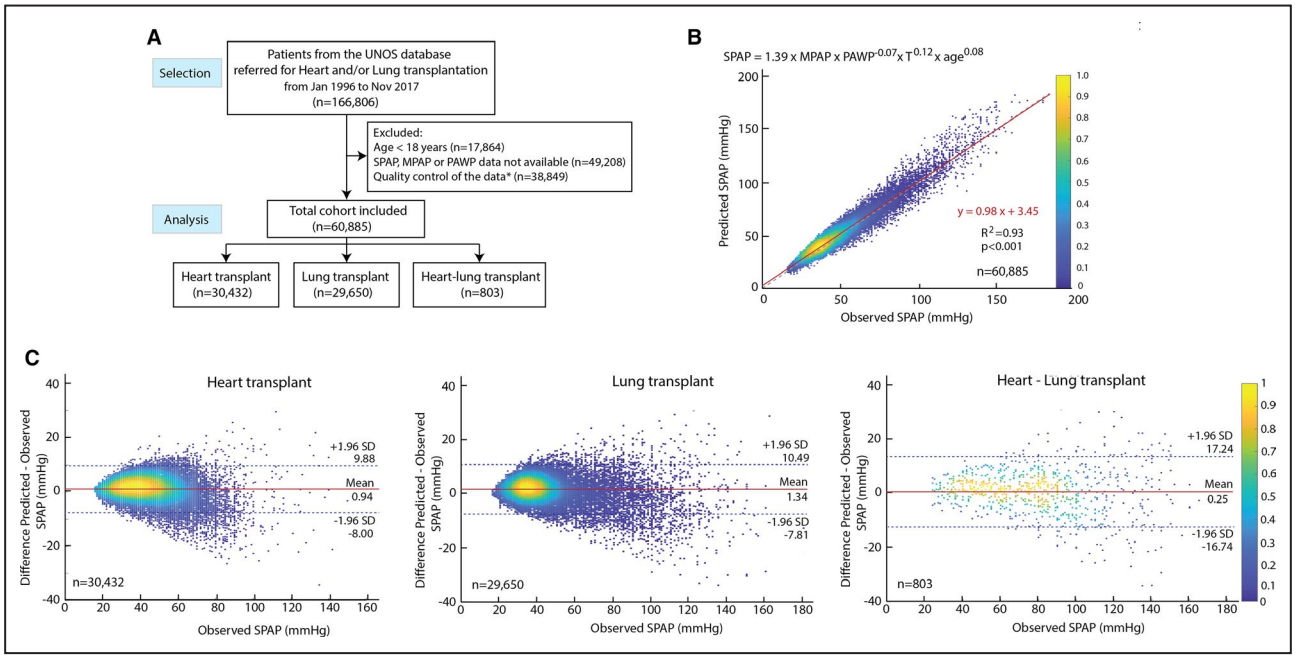


**Figure 3. Equation validation in the United Network for Organ Sharing (UNOS) cohort.**
**A**, Flow chart of the validation cohort derived from the UNOS data set. **B**, Linear regression assessing the correlation between predicted and observed systolic pulmonary arterial pressure (SPAP), illustrated by the density of the points (yellow indicating high density and blue indicating low density) in the total cohort. **C**, Bland-Altman analysis plots of assessing the correlation between predicted and observed SPAP according to the type of organ patients were listed for. MPAP indicates mean pulmonary arterial pressure; and PAWP, pulmonary arterial wedge pressure.

corresponding to a HR of 50 to 140 bpm. The allometric coefficients of the equation were first verified in the UNOS data set by performing the same multivariable model: the B coefficient obtained for ln(PAWP) was −0.071 [−0.072; −0.069] and for ln(age)=0.055 [0.052; 0.057] (both $P<0.0001$).

When using the equation ($SPAP=1.39\times MPAP\times PAWP^{-0.07}\times T^{0.12}\times age^{0.08}$), the regression line between the predicted and observed SPAP (Figure 3B) differed minimally from the line of identity for the total UNOS cohort ($R^2=0.93$) and regardless of the organ(s) patients were listed for ($R^2=0.91$ for heart recipients, $R^2=0.94$ for lung recipients and $R^2=0.93$ for heart-lung recipients, all $P<0.001$). Bland-Altman plots demonstrated a good degree of accuracy and precision in each organ group (Figure 3C). The analysis was also performed in the UNOS cohort without excluding patients with "non-physiologic" data (Figure S4) showing good correlation ($R^2=0.91$, $P<0.001$), accuracy, and precision of the predicted SPAP (mean of the difference 2.26 [−8.26; 11.74]).

## Clinical Implications on SPAP Thresholds

According to the validated equation, the SPAP threshold for MPAP=25 mm Hg is lower in a typical patient with left heart failure and reduced ejection fraction (37.2 mm Hg) than in a typical patient with PAH (40.1 mm Hg), as illustrated in Figure 4. Figure S5 illustrates the variability of the SPAP-MPAP relation with changes in age, HR, and PAWP.

## Longitudinal Data

The stability over time of the MPAP/SPAP ratio derived from the equation (predicted $MPAP/SPAP=0.7\times PAWP^{0.07}\times T^{-0.12}\times age^{-0.08}$) was explored in 186 patients with PAH and repeated catheterization (mean age 45.3±13.7 years, 83.3% of female, 58.1% in NYHA III or IV at time of first catheterization, Table S2). The average time interval between the 2 catheterizations was 2.35±1.49 years. Based on the equation, the predicted MPAP/SPAP ratio was found to be stable (0.63±0.03 at baseline and follow-up catheterization, $P=0.43$), and demonstrated significantly lower variance than the observed MPAP/SPAP ratio and the resistance-compliance time product at each time point (all $P<0.001$, Figure 5).

| | Estimated SPAP* (mmHg) | |
|---|---|---|
| | MPAP 20mmHg | MPAP 25mmHg |
| Patient with PAH<br>*50yo, PAWP=7, HR=80* | 32.0 | 40.1 |
| Patient with HF<br>*50yo, PAWP=20, HR=80*<br>*80yo, PAWP=20, HR=80* | 29.8<br>30.9 | 37.2<br>38.6 |
| Patient with AS<br>*80yo, PAWP=15, HR=70* | 32.1 | 40.1 |

*based on $SPAP = 1.39 \times MPAP \times PAWP^{-0.07} \times T^{0.12} \times Age^{0.08}$

**Figure 4. Examples of the variability of systolic pulmonary arterial pressure (SPAP) and corresponding to mean pulmonary arterial pressure (MPAP) thresholds of 25 and 20 mm Hg, according to age, pulmonary arterial wedge pressure (PAWP), and heart rate (HR).**
AS indicates aortic stenosis; HF, heart failure; and PAH, pulmonary artery hypertension.

# DISCUSSION

Our study demonstrates and quantifies the influence of increased filling pressure (PAWP), age, and heart period on the systolic thresholds for detection of PH. For diagnosis purposes, these factors appear to minimally influence the threshold used for echocardiographic screening as the variability of the SPAP threshold likely falls within the Doppler measurement error. Our equation, however, explains the frequent use of lower RVSP thresholds for PH detection in left heart failure screening studies. Overall, the SPAP corresponding to the new PH threshold (MPAP 20 mm Hg) is 30 mm Hg, which is consistent with the recent large echocardiography-based report from the National Echocardiography Database of Australia cohort (n=157 842), showing an inflection of the mortality rate after 30 mm Hg across PH etiology.[17] In addition, the stability of the predicted MPAP/SPAP ratio over time supports its potential use for the quality control of right heart catheterization data and identification of outliers or potentially erroneous values in large databases.

Although the relation between SPAP and MPAP has been widely reported in patients with precapillary PH or healthy controls, it has not been well characterized in patients with elevated PAWP. Harvey et al first summarized the evidence on the correlation between PAWP and diastolic pulmonary arterial pressure, and indirectly SPAP,[8] but did not explore the effect of PAWP on the MPAP-SPAP relation. In our study, we demonstrate that the PAWP is an independent factor contributing to SPAP, in addition to MPAP (which accounts for the majority of the effect size). An increase in PAWP is associated with a higher MPAP/SPAP ratio, corresponding to higher MPAP for a given SPAP (systolic accentuation).

Heart rate (or heart period) and chronological age were also found to affect, albeit in a lesser extent, the MPAP-SPAP relation. A longer cardiac cycle period (lower HR) is associated with a wider pulse pressure, corresponding to a lower MPAP for a given SPAP (Figure 2D).[9] Our findings are also consistent with several invasive and noninvasive reports of increased systolic pressures with aging.[14,18,19] Although

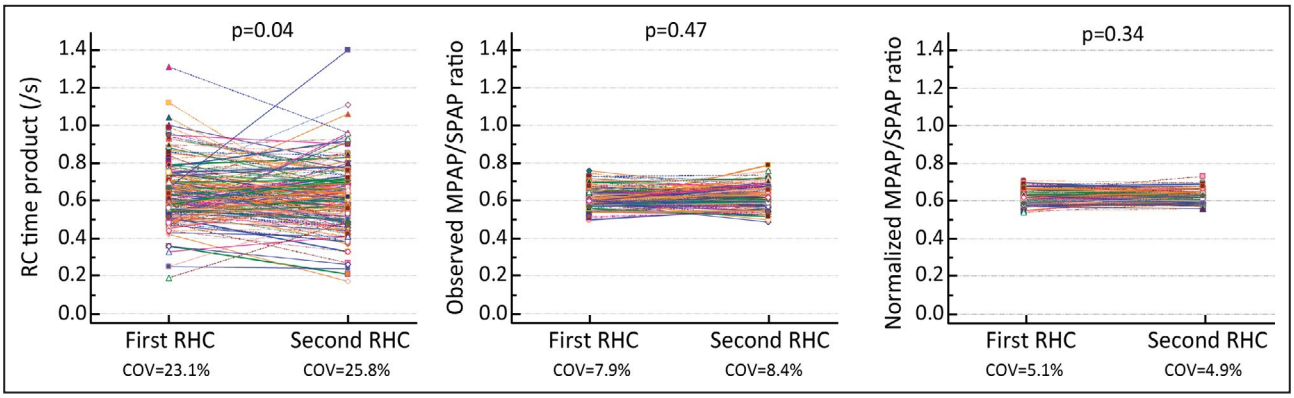


**Figure 5. Changes in the resistance-compliance (RC) time product, observed MPAP/SPAP, and predicted MPAP/SPAP ratio over time in 186 patients with pulmonary arterial hypertension.**
Comparisons were performed using paired *t* test. COV indicates coefficient of variation; MPAP, mean pulmonary arterial pressure; RHC, right heart catheterization; and SPAP, systolic pulmonary arterial pressure.

previous studies have primarily considered concomitant left ventricular diastolic dysfunction or systemic hypertension (increasing PAWP) as the main cause of increased pulmonary pressures in elderly subjects, age was found to be an independent factor to PAWP in our study. This supports intrinsic pulmonary arterial changes with age, marked by an increased stiffness of the pulmonary vessels secondary to a decrease in the elastic content of the pulmonary arteries and veins.[20] Albeit modest, the consequence of such an increased stiffness is higher SPAP values for corresponding MPAP thresholds.

Our study not only highlights the importance of taking into consideration age, heart rate, and PAWP when analyzing the SPAP-MPAP relation but also the need to more systematically report them in publications. As an example, difference in age might explain the observed difference in SPAP/MPAP between patients with chronic thromboembolic pulmonary hypertension and those with PAH, as demonstrated in our study. Prior small studies have reported conflicting results regarding the impact of wave reflection on pulmonary artery pressure waveforms in chronic thromboembolic pulmonary hypertension (potentially earlier wave reflection depending on level of obstruction than in PAH) but often comparing cohorts with different age.[21,22] Similarly, older age and lower HR seem to partially explain the difference in the SPAP/MPAP ratio in patients with aortic stenosis as compared with those with heart failure with reduced ejection fraction. The practical consequence is a higher SPAP threshold (40 mm Hg) corresponding to a MPAP of 25 mm Hg in patients with aortic stenosis, consistent with a recent study including 1400 patients with aortic stenosis of similar age and PAWP levels.[23] It should be noted that heart rate at time of catheterization was not reported in this study, which strengthens the need to systematically report it in future studies.

One of the strengths of our study is the validation of the equation in the large UNOS data set. Regardless of the organ(s) patients were listed for, the accuracy and precision of the equation were good, given the range of error induced by a fixed HR of 80/min, which can be estimated to be from –1.50 mm Hg for a HR of 50/min, to +3.00 mm Hg for a HR of 140/min. The allometric coefficients were similar in the UNOS cohort as the derived equation, with a lower age coefficient (0.05 versus 0.08 in the derivation cohort, due to a lower age range in UNOS patients referred for transplant). One pitfall of using a large data set is the suboptimal quality or incomplete nature of the data, as illustrated by our findings, commending the need of quality improvement measured to ensure the accuracy of large national cohorts. The predicted SPAP/MPAP ratio generated in this study if validated could be implemented to identify hemodynamic outliers in longitudinal studies. Regardless, the accuracy and precision of the equation were similar in the total cohort before exclusion of outliers.

In clinical practice and epidemiology studies, the diagnosis of PH relies on cutoffs (currently 20 mm Hg of MPAP, previously 25 mm Hg of MPAP). Therefore, equations relating MPAP and SPAP provide a corresponding best-fitted systolic value. Our results derive examples of best-fitted SPAP corresponding to a MPAP of 20 and 25 mm Hg for “typical” patients with precapillary and postcapillary PH. However, one needs to nuance the determination of “best fitted” pressure values of PH (required for guidelines and epidemiological studies) by the variability of invasive pressure measurements and in a greater extent of echocardiographic estimates. For epidemiological-based echocardiographic studies, reporting the different prevalence of PH using 30, 35, or 40 mm Hg RVSP thresholds appears preferable.

One originality of this study is the demonstration of the relative stability over time of the predicted

MPAP/SPAP in patients with PAH, which suggests its use as a quality control when reporting pulmonary pressures during longitudinal studies or clinical trials incorporating pulmonary hemodynamic. Further studies are ongoing to demonstrate the stability over time of the predicted MPAP/SPAP in other populations more exposed to changes in PAWP or heart rate than patients with PAH. Another potential theoretical application requiring prospective validation is the use of the predicted MPAP/SPAP to monitor for increase in PAWP, in intensive care or perioperative settings. One could theorize that an increase in MPAP/SPAP would reflect an increase in wedge pressure (after normalization for HR). If prospectively validated, this could obviate the need for frequent pulmonary artery catheter manipulations and use a predicted MPAP/SPAP ratio to monitor for possible increases in PAWP.

This study is limited by the use of pressure data obtained using fluid-filled catheters rather than high-fidelity micro manometer-tipped catheters. However, our objective was to assess the proportionality of pulmonary pressures and their practical implications in a clinical setting. In addition, as echocardiographic data in a close proximity to the right heart catheterization was not available in all patients, this study could not explore the practical implications of the variability of MPAP-SPAP relationship on PH detection using Doppler-echocardiography. The third limitation relates to the absence of HR data available at the time of catheterization in the current UNOS database. Prospectively, adding HR at time of catheterization to the list of collected data should be considered. We estimate that the error associated with a fixed HR of 80 bpm ranges from –1.50 to +3.00 mm Hg (corresponding to a HR of 50–140 bpm). Finally, our study only included operable patients with chronic thromboembolic pulmonary hypertension undergoing pulmonary endarterectomy, which reflects mainly patients with proximal obstruction. Further studies are needed to validate our equation in patients with distal chronic thromboembolic pulmonary hypertension.

In conclusion, PAWP, HR, and age influence the linear relation between MPAP and SPAP. This supports lower SPAP best-fitted thresholds for PH screening in patients with postcapillary PH than in those with precapillary PH for epidemiological studies. If validated, the predicted MPAP/SPAP could play a role in assessing the quality of longitudinal data sets and to theoretically estimate the likelihood of increasing PAWP in invasively monitored patients.

## ARTICLE INFORMATION

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### Disclosures

Tedford serves as a consultant to Actelion-Janssen and Merck (hemodynamic core lab), Arena Pharmaceuticals, United Therapeutics, Medtronic (steering committee) and Abiomed (research advisory group). Amsallem received a Young Investigator Award from Vera Moulton Wall Center at Stanford and received speaker fees from Bayer. Haddad received research grants from Actelion-Janssen and Philips. The remaining authors have no disclosures to report.

### Supplementary Materials

**Data S1**
**Tables S1–S2**
**Figures S1–S5**

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# SUPPLEMENTAL MATERIAL

**Data S1.**

## SUPPLEMENTAL METHODS

*Derivation cohort*

This retrospective cohort included a total of 1,135 adults (age >18 years) with confirmed or suspected PH with complete right heart catheterization data including HR. Patients were selected with five different primary diagnoses to represent the spectrum of WHO PH groups: [1] 307 patients with idiopathic, hereditary, drug and toxins or connective tissue disease related PAH, who underwent catheterization from 2003 to 2014, [2] 332 patients with heart failure with reduced ejection fraction (HFrEF) either referred for heart transplant (n=142) or for left ventricular assist device implantation (n=190) from 2008 to 2016, [3] 86 patients with pressure-overloaded left heart disease secondary to aortic stenosis who underwent catheterization in the pre-procedure evaluation prior to trans catheter aortic valvular replacement from 2009 to 2017, [4] 349 patients with advanced lung disease (i.e. 49.6% with interstitial lung disease with or without pulmonary fibrosis secondary to connective tissue disease, 36.4% Global Initiative for Chronic Obstructive Lung Disease GOLD 3 or 4 severe chronic obstructive pulmonary disease and 14.0% with cystic fibrosis) referred between 2006 to 2012 for pre-lung transplant evaluation, and [5] 61 patients with operable chronic thromboembolic pulmonary hypertension (CTEPH) who underwent catheterization in the preoperative evaluation prior to pulmonary artery endarterectomy from 2012 to 2015. Groups 1-4 were recruited at Stanford Health Care and group 5 at Marie Lannelongue Hospital.

*Hemodynamics*

Right heart catheterization was performed through the internal jugular or right femoral vein at Stanford using fluid-filled catheters (Edwards Lifescience, Irvine, CA) and through the right or left femoral vein at Marie Lannelongue Hospital using Oximetry Thermodilution Pulmonary Artery Catheters (Edwards Lifescience, Irvine, CA). HR at the time of MPAP measurement was collected in all patients. Mean right atrial pressure (RAP), SPAP, MPAP and diastolic pulmonary arterial pressures (DPAP), PAWP were measured during end-expiratory under resting supine conditions with minimal sedation for vascular access when needed.

The MPAP values were computer-generated (Mac-Lab*, GE Healthcare, Boston, MA) from integration of pressure curves, averaged for several cardiac cycles, then verified by an experienced physician. Cardiac output was calculated using indirect Fick (AVOXimeter 1000E, Instrumentation Laboratory, Werfen, Austria) and/or thermodilution method. The indirect Fick method was preferentially used at Stanford or in the presence of severe tricuspid regurgitation at Marie Lannelongue Hospital. Pulmonary vascular resistance (R, expressed in Wood Units) was calculated as (MPAP – PAWP)/cardiac output. Pulmonary arterial compliance (C, expressed in mL/mmHg) was calculated as stroke volume/pulmonary pulse pressure. The RC time product was calculated as the product of resistance and compliance (in seconds).

**Table S1. Characteristics of the UNOs validation cohort, according to the type of transplant.**

| | **Total UNOs cohort n=60,885** | **Heart transplant n=30,432** | **Lung transplant n=29,650** | **Heart-lung transplant n=803** |
|---|---|---|---|---|
| Age (years) | 52.6 ±12.1 | 52.3 ±11.6 | 53.3 ±12.5 | 41.4 ±11.7 |
| Female sex | 22,272 (36.6) | 7,717 (25.4) | 14,108 (47.6) | 447 (55.7) |
| SPAP (mmHg) | 45.5 ±17.9 | 45.5 ±15.3 | 44.4 ±18.8 | 81.3 ±31.5 |
| MPAP (mmHg) | 30.5 ±12.1 | 31.0 ±10.9 | 29.2 ±12.2 | 54.3 ±21.5 |
| DPAP (mmHg) | 21.8 ±9.8 | 23.1 ±9.2 | 19.9 ±9.3 | 38.6 ±17.3 |
| PAWP (mmHg) | 14.3 ±7.9 | 18.3 ±8.2 | 10.3 ±4.9 | 14.5 ±8.2 |
| CO (L/min) | 4.8 ±1.5 | 4.4 ±1.4 | 5.3 ±1.5 | 4.4 ±1.7 |

Data is presented as mean ± standard deviation or number (percentage). CO: cardiac output; DPAP: diastolic pulmonary arterial pressure; MPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; SPAP: systolic pulmonary arterial pressure.

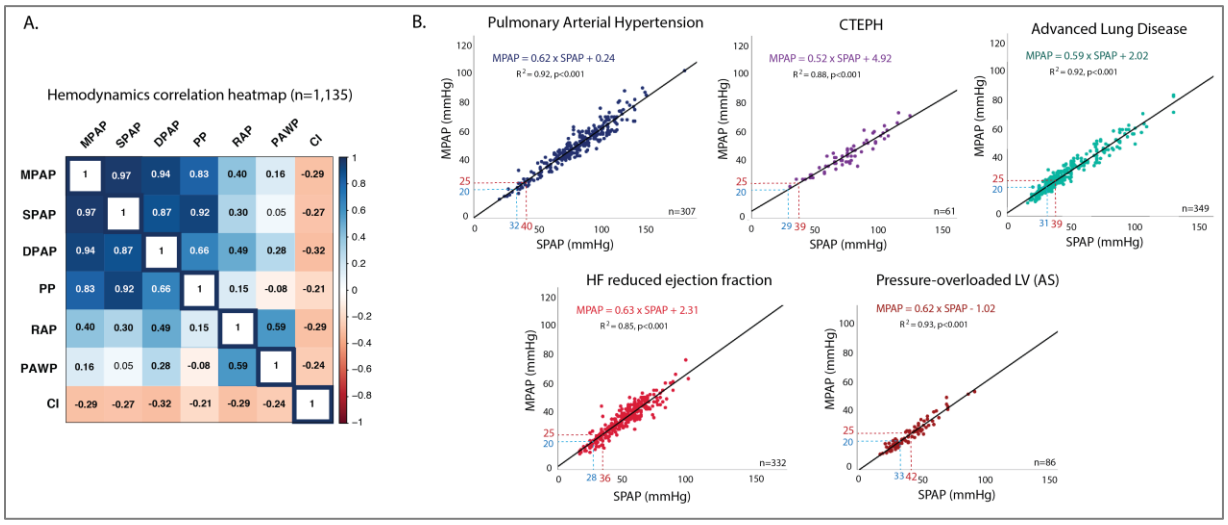
**Table S2. Characteristics of the validation longitudinal cohort (n=186) at the time of the first and the second catheterizations.**

| | First RHC | Second RHC |
|---|---|---|
| Age (years) | 45.3 ±13.7 | 47.6 ±13.7 |
| Female sex | 155 (83) | - |
| Etiology of PAH | | |
| Idiopathic or heritable | 61 (33) | - |
| Connective tissue disease | 78 (42) | - |
| Drug or toxins | 47 (25) | - |
| New York Heart Association class | n=186 | n=154 |
| I | 15 (8) | 6 (4) |
| II | 64 (34) | 62 (40) |
| III | 93 (50) | 71 (46) |
| IV | 15 (8) | 15 (10) |
| Heart rate (bpm) | 78.4 ±12.9 | 77.1 ±16.2 |
| Right atrial pressure (mmHg) | 8.9 ±5.5 | 8.2 ±4.6 |
| SPAP (mmHg) | 81.0 ±22.0 | 76.1 ±24.2 |
| DPAP (mmHg) | 31.3 ±11.6 | 29.5 ±13.5 |
| MPAP (mmHg) | 50.5 ±14.3 | 46.9 ±14.3 |
| Pulmonary arterial wedge pressure (mmHg) | 9.4 ±4.1 | 10.5 ±4.4 |
| Pulmonary vascular resistance (R, WU) | 12.3 ±5.9 | 9.9 ±5.2 |
| Compliance (C, mL/mmHg) | 1.2 ±0.8 | 1.3 ±0.8 |
| RC time product | 0.64 ±0.16 | 0.61 ±0.19 |
| MPAP/SPAP | 0.62 ±0.05 | 0.62 ±0.05 |
| Normalized MPAP/SPAP ratio | 0.63 ±0.03 | 0.63 ±0.03 |
| PAH-specific therapy | | |
| Treatment naïve | 55 (30) | 29 (16) |
| Prostanoids | 42 (23) | 69 (37) |
| Endothelin receptor antagonists | 48 (26) | 66 (36) |

| | | |
|---|---|---|
| Phosphodiesterase inhibitors | 54 (29) | 91 (49) |
| Calcium channel blocker | 38 (20) | 39 (21) |

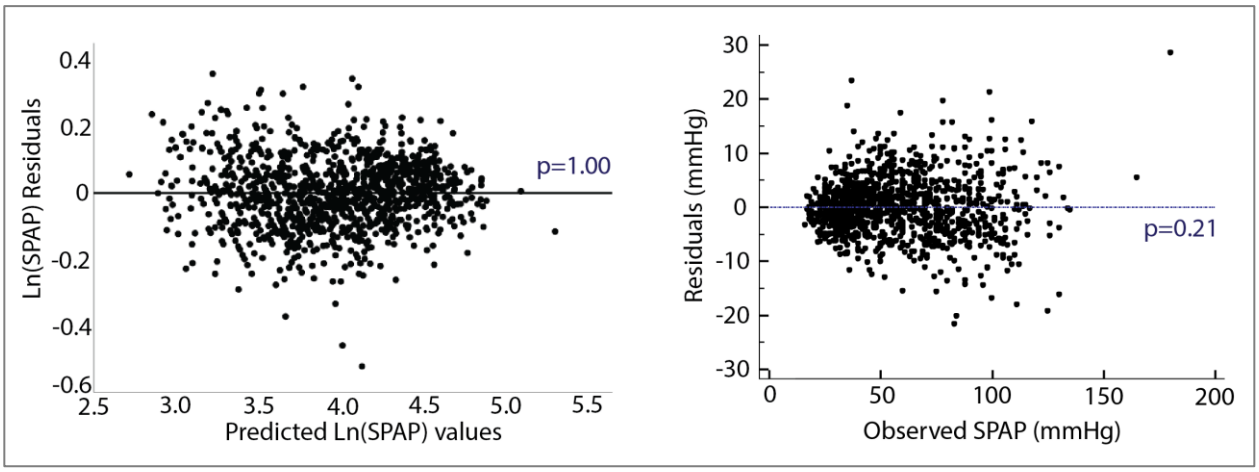
DPAP: diastolic pulmonary arterial pressure; MPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; SPAP: systolic pulmonary arterial pressure

**Figure S1. (A) Correlation heatmap between hemodynamics in the total derivation cohort (n=1,135) and MPAP-SPAP relation according to disease groups.**



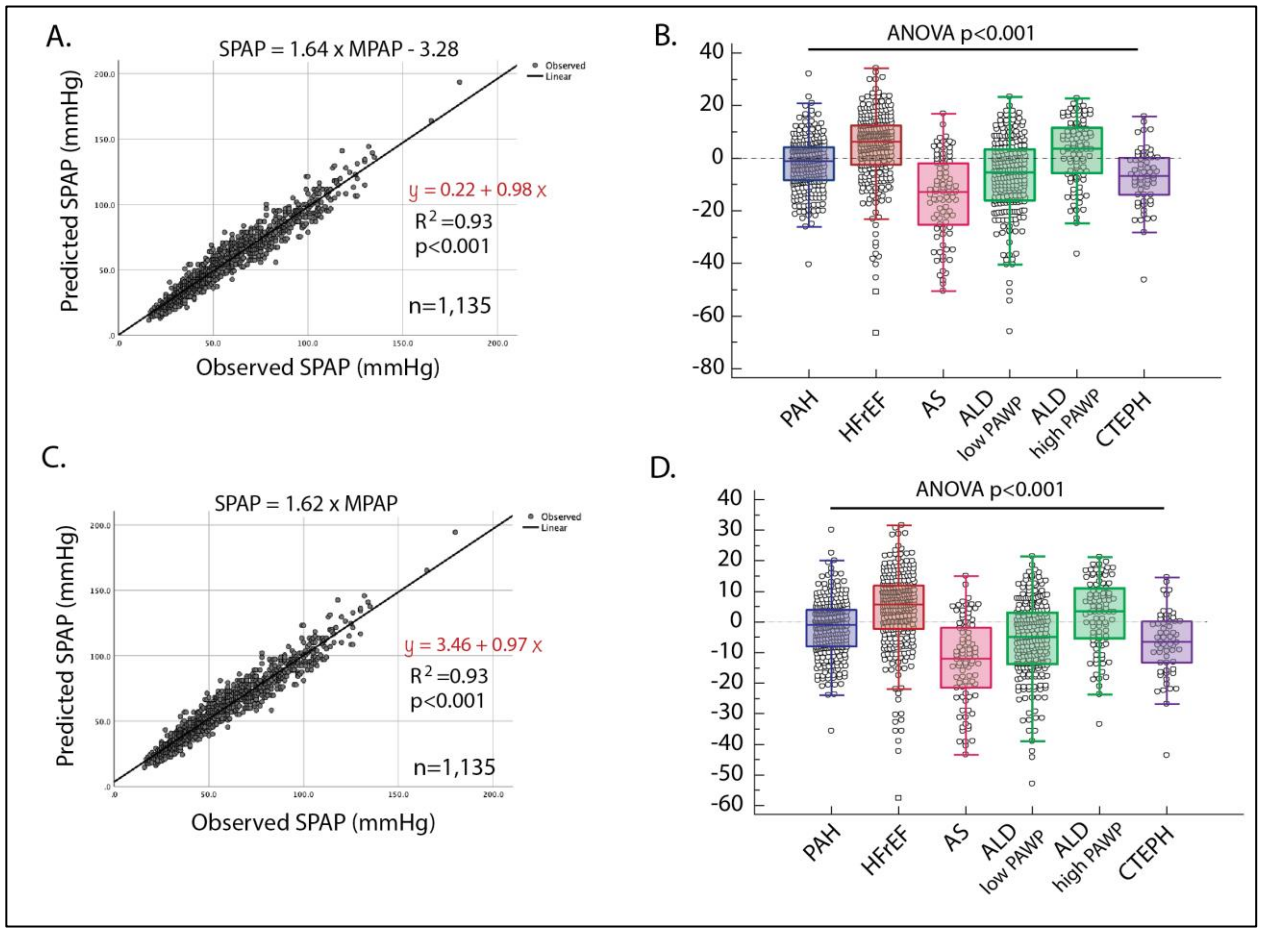

Correlations are presented by their Pearson r coefficient and significant correlations ($p<0.05$) are presented in bold. The linear relation between mean MPAP and systolic pulmonary arterial pressure SPAP is expressed as the Pearson correlation coefficient ($R^2$ and p value). ALD: advanced lung disease; AS: aortic stenosis; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; DPAP: diastolic pulmonary arterial pressure; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; LV: left ventricle; MPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary arterial wedge pressure; PP: pulse pressure; RAP: right atrial pressure; SPAP: systolic pulmonary arterial pressure.

**Figure S2. (A) Plots of the residuals value of the novel equation (SPAP = 1.39 x MPAP x $PAWP^{-0.07}$ x $T^{0.12}$ x $age^{0.08}$) and the predicted values (left panel) and observed SPAP value (right panel), showing the absence of heteroscedasticity.**




MPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; SPAP: systolic pulmonary arterial pressure; T: heart period (defined as 60/heart rate).

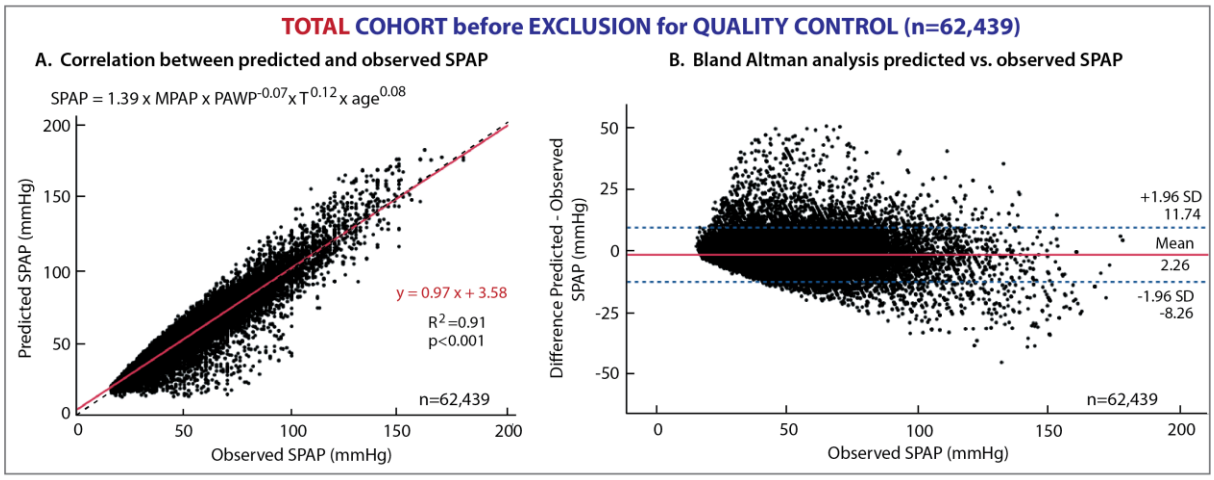
**Figure S3. Performance of the two equations published by Chemla et al. in our derivation cohort.**




**(A)** Graphic representation of the relation between observed SPAP and predicted SPAP from the equation published by Chemla et al. in 2004 (SPAP = 1.64 x MPAP – 3.28 mmHg corresponding to MPAP = 0.61 x SPAP + 2mmHg). **(B)** Residuals of the predicted SPAP showing significant statistical difference according to disease groups using ANOVA, particularly in patients with high PAWP (HFrEF or ALD with high PAWP) or in patients with aortic stenosis. **(C)** Graphic representation of the relation between observed SPAP and predicted SPAP from the equation derived from the golden number (SPAP = 1.62 x MPAP). **(D)** Residuals of the predicted SPAP showing significant statistical difference according to disease groups using ANOVA, particularly

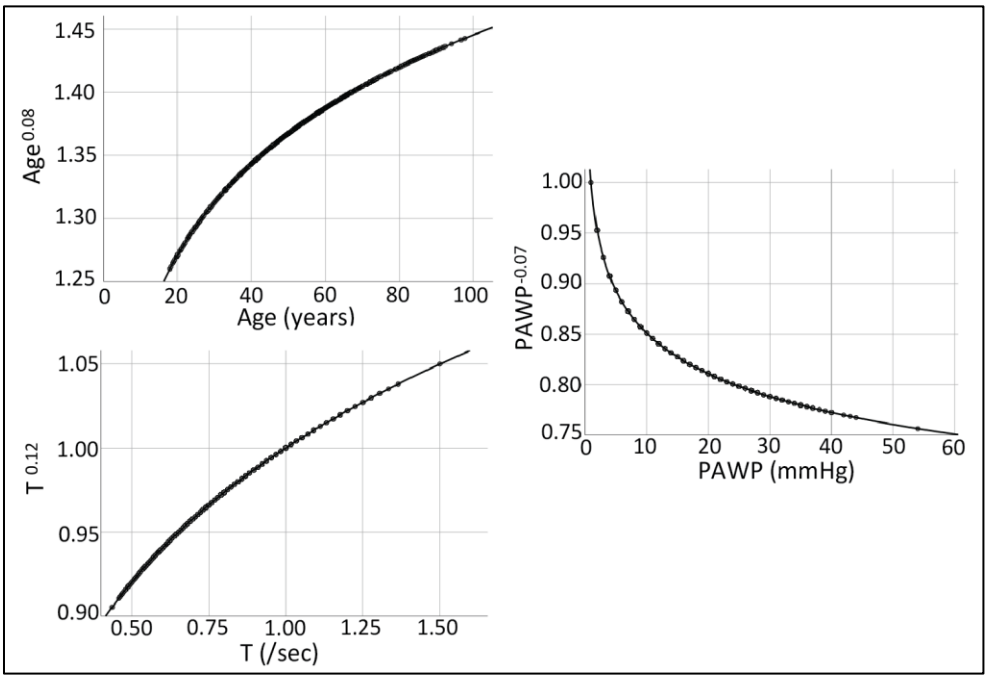
in patients with high PAWP (HFrEF or ALD with high PAWP) or in patients with aortic stenosis. ALD: advanced lung disease; AS: aortic stenosis; CTEPH: chronic thromboembolic pulmonary hypertension; HFrEF: heart failure with reduced ejection fraction; PAH: pulmonary arterial hypertension; PAWP: pulmonary artery wedge pressure.

**Figure S4. Validation of the equation in the total UNOS cohort before exclusion of the outliers for data physiological quality purposes.**




Linear regression and Bland-Altman analysis plots assessing the correlation between predicted and observed SPAP, colored by the density of the points (yellow indicating high density and blue indicating low density). Pearson coefficients are presented as $R^2$ values. MPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; SPAP: pulmonary arterial pressure; T: period (60/heart rate) assumed to be 80/min as the heart rate was not available at the time of catheterization in the UNOS database.

**Figure S5. Range of variability of each variable of the equation ($Age^{0.08}$, $T^{0.12}$, and $PAWP^{-0.07}$) as a function of the original variable (Age, T and PAWP respectively).**




As an example, when age varies from 40 to 80, $Age^{0.08}$ increased from 1.34 to 1.42 (a 0.08 difference), which being multiplicative in the equation [$SPAP = 1.39*MPAP*PAWP^{-0.07}*T^{0.12}*Age^{0.08}$] results in a 8% difference in SPAP. MPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; SPAP: systolic pulmonary arterial pressure; T: heart period (60/heart rate).