Original Research Article

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Hemodynamic trajectories and outcomes in patients with pulmonary arterial hypertension

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Abstract

The relative pulmonary to systemic pressure ratio (mean pulmonary arterial pressure/mean arterial pressure) has been proven to be valuable in cardiac surgery. Little is known on the prognostic value of baseline and trajectory of mean pulmonary arterial pressure/mean arterial pressure in pulmonary arterial hypertension. Patients with confirmed idiopathic, familial, drug and toxins, or connective tissue disease-related pulmonary arterial hypertension and at least one complete right heart catheterization were included and prospectively followed-up for 5.9 ± 4.03 years. Correlates of the primary end point (i.e. death or lung transplant need) during follow-up were determined using Cox regression modeling. Results showed that among the 308 patients included, 187 had at least one follow-up catheterization (median time between catheterizations: 2.16 (1.16–3.19) years). In the total cohort (mean age 47.3 ± 14.9 years, 82.8% of female and 58.1% in New York Heart Association class 3 or 4), mean pulmonary arterial pressure/mean arterial pressure (1.38 (1.07–1.77)) was associated with outcome ($p = 0.01$). Mean pulmonary arterial pressure/mean arterial pressure was incremental to a basic model (including right atrial pressure, systolic blood pressure, New York Heart Association class 3 or 4, and connective tissue disease) for outcome prediction, while mean pulmonary arterial pressure was not. In the 187 patients with a follow-up catheterization, both delta mean pulmonary arterial pressure and delta mean pulmonary arterial pressure/mean arterial pressure were associated with outcome (1.32 (1.11–1.58) and 1.31 (1.1–1.57) respectively, $p < 0.01$). Mean pulmonary arterial pressure and mean pulmonary arterial pressure/mean arterial pressure were both incremental to the basic model, while worsening in mean pulmonary arterial pressure or mean pulmonary arterial pressure/mean arterial pressure did not reach significance. In conclusion, mean pulmonary arterial pressure/mean arterial pressure at baseline prognosticates long-term outcome with a significant, albeit modest, incremental value to basic variables.

Keywords

outcomes, physiology, pulmonary circulation, pulmonary hypertension, right heart catheterization

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Introduction

The relative pulmonary pressure is defined by the ratio of mean pulmonary arterial pressure (MPAP) to systemic mean arterial pressure (MAP). Integrating both pulmonary and systemic circulation into one metric, the relative pulmonary pressure (MPAP/MAP) theoretically offers the advantage to be less susceptible to changes in cardiac

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output (CO) or changes in MPAP (secondary to sedation during catheterization or drugs) than absolute MPAP.[1] The relative pulmonary pressure has been proven to be valuable for risk prediction of perioperative outcomes in patients undergoing cardiac surgery.[2–5] Similarly, the concept of relative pulmonary hypertension (PH) (defined by the pulmonary vascular resistance to systemic vascular resistance ratio, PVR/SVR) has been used in children with congenital heart disease for management of PH.[6] However, little is known on the prognostic value of these ratios or their trajectory over time in adult patients with pulmonary arterial hypertension (PAH).

In PAH, the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) registry has identified systemic blood pressure, but not MPAP, as an independent predictor of outcome, which might reflect the CO-dependency of MPAP.[7] As the disease progresses and the right heart fails, the decrease in CO can be associated with a decrease in MPAP, which should not be interpreted as an improvement in the disease severity.[8] In this study, we hypothesized that the relative pulmonary pressure and its trajectory would be more predictive than MPAP in patients with PAH.

The first objective was to compare the prognostic value of relative pressure ratios to other hemodynamics metrics in a large prospective cohort of adult patients with PAH evaluated at a single tertiary care center. The second objective was to compare the trajectory of the MPAP/MAP to other invasive metrics in the subgroup of patients with at least one follow-up right heart catheterization (RHC), and to assess their prognostic value. The third objective was to compare the changes in right ventricular pressure and the relative right ventricular pressure ratio in response to experimental modulations of volume loading and inotropy in a piglet PH model with a wide range of hemodynamic severity.

Methods

Study population

Between 1997 and 2016, 508 patients were included in the Stanford prospective PAH registry. Inclusion criteria included a diagnosis of idiopathic, familial, drug and toxins, or connective tissue disease-related PAH (MPAP $\geq$ 25 mmHg and pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg) and complete RHC data as defined below available at inclusion (defined by the date of first RHC). Exclusion criteria included other PAH etiologies (with shunts such as congenital systemic-to-pulmonary shunts or portal hypertension, HIV-related, or non-WHO group 1 causes) or incomplete or unavailable RHC data. A total of 308 patients were included and will be referred to as the ''total cohort.'' Follow-up RHC was available in 187 patients (including 99 patients with more than one follow-up RHC) who will be referred to as the ''follow-up cohort.'' This retrospective study based on a prospective registry was approved by the Stanford University Institutional Review Board and was conducted in agreement with the Helsinki-II Declaration. All patients gave written informed consent.

Hemodynamic assessment

The baseline was defined as the date of the first RHC. Catheterization was performed through the internal jugular or right femoral vein under, at most, mild sedation. Heart rate and noninvasive MAP were measured at the time of MPAP measurement to allow determination of relative pressure ratios. Mean right atrial pressure (RAP), systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), and MPAPs, and PAWP were measured. CO was measured using the indirect Fick method or thermodilution, and indexed on body surface area (cardiac index (CI)). The PVR (Wood Units (WU)) was calculated as the (MPAP – PAWP) divided by the CO. Pulmonary arterial compliance (mL/mmHg) was estimated by the stroke volume/pulse pressure ratio, with pulse pressure being defined by (SPAP – DPAP). The transpulmonary gradient was calculated as MPAP – PAWP, and diastolic pulmonary gradient was calculated as DPAP – PAWP. The pulmonary arterial pulsatility index was calculated as (SPAP – DPAP)/RAP. SVR (in WU) was calculated as (MAP – RAP)/CO. The following relative ratios were calculated for all patients: MPAP/MAP, RAP/PAWP, and PVR/SVR.

Clinical, laboratory and therapy data

Clinical and functional characteristics (demographics, body surface area, New York Heart Association (NYHA) functional class, six-minute walking test distance) at baseline and at the time of follow-up RHCs were collected. PH-specific therapy at the time of each RHC was collected from patient chart review.

Follow-up and end points

Patients were prospectively followed after enrollment in the registry. Follow-up was concluded in June 2018. The primary combined endpoint was death, or bilateral lung or heart–lung transplant. Death was verified through the National Social Security Death Index (current as of 28 February 2014) as well as thorough chart review, while transplantation was verified through chart review and follow-up. Follow-up RHCs performed at Stanford were collected following the same methodology as for the first RHC.

Animal models

The Marie Lannelongue Hospital (Le Plessis-Robinson, France) institutional animal care committee approved all

procedures that were performed according to institutional guidelines complying with national and international regulations.

A first group of eight large white pigs (*Sus scrofa*) at six-weeks of age at the time of study enrollment (referred to as early PH (ePH)) included four healthy pigs and four pigs in whom mild PH was induced by performing an extra-pericardial left pulmonary artery ligation followed by right lower lobe embolizations with embucrylate (Histoacryl®, B Braun Medical, France) once a week for three weeks as previously described.[9,10] Hemodynamics were analyzed at baseline (ePH) and after 5 µg/kg/min dobutamine infusion (ePH dobu5) to assess the variability of the invasive relative pressure ratio (i.e. the maximal systolic RV pressure (RVPmax) by RHC divided by the maximal systolic LV pressure (LVPmax) by left heart catheterization, RVPmax/LVPmax, which serves as surrogate of the MPAP/MAP ratio which was measured at baseline).

A second group of six additional pigs was evaluated after 16 weeks of the development of chronic thromboembolic PH (referred to as CPH). Hemodynamics was measured in baseline conditions (CPH) and after volume loading (60 mL/kg of saline infusion). In the same animals, after volume loading, further acute pulmonary embolism (bolus of 0.15 mL of embucrylate until the systemic systolic arterial pressure dropped under 90 mmHg or the systemic to pulmonary systolic pressure ratio reached 0.9) and dobutamine infusion (5 µg/kg/min) allowed the measurement of hemodynamics during acute hemodynamic compromise (acute on chronic pulmonary hypertension (ACPH)) and hemodynamic stabilization using dobutamine (ACPH dobu5) respectively, as previously published.[9,10]

The protocols for animal preparation, anesthetic maintenance, and mechanical ventilation have been previously reported.[11,12] Maximal RVPmax and LVPmax were simultaneously measured using fluid-filled catheters at different conditions. A period of 15 min of hemodynamic stabilization was observed during each condition prior to data acquisition and after return to baseline. Hemodynamic data were measured during short end-expiratory apnea. Pressures were recorded on a dedicated computer. CO was measured by the thermodilution method, total pulmonary resistance was calculated by MPAP (measured using a Swan-Ganz catheter) divided by CO.

Statistical analysis

In the clinical cohort, continuous data were expressed as mean ± standard deviation if normally distributed or median and interquartile range if not normally distributed. Continuous variables were compared using the two-sided Student's paired *t*-test or Mann–Whitney test as appropriate. Categorical data were presented as numbers (percentage) and compared using the Chi-square test. Longitudinal changes in continuous hemodynamic variables between the first and second RHC were expressed as relative changes $100 \times$ (second RHC – first RHC)/first RHC. Significant changes were pre-defined as >15% increase or <15% decrease in hemodynamics between the two RHCs, to account for the variability of the measurements. Correlations between the continuous variables were presented as Pearson correlation coefficients (r) and their *p* values. Kaplan–Meier statistics were used to estimate overall transplant-free survival distribution (patients were censored at the time of transplantation). Cox proportional hazards regression models were used to determine the correlates of outcomes (i.e. death or lung or heart–lung transplant) at five years. To assess the assumption of proportional hazards, scaled Schoenfeld residuals for each independent variable were plotted against time; these correlations were found to be nonsignificant for all variables included in the multivariable models. The linear relationship between the continuous variables and the logit of the outcomes was also verified. In case of a nonlinear relationship, the continuous variable was log transformed or presented as categories. Variables with $p < 0.10$ were then entered in the model and selected using a stepwise procedure with a threshold of $p < 0.05$. Hazard ratios are presented per standard deviation of the considered continuous variables to correct for variations of units. Results were considered significant when two-sided *p*-values < 0.05. Statistical analyses were performed using SPSS statistical software (SPSS v.25, Inc., Chicago, IL) and MedCalc v.18.

In the experimental cohort, hemodynamic data were presented as median and interquartile range. Values were compared using the non-parametric Mann–Whitney test for unpaired values and the Wilcoxon rank test for paired values using GraphPad Prism (8.3.0). Results were considered significant when two-sided *p*-values < 0.05.

Results

Baseline characteristics of the clinical cohorts

Among the 508 patients with PAH screened (Fig. 1), 308 patients were included (baseline mean age 47.3 ± 14.9 years, 83% female, 58% NYHA class III or IV (Table 1)). The follow-up cohort consisted of the 187 patients with at least one follow-up RHC. The baseline characteristics of this "follow-up cohort" at the time of first RHC are presented in Table 1, showing similar demographics and disease severity at baseline. MPAP was strongly correlated with SPAP, the transpulmonary gradient, DPAP and PVR ($r = 0.96$, 0.96, and 0.68, respectively, all $p < 0.01$). In contrast, the same correlations for MPAP/MAP were all weaker ($r = 0.81$, 0.83, 0.75, and 0.60, respectively, all $p < 0.01$) (Supplementary Fig. S1).

Longitudinal analysis of the "follow-up cohort" (n = 187)

The mean period of time between the first and second RHC was 2.37 ± 1.52 years (ranging from 2 months to 8.8 years).

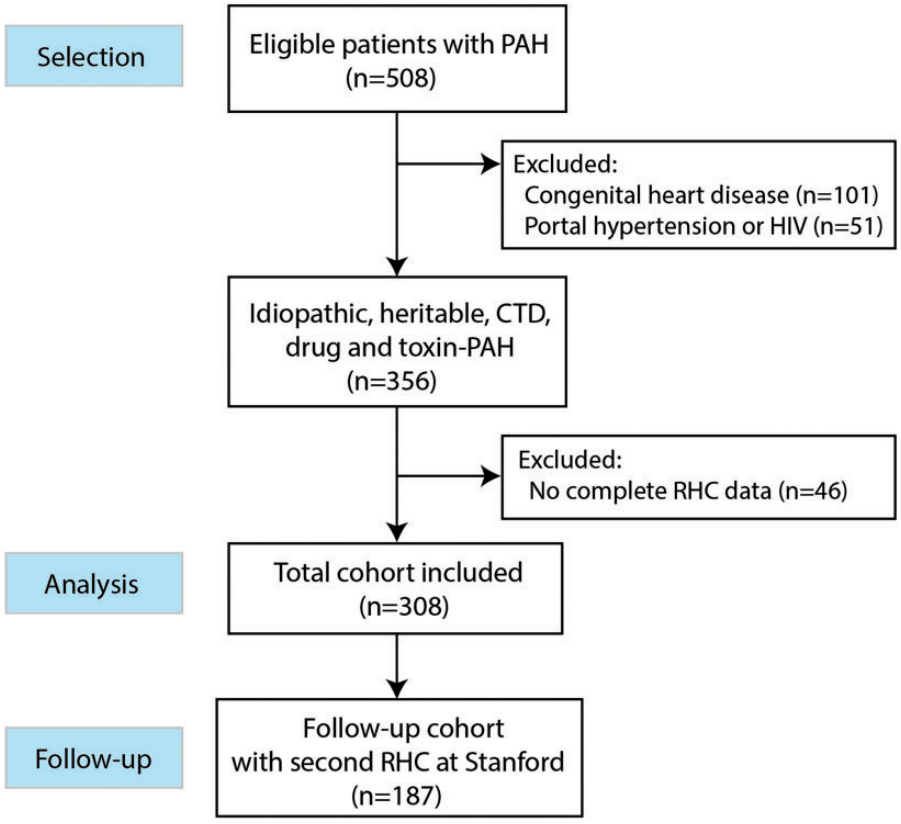

Fig. 1. Flow chart of the clinical population.
CTD: connective tissue disease; HIV: human immunodeficiency virus; PAH: pulmonary arterial hypertension; RHC: right heart catheterization.

Among them, $n = 100$ patients underwent three or more RHCs at our center. Table 1 compares the characteristics at the time of the first RHC and those at the time of the second RHC in the "follow-up cohort", and shows a decrease in PVR, pulmonary arterial compliance, MPAP, SPAP, and a significant increase in stroke volume and CI. Systemic pressures (MAP and diastolic blood pressure but not systolic blood pressure) and SVR decreased, but to a lower extent than pulmonary pressures and PVR, resulting in a significant decrease in the relative pressure ratios (MPAP/MAP and PVR/SVR) during follow-up. Fig. 2a illustrates the changes in systolic blood pressure, MPAP, MPAP/MAP, PVR, and heart rate between the first and the second RHC. At the time of first RHC, 161 patients were already on single or combined PH-specific therapy. PH-specific therapy was introduced after the first RHC in 52 patients. At the time of the second RHC, $n = 184$ patients were receiving at least one PH-specific therapy (Table 1).

Fig. 2b–d illustrate the discordance between changes in hemodynamics during follow-up. About 70% of patients showed significant improvement in at least one of the three hemodynamic parameters: MPAP/MAP, PVR, or stroke volume index (Fig. 2b). Among them, only one-fourth (17.5% of the total cohort) showed improvement in all three parameters. Improvement in only MPAP/MAP was found in 10 patients (5.3%). Relative changes in MPAP/MAP according to changes in CI are displayed in Fig. 2c. Table 2 compares the baseline characteristics and changes in hemodynamics of patients who experienced improved, stable, or worsened CI during follow-up. Baseline MPAP/MAP did not differ between the groups, while MPAP and PVR did. Patients in whom CI improved during follow-up had more improvement in MPAP/MAP than those who were stable or worsened during follow-up ($p = 0.01$). Fig. 2d presents the correlations between relative changes in hemodynamics highlighting the strong correlation between change in MPAP/MAP and change in MAP ($r = 0.83$), the moderate correlation with change in PVR (0.44), and the weak inverse correlation with change in CI ($r = -0.21$).

Outcome analysis

During a mean follow-up of 6.03 ± 4.10 years (maximum 17.01 years), 125 patients reached the primary endpoint of death or transplant (112 deaths, 17 double lung transplant, and 1 heart–lung transplant). Transplant-free survival rates (standard error) were 90.4 (1.7)% at 1 year, 86.4 (2.0)% at 2 years, 78.6 (2.4)% at 3 years, 72.0 (2.7)% at 5 years, and 51.7 (3.6)% at 10 years (Supplementary Fig. S2).

The correlates of the primary endpoint (death or lung transplant) at five years in the total cohort ($n = 308$) among variables at the time of the first RHC, using

Table 1. Comparative characteristics of the total cohort with pulmonary arterial hypertension PAH ($n = 308$) at baseline, and of the subgroup ($n = 187$) with available follow-up right heart catheterization data at the time of baseline and follow-up.

Variables	Total cohort at baseline ($n = 308$)	Follow-up cohort at baseline ($n = 187$)	Follow-up cohort at follow up ($n = 187$)
Age (years)	47.3 ± 14.9	45.2 ± 13.7	47.5 ± 13.8[a]
Female sex (%)	255 (82.8%)	156 (83.4%)	156 (83.4%)
Body surface area (m^2)	1.83 ± 0.27	1.81 ± 0.25	1.80 ± 0.26
PAH etiology			
Idiopathic, heritable, familial	92 (29.9%)	61 (32.3%)	61 (32.3%)
Connective tissue disease	127 (41.2%)	79 (42.2%)	79 (42.2%)
Drug and toxin	89 (28.9%)	47 (24.9%)	47 (24.9%)
NYHA class (%)			
Class I	25 (8.1%)	15 (8.0%)	7 (3.7%)
Class II	98 (31.6%)	65 (34.8%)	80 (42.9%)
Class III	152 (49.0%)	92 (49.2%)	83 (44.4%)
Class IV	35 (11.3%)	15 (8.0%)	17 (9.1%)
Heart rate (bpm)	79.1 ± 14.7	78.7 ± 13.6	77.2 ± 16.1
Systolic blood pressure (mmHg)	118.8 ± 20.8	116.0 ± 20.0	114.5 ± 17.3
Diastolic blood pressure (mmHg)	66.8 ± 14.6	66.0 ± 14.4	61.8 ± 11.3[a]
Systolic blood pressure < 110 mmHg (%)	118 (38.3%)	77 (41.2%)	76 (40.6%)
Mean arterial pressure (mmHg)	86.8 ± 14.8	85.3 ± 14.2	81.3 ± 11.1[a]
Right atrial pressure (mmHg)	9.3 ± 6.1	8.8 ± 5.5	8.1 ± 4.6
Systolic pulmonary arterial pressure (mmHg)	78.8 ± 24.1	80.6 ± 22.4	75.7 ± 24.6[b]
Diastolic pulmonary arterial pressure (mmHg)	30.7 ± 12.3	31.1 ± 11.8	29.4 ± 13.6
Mean pulmonary arterial pressure (mmHg)	48.9 ± 15.5	50.1 ± 14.8	46.7 ± 14.6[a]
Pulmonary artery wedge pressure (mmHg)	9.9 ± 4.6	9.3 ± 4.1	10.5 ± 4.4[b]
Pulmonary vascular resistance (PVR) (Woods Unit)	12.0 ± 7.2	12.3 ± 6.0	9.9 ± 5.3[a]
Systemic vascular resistance (SVR) (Woods Unit)	22.6 ± 9.2	22.2 ± 8.8	19.4 ± 6.5[a]
PVR/SVR	0.54 ± 0.29	0.57 ± 0.24	0.51 ± 0.21[a]
Pulmonary arterial compliance (mL/mmHg)	0.12 ± 0.08	0.11 ± 0.07	0.13 ± 0.08[b]
Right atrial pressure/pulmonary capillary wedge pressure	1.01 ± 0.78	1.01 ± 0.71	0.81 ± 0.47
Mean pulmonary arterial pressure/mean arterial pressure	0.57 ± 0.19	0.59 ± 0.19	0.57 ± 0.18
Mean pulmonary arterial pressure/systolic blood pressure	0.42 ± 0.15	0.44 ± 0.14	0.41 ± 0.14
Cardiac output (L/min)	3.83 ± 1.35	3.83 ± 1.35	4.04 ± 1.04
Cardiac index (L/min/m^2)	2.10 ± 0.67	2.12 ± 0.68	2.27 ± 0.53[b]
Stroke volume (mL)	49.9 ± 19.6	50.2 ± 20.2	54.0 ± 15.6[b]
Stroke volume index (mL/m^2)	27.3 ± 9.6	27.8 ± 10.4	29.7 ± 8.0[b]
PH-specific therapy	161 (52.3%)	132 (70.6%)	184 (98.4%)
Phosphodiesterase 5 inhibitor (PDE5I)	68 (42.2%)	55 (29.4%)	98 (52.4%)
Endothelin receptor antagonist (ERA)	57 (35.4%)	48 (25.7%)	73 (39.0%)
Prostacyclins	68 (42.2%)	58 (31.0%)	95 (50.8%)
Calcium channel blockers	48 (29.8%)	39 (20.9%)	45 (24.1%)
Double therapy (PDE5I and ERA, or PDE5I and prostacyclins, or ERA or prostacyclins)	28 (9.1%)	27 (14.4%)	72 (38.5%)
Triple therapy (PDE5I, ERA, and prostacyclins)	6 (1.9%)	5 (2.8%)	9 (4.8%)

Note: Baseline was defined as the date of the first right heart catheterization. The median time (25th–75th) between the two RHCs was 2.16 years (1.16–3.19). There was no statistical difference between baseline characteristics of the "total cohort" and the "follow-up cohort".

[a] $p < 0.001$ for comparison of hemodynamics between baseline and follow-up in the "follow-up cohort".

[b] $p < 0.05$.

PH: pulmonary hypertension.

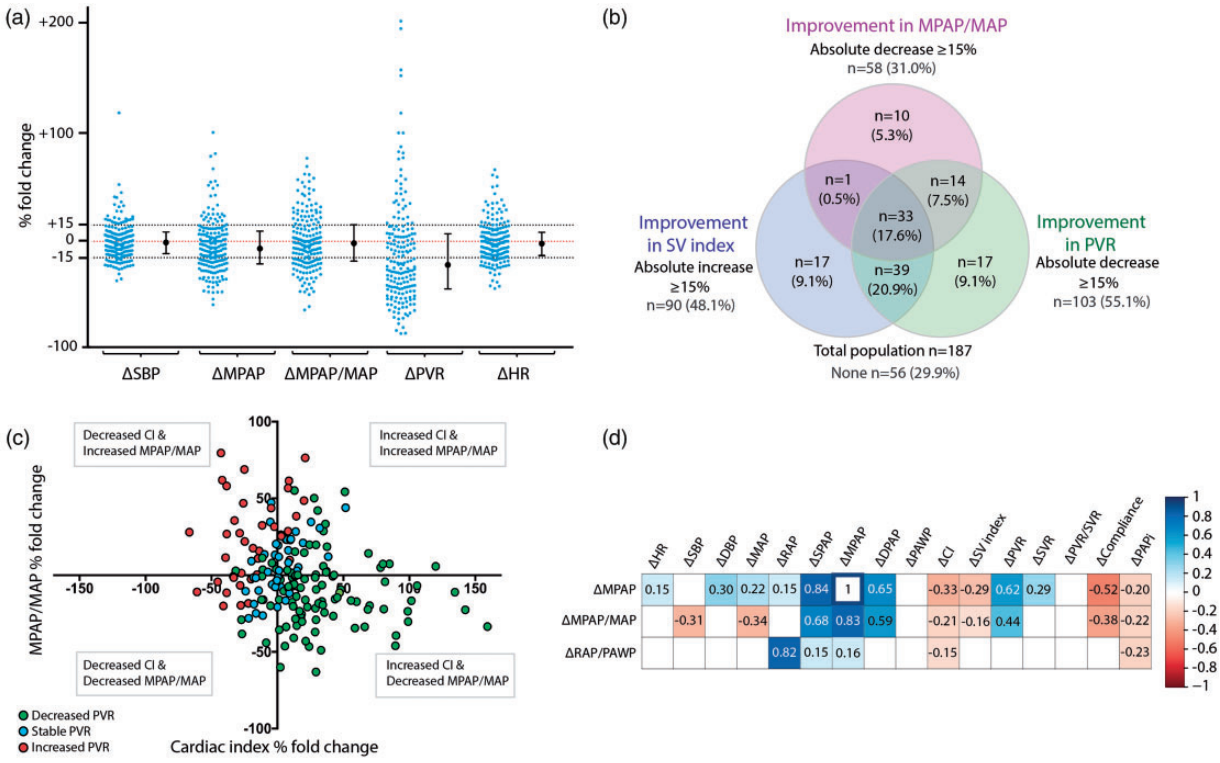

Fig. 2. Changes in hemodynamics with follow-up. (a) Scatter box plots for percent changes of hemodynamic variables ($n = 187$) between two right heart catheterizations (RHC). Δ denotes a relative change percentage between first and second RHC as follows: 100 × (second – first)/first. (b) Venn diagram of improvement in relative pressure (mean pulmonary arterial pressure/mean arterial pressure (MPAP/MAP)), stroke volume (SV) index, and pulmonary vascular resistance (PVR). (c) Scatterplot of linear regression correlation coefficient model of cardiac index change and relative pressure change ($R^2 = 0.045$, $p = 0.003$). (D) Correlation heatmap of the relative change in hemodynamics between the first and second RHC in the follow-up cohort ($n = 187$). Δ denotes a relative change percentage between first and second RHC as follows: 100 × (second – first)/first. Correlations are expressed using Pearson (r) correlations between variables; only statistically significant correlations (p values < 0.05) are shown.

CI: cardiac index; DBP: diastolic blood pressure; DPAP: diastolic pulmonary arterial pressure; HR: heart rate; PAWP: pulmonary arterial wedge pressure; RAP: right atrial pressure; SBP: systolic systemic blood pressure; SPAP: systolic pulmonary arterial pressure; SVR: systemic vascular resistance; PAPi index: pulmonary arterial pulsatility index.

univariable Cox regression analysis, included heart rate, systolic blood pressure, stroke volume index, CI, RAP, and the relative ratios MPAP/MAP, MPAP/SBP, and RAP/PAWP (Table 3). In order to build the multivariable Cox regression stepwise model for prediction of death or lung transplant at five years, nine variables were chosen among previously validated prognostic markers (age, connective tissue disease etiology, heart rate, SBP, NYHA functional class III or IV, RAP, CI). Among them, SBP (adjusted HR (95%CI) = 0.65 (0.53–0.81), $p = 0.004$), NYHA III or IV class (HR = 1.6 (1.04–2.47), $p = 0.033$), RAP (HR = 1.41 (1.19–1.69), $p = 0.001$), and connective tissue disease etiology (HR = 1.57 (1.08–2.29), $p = 0.018$) were retained in the model (Chi-square = 36.2, $p < 0.0001$), referred to as the basic model. As illustrated in Fig. 3a, adding MPAP/MAP (Chi-square = 40.3, $p < 0.0001$) was incremental to the basic model ($p = 0.04$) for risk prediction of death or lung transplant at five years, while adding MPAP did not reach significance ($p = 0.07$).

The correlates of the primary endpoint (death or lung transplant) at five years in the "follow-up" cohort ($n = 187$) among variables at the time of the second RHC using univariable Cox regression analysis are presented in Table 3. An increase of at least 15% in MPAP or MPAP/MAP between the two RHCs were both predictors of the primary end point, while neither change in CI nor stroke volume index were significantly associated with outcomes (Table 4). We then assessed the potential incremental prognostic value of MPAP or MPAP/MAP or their relative change on a similar basic model (Chi-square = 44.2, $p < 0.0001$) to the one used for the total cohort, including delta time between the two RHCs in addition to systolic blood pressure, NYHA III or IV class, RAP, and connective tissue disease etiology. Adding MPAP (Chi-square = 48.5, $p < 0.0001$) or MPAP/MAP (Chi-square = 50.8, $p < 0.0001$) at the time of second RHC were significantly incremental to the basic model for risk prediction of death or lung transplant at three years (Fig. 3b). In contrast, adding an increase

Table 2. Comparative characteristics of patients from the follow-up cohort ($n = 187$) according to changes in cardiac index.

	Improved cardiac index (>15%) $n = 73$	Stable cardiac index (+15%; −15%) $n = 79$	Worsened cardiac index (<15%) $n = 35$	*p* Values
Age, years	46.0 (37.4–55.0)	45.0 (34.0–53.0)	45.0 (38.0–54.0)	0.81
Female sex	59 (80.8%)	68 (86.1%)	29 (82.9%)	0.68
Connective tissue disease etiology	30 (41.1%)	35 (44.3%)	14 (40.0%)	0.88
NYHA class III or IV	43 (58.9%)	47 (59.5%)	17 (48.6%)	0.52
Time between the two RHC	2.3 (1.3–3.4)	1.8 (1.0–2.9)	1.3 (1.2–3.2)	0.27
Hemodynamics at baseline				
RAP (mmHg)	6.0 (3.0; 12.0)	8.0 (5.0; 12.0)	10.0 (5.0; 14.0)	0.12
MPAP (mmHg)	48.0 (33.0; 52.0)	51.0 (44.0; 59.0)	55.0 (44.0; 61.0)	**0.02**
MPAP/MAP	0.60 (0.50; 0.72)	0.62 (0.48; 0.72)	0.60 (0.42; 0.70)	0.54
PVR (WU)	7.2 (4.9; 10.2)	11.7 (8.4; 14.7)	15.0 (12.0; 18.3)	<**0.0001**
Hemodynamics trajectory				
Delta RAP (%)	−16.7 (–50.0; 0.0)	0.0 (–33.3; 62.8)	7.7 (–26.6; 50.0)	**0.001**
Delta MPAP (%)	−14.7 (–28.2; 0.8)	–3.1 (–17.2; 12.2)	1.7 (–13.7; 25.0)	<**0.0001**
Delta MPAP/MAP (%)	–9.3 (–23.5; 7.3)	–0.1 (–11.7; 16.2)	–0.8 (–11.5; 26.7)	**0.01**
Delta PVR (%)	–43.5 (–57.8; –28.0)	–9.5 (–29.0; 7.4)	33.9 (3.9; 82.5)	<**0.0001**

Continuous data are presented as median and interquartile range and compared using Kruskall–Willis test, and categorical data is presented as number and percentage and compared using Chi-square test.
MPAP: mean pulmonary arterial pressure; MPAP/MAP: mean pulmonary arterial pressure/mean arterial pressure; PVR: pulmonary vascular pressure; RAP: right atrial pressure; NYHA: New York Heart Association; RHC: right heart catheterization.

of at least 15% in MPAP or in MPAP/MAP between the two RHCs did not reach significance.

Variability of the relative ratio in the piglet PH models

The RVPmax/LVPmax, used as a surrogate of MPAP/MAP in the piglet models, was strongly correlated to the MPAP/MAP in all groups (ePH, CPH, ACPH) at baseline conditions ($R^2 = 0.91$, $p < 0.0001$) (Supplementary Fig. S3). Fig. 4a compares the RVPmax/LVPmax ratio at baseline between ePH, CPH, and ACPH. At baseline, the RVPmax/LVPmax was significantly higher in ACPH pigs than in ePH, while it did not reach significance when comparing CPH and ePH. In ePH pigs, RVPmax, LVPmax, and CO increased during dobutamine infusion, whereas the RVPmax/LVPmax remained stable (Fig. 4b). Similarly, in hemodynamically compromised animals (ACPH), LVPmax and CO increased during dobutamine infusion, whereas the RVPmax/LVPmax remained stable. In pigs with chronic PH (CPH), volume loading had no significant effect on ventricular pressures, RVPmax/LVPmax, resistance, or CO (Supplementary Fig. S4).

Discussion

This study has three main findings informing hemodynamic analysis of patients with PAH. First, the relative pulmonary pressure (MPAP/MAP) is prognostic of long-term outcomes in patients with PAH, though its incremental value over classic hemodynamics (MPAP) appears to be marginal. Second, while hemodynamic trajectories based on relative pressure or PVR are predictive of long-term outcome, they are not more predictive than the corresponding absolute value on the follow-up RHC. Third, the animal model highlights the stability of the relative pressure ratio in the setting of acute changes in CI, supporting its physiologic utility in acute care settings.

Invasive pulmonary hemodynamics have been used for several decades as prognostic markers of long-term outcome in patients with PAH. MPAP was initially shown to be independently predictive of death or heart–lung transplant need in the 1991 National Institute of Health multicenter PH registry, along with CI and RAP.[13] Since then, MPAP was more inconsistently associated with outcomes in large PAH prospective registries. In the Pulmonary Hypertension Connection study, MPAP was predictive of survival independently from CI and RAP,[14] while it was not retained in the models derived from the French or the UK national registries.[15,16] The CO-dependency of MPAP limits its value to reflect pulmonary disease severity. As right heart failure progresses, a decrease in CO (clinically observed by a decrease in systemic pressures) can lead to a decrease in MPAP.[17] One way to overcome this phenomenon is to correct the MPAP by the CO, which defines PVR. The prognostic value of PVR has been validated by the REVEAL registry, consistent with our findings.[7] However, PVR estimation requires invasive measurement of the CO during RHC, which can be associated with estimation errors

Table 3. Univariable Cox regression analysis for correlates of death or lung transplant need at five years variables at the time of first RHC for the total cohort ($n = 308$) and variables at the time of second RHC for the "follow-up" cohort ($n = 187$).

	Total cohort ($n = 308$)		"Follow-up" cohort ($n = 187$)	
Variables	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	0.94 (0.73–1.21)	0.65	1.16 (0.91–1.50)	0.22
Body surface area (m^2)	0.91 (0.70–1.18)	0.47	1.03 (0.79–1.34)	0.83
Heart rate (bpm)	1.63 (1.05–2.56)	0.03	1.52 (1.01–2.31)	0.04
Systolic blood pressure (mmHg)	0.62 (0.46–0.81)	<0.01	0.71 (0.55–0.92)	0.01
Systolic blood pressure <110 mmHg	1.94 (1.17–3.21)	0.01	1.82 (1.09–3.03)	0.02
Diastolic blood pressure (mmHg)	0.66 (0.52–0.85)	<0.01	0.69 (0.54–0.87)	<0.01
Mean arterial pressure (mmHg)	0.58 (0.44–0.78)	<0.001	0.63 (0.48–0.83)	<0.01
Right atrial pressure (RAP) (mmHg)	1.47 (1.14–1.92)	<0.01	2.21 (1.65–2.97)	<0.01
Systolic pulmonary arterial pressure (mmHg)	0.86 (0.68–1.10)	0.25	0.80 (0.63–1.02)	0.08
Diastolic pulmonary arterial pressure (mmHg)	0.91 (0.70–1.16)	0.44	0.89 (0.69–1.14)	0.34
Mean pulmonary arterial pressure (mmHg)	0.87 (0.69–1.11)	0.28	0.81 (0.64–1.14)	0.09
Pulmonary vascular resistance (PVR) (WU)	1.08 (1.03–1.15)	0.02	1.16 (1.02–1.32)	0.03
Pulmonary arterial wedge pressure (PAWP) (mmHg)	0.84 (0.55–1.01)	0.07	0.83 (0.63–1.09)	0.18
Systemic vascular resistance (SVR) (WU)	0.63 (0.46–0.87)	<0.01	0.65 (0.47–0.89)	<0.01
PVR/SVR	1.14 (0.94–1.39)	0.19	1.13 (0.88–1.45)	0.33
Pulmonary compliance (mL/mmHg)	1.02 (0.99–1.04)	0.15	1.23 (0.88–1.45)	0.05
PAPi index	0.71 (0.48–1.04)	0.08	0.68 (0.45–1.03)	0.07
RAP/PAWP	1.29 (1.13–1.46)	0.01	1.18 (0.98–1.43)	0.08
Mean pulmonary arterial pressure/mean arterial pressure	1.38 (1.07–1.77)	0.01	1.36 (1.07–1.73)	0.01
Mean pulmonary arterial pressure/systolic blood pressure	1.20 (1.02–1.41)	0.04	1.37 (1.08–1.74)	0.02
Cardiac index ($L/min/m^2$)	1.28 (1.03–1.58)	0.02	1.24 (1.00–1.54)	0.05
Stroke volume index (mL/m^2)	0.76 (0.62–0.94)	0.01	1.14 (0.97–1.42)	0.09

Note: For continuous variables, hazard ratios and their 95% confidence interval are adjusted by the standard deviation of the variable (as hazard ratiôstandard deviation) for comparison purposes.
PAPi index: pulmonary arterial pulsatility index.

particularly when using the indirect Fick method or the thermodilution method. In contrast, the gold standard direct Fick method for CO measurement increases accuracy in the CO estimation but takes time and material that limits clinical workflow in the catheterization laboratory. Being able to correct the MPAP by a non-invasive measure, such as the MAP, could offer an advantage for continuous patients' monitoring using a Swan-Ganz.

The value of relative pressure ratios has been previously reported in perioperative settings prone to acute changes in hemodynamics. Several studies have reported the prognostic value of the reversed pulmonary relative pressure ratio (MAP/MPAP) for in-hospital and long-term outcomes after cardiac surgery. In a large cohort of 1439 patients undergoing cardiac surgery after induction of anesthesia, MAP/MPAP was shown to be a strong predictor of in-hospital surgical outcome (i.e. death, resuscitated cardiac arrest, use of vasopressive drugs for > 24 h postoperatively, or the use of an intra-aortic balloon pump).[2] In addition, the ratio was not significantly altered after induction of anesthesia, suggesting its promising value in perioperative settings. The same group showed that MAP/MPAP was superior to hepatic venous flow to predict difficult separation from cardiopulmonary bypass in 121 cardiac surgical patients.[3] Regarding long-term outcomes, the MAP/MPAP was associated with five-year outcome after aortic valve replacement in 199 patients,[4] while preoperative MAP/MPAP ≤ 3 was independently associated with reduced one-year survival in 126 consecutive patients undergoing orthotopic heart transplantation.[5] Relative pulmonary-systemic ratios, based on pressure or resistance, have shown to be useful in other settings, including predicting outcomes after orthotopic liver transplantation for MAP/MPAP,[18] or assessing operability in patients with congenital heart disease-associated PAH by using PVR/SVR.[6]

The value of relative pulmonary to systemic ratios has not been extensively studied in adults with PH. Emerging evidence on the prognostic value of MPAP/MAP in PAH has suggested that this ratio could be used to better adjust variations of MPAP due to decrease in CI secondary to right heart failure.[19] The present study further confirms the prognostic value of relative ratios such as the MPAP/MAP, finding a modest, albeit statistically significant, incrementally prognostic value over a basic model including NYHA

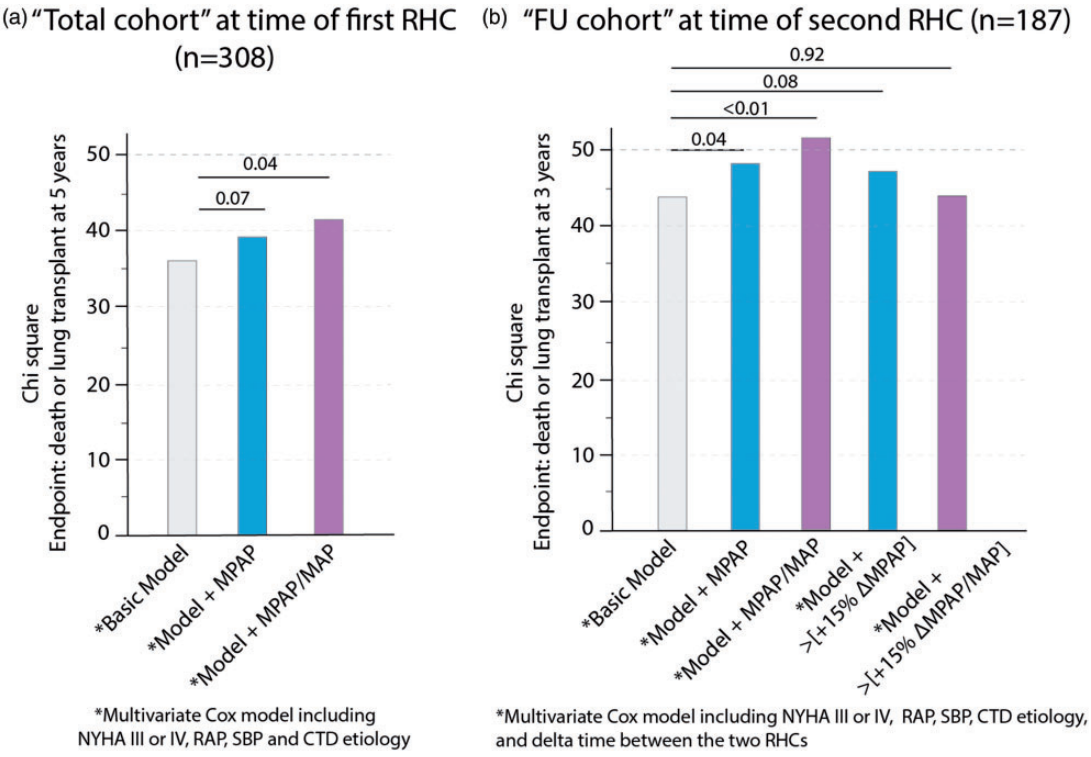

Fig. 3. Incremental value of mean pulmonary arterial pressure, relative pressure ratio (MPAP/MAP), and their trajectory for prediction of long-term outcomes in pulmonary arterial hypertension. (a) Incremental value of MPAP and MPAP/MAP over a basic model (including NYHA class III or IV, RAP, SBP, and CTD etiology) at the time of first right heart catheterization (RHC) assessed by their Chi-square of the models in the total cohort ($n = 308$) for prediction of transplant-free survival at five years after first RHC. (b) Incremental value of MPAP and MPAP/MAP over the same basic model (including delta time between the two RHCs) at the time of second RHC for prediction of transplant-free survival at three years after second RHC in the follow-up cohort ($n = 187$). The inclusion of worsening in MPAP or MPAP/MAP between the two RHCs did not add any value to the prediction of transplant-free survival.
CTD: connective tissue disease; MAP: mean systemic arterial pressure; MPAP: mean pulmonary arterial pressure; RAP: right atrial pressure; SBP: systolic blood pressure; NYHA: New York Heart Association; Δ denotes a relative change percentage between first and second RHC as follows: 100 × (second RHC – first RHC)/first RHC.

Table 4. Univariable Cox regression analysis for correlates of death or lung transplant need during follow-up after the second RHC, among hemodynamics trajectories between the first and second RHC, in the "follow-up" cohort ($n = 187$).

Variables categories	HR (95% CI)
MPAP relative change:	
Improvement in MPAP > 15% of baseline ($n = 68$)	1 (Ref.)
Stability of MPAP between (–15% to + 15%) ($n = 85$)	1.46 (0.84–2.54)
Worsening in MPAP > 15% of baseline ($n = 35$)	2.02 (1.04–3.91)*
MPAP/MAP relative change:	
Improvement in MPAP/MAP > 15% of baseline ($n = 58$)	1 (Ref.)
Stability of MPAP/MAP between (–15% to + 15%) ($n = 83$)	1.85 (1.01–3.35)*
Worsening in MPAP/MAP > 15% of baseline ($n = 48$)	2.05 (1.07–3.95)*
Cardiac index fold change:	
Improvement in cardiac index > 15% of baseline ($n = 73$)	1 (Ref.)
Stability of cardiac index between (–15% to + 15%) ($n = 81$)	0.93 (0.49–1.77)
Worsening in cardiac index > 15% of baseline ($n = 35$)	0.89 (0.52–1.49)
Stroke volume index fold change:	
Improvement in stroke volume index > 15% of baseline ($n = 90$)	1 (Ref.)
Stability of stroke volume index between (–15% to + 15%) ($n = 60$)	1.12 (0.61–2.05)
Worsening in stroke volume index > 15% of baseline ($n = 39$)	1.12 (0.65–1.93)

MPAP/MAP: mean pulmonary arterial pressure/mean arterial pressure.

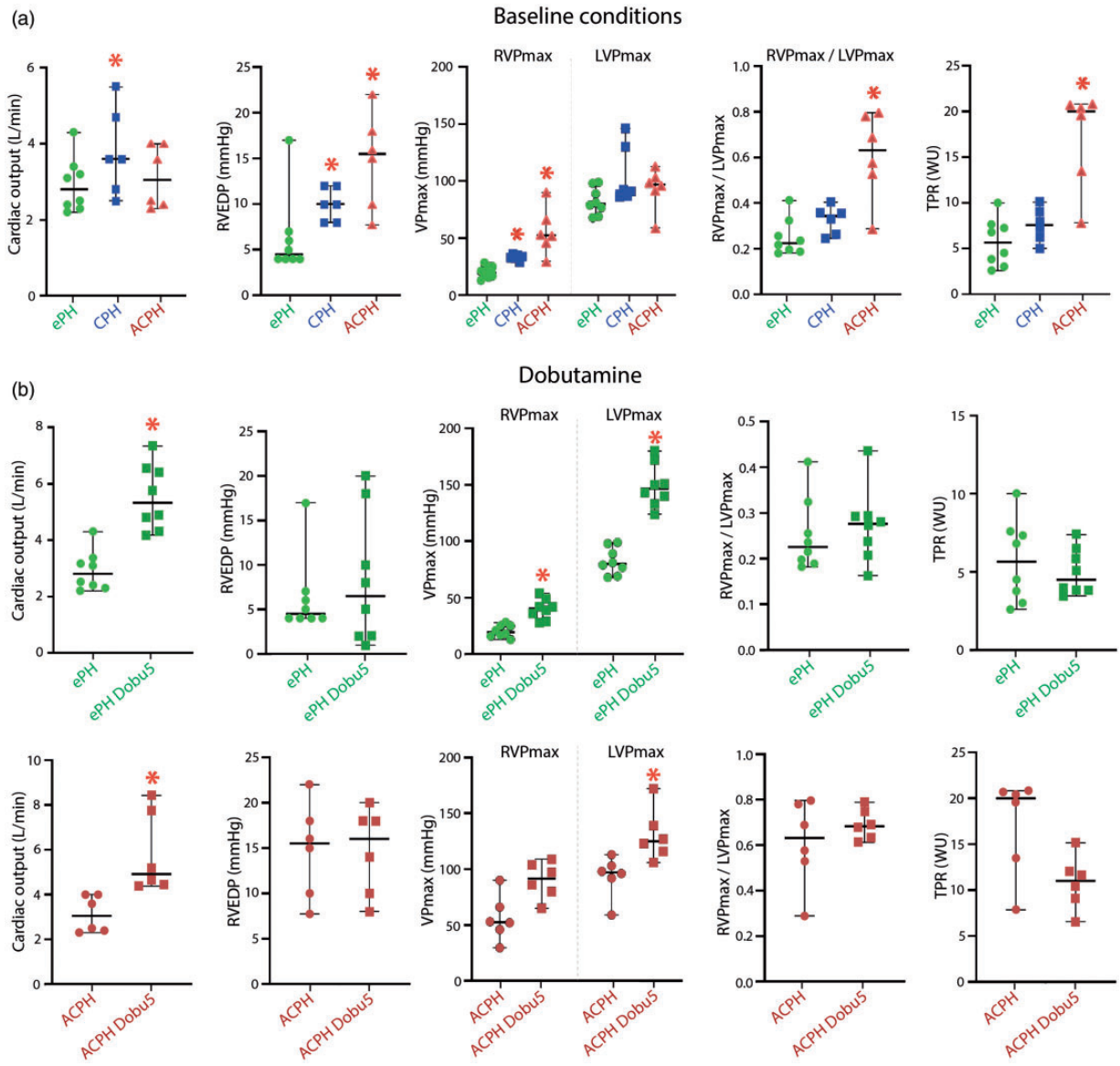

Fig. 4. Changes in the relative pressure ratio (RVPmax/LVPmax) and other invasive hemodynamics with dobutamine in pigs with early (ePH) or acute on chronic pulmonary hypertension (ACPH). (a) Comparison of RVPmax/LVPmax and other invasive hemodynamics between pigs with early PH (ePH), chronic (CPH), and acute on chronic PH (ACPH) at baseline conditions (*$p < 0.05$ versus ePH). (b) Changes in hemodynamics with dobutamine (Dobu5 = 5 μg/kg/min) in ePH and ACPH (*$p < 0.05$ versus baseline).
LVPmax: left ventricular maximal pressure; RVEDP: right ventricular end-diastolic pressure; RVPmax: right ventricular maximal pressure; TPR: total pulmonary resistance; VPmax: ventricular maximal pressure.

class III or IV, RAP, systolic blood pressure, and connective tissue disease etiology.

One of the novelties of the present study is that it compares the prognostic value of hemodynamics and their trajectory in a large single tertiary center cohort of 187 patients with PAH. Our "real-life" data contributes to the body of evidence questioning the use of hemodynamics (and particularly MPAP) as surrogate end points in PH. Indeed, Ventetuolo et al. performed a patient-level pooled analysis of four randomized, placebo-controlled trials assessing the effect of 12-week PH-specific therapy on hemodynamics and their trajectory.[20] While active treatment significantly lowered MPAP and PVR and increased CI, changes in hemodynamics (such as improvement in CI) accounted for a minor part of the overall treatment effect (estimated to range from 1.2% to 13.9%). In addition, changes in MPAP with treatment were not significantly associated with risk of events (i.e. death, lung transplantation, atrial septostomy, PAH hospitalization, withdrawal for clinical worsening, or escalation in PAH therapy) during the 12-week randomized portion of the trials. Our study further expands on these results by estimating the prognostic value of changes in MPAP or MPAP/MAP between two RHCs (separated by a median time of two years). Before using Cox

regression survival modeling, we identified a non-linear relationship between change in MPAP or MPAP/MAP and the odds of events, prompting the use of these parameters as categorical (rather than continuous) variables. Worsening in MPAP and MPAP/MAP between the first and second RHC (i.e. pre-defined by an increase of at least 15% in the variable) was associated with worse three-year transplant-free survival in our cohort. However, worsening in MPAP or MPAP/MAP was not incremental to the basic prognostic model, while MPAP or MPAP/MAP levels at the time of the second RHC were incremental, highlighting the fact that the trajectory in hemodynamics appears less predictive of outcome than the hemodynamics levels at a certain time point.

Finally, our animal PH study allows us to model acute changes in volume loading or CO in order to compare the changes in MPAP and MPAP/MAP. In this model, the invasive measurement of the RVPmax/LVPmax ratio was used as a surrogate of the MPAP/MAP ratio (showing strong correlation). Our experimental results demonstrate that in contrast to the RVPmax level, the relative pressure ratio remains stable with changes in CO secondary to dobutamine-induced increase in inotropy or secondary to a hemodynamic compromise in the acute on chronic PH model. This supports the use of the relative pressure ratio to monitor pulmonary hemodynamics in the setting of acute changes in CO, such as cardiac surgery or critical care setting.

This study has several limitations. The first limitation is inherent to the observational study design. Indeed, the indication of a second RHC in this observational study based on a prospective registry was clinically driven and chosen by the treating physician. Therefore, the time between the first and second catheterization was variable. For outcome analysis, this variability was adjusted by integrating the time between the two catheterizations in the multivariable analysis. Similarly, the therapeutic escalation between the first and second RHC was left at the discretion of the physician, and is therefore heterogeneous. This provides "real-life" data complementary to the analysis of clinical trials by Ventetuolo et al.[20] The second limitation of the longitudinal analysis, as in any study relying on follow-up data, is the risk of survival bias, as the follow-up analysis only includes survivors at time of the second RHC. The third limitation originates from the use of the indirect Fick or thermodilution methods to estimate CO in our retrospective study. As discussed previously, this might have added imprecision in the estimation of the CO but it reflects the reality of most catheterization laboratories in which use of direct Fick can be cumbersome for clinical workflow. Overall, this highlights the need for novel metrics independent of CO estimation. Finally, it should be acknowledged that the incremental value of MPAP/MAP or MPAP was evaluated using a basic hemodynamic model, instead of recent more established risk scores such as the REVEAL score (as not all its variables were available for all patients in close proximity to the RHC).

In conclusion, MPAP/MAP is prognostic of long-term outcomes in patients with PAH while MPAP is not. The incremental value of MPAP/MAP to NYHA functional class, systolic blood pressure, and RAP remains modest. While hemodynamic trajectories based on relative pulmonary pressure or PVR are predictive of long-term outcome, they provide similar prognostic value to the corresponding hemodynamic parameters. The stability of the relative pressure ratio (MPAP/MAP) during acute changes in CO confirmed in our experimental model supports the use of the relative pressure ratio to monitor pulmonary hemodynamics in cardiac surgery or critical care settings.

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Contributorship

M.A., S.P.B., and F.H. have contributed to the conception and design of the study, the acquisition, analysis and interpretation of data, drafting the manuscript, giving final approval of the version submitted, and agreeing to be accountable of all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. D.B., R.Z., and O.M. have contributed to the conception of the study, the interpretation of the data, revising the manuscript critically for important intellectual content, giving final approval of the version submitted, and agreeing to be accountable of all aspects of the work. A.D., A.J.S., K.T.K., Y.K.S., J.A.F., and E.F. have contributed to the acquisition and interpretation of the data, revising the manuscript critically for important intellectual content, giving final approval of the version submitted, and agreeing to be accountable of all aspects of the work.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Ethical approval

This retrospective study based on a prospective registry was approved by Stanford University Institutional Review Board (IRB-25673) and was conducted in agreement with the Helsinki-II Declaration. Marie Lannelongue Hospital (Le Plessis-Robinson, France) institutional animal care committee approved all procedures that were performed according to institutional guidelines complying with national and international regulations.

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Guarantors

M.A. and F.H. are the guarantors of the accuracy of the data presented.

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