Strong linear relationship between heart rate and mean pulmonary artery pressure in exercising patients with severe precapillary pulmonary hypertension

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Chемla D, Castelain V, Hoette S, Creuzé N, Provencher S, Zhu K, Humbert M, Herve P. Strong linear relationship between heart rate and mean pulmonary artery pressure in exercising patients with severe precapillary pulmonary hypertension. Am J Physiol Heart Circ Physiol 305: H769–H777, 2013. First published June 21, 2013; doi:10.1152/ajpheart.00258.2013.—The contribution of heart rate (HR) to pulmonary artery hemodynamics has been suggested in pulmonary hypertension (PH). Our high-fidelity pressure, retrospective study tested the hypothesis that HR explained the majority of mean pulmonary artery pressure (mPAP) and pulse pressure (PApp) variation in 12 severe precapillary PH patients who performed incremental-load cycling while in the supine position. Seven idiopathic pulmonary arterial hypertension patients and five chronic thromboembolic PH patients were studied. In four to five PAP-thermodilution cardiac output (CO) points (mean: 4.4) were obtained. At rest, mPAP was 57 ± 9 mmHg. PApp was 51 ± 11 mmHg. HR was 90 ± 12 beats/min, and stroke volume (SV) was 50 ± 22 ml. At peak exercise, mPAP was 76 ± 10 mmHg. PApp was 67 ± 11 mmHg, and HR was 123 ± 18 beats/min (i.e., 71 ± 10% of maximum HR, each P < 0.05), whereas SV was 51 ± 20 ml (P = not significant). The input resistance did not change (mPAP/CO = 14.1 ± 4.1 vs. 13.5 ± 4.4 mmHg·min⁻¹·l⁻¹). The relative increase in mPAP was related to the relative increase in HR (n = 12, r² = 0.74) but not in CO. mPAP was linearly related to CO in 8 of 12 patients (median r² = 0.83) and to HR in 12 of 12 patients (median r² = 0.985). The parsimony principle favored the latter fit. PApp was linearly related to mPAP in 12 of 12 patients (median r² = 0.985), HR in 10 of 12 patients (median r² = 0.97), CO in 7 of 12 patients (median r² = 0.87), and SV in 1 of 12 patients. A strong linear relationship between HR and mPAP was consistently documented in severe precapillary PH patients who performed supine exercise. The limited value of thermodilution CO to predict mPAP could be explained by unavoidable precision errors in CO measurements, unchanged/decreased SV on exercise, curvilinearity of the mPAP-CO relationship at high flow, or flow-independent additional mechanisms increasing mPAP on exercise.

pulmonary artery pressure; pulmonary hypertension; heart rate; pulse pressure; right ventricle; cardiac output; exercise

DURING INCREMENTAL-LOAD EXERCISE, the normal pulmonary vasculature can easily accommodate the increase in cardiac output (CO) thanks to the characteristics of the pulmonary circulation, namely, low resistance, high compliance, and capabilities of recruitment and distension in reserve (25, 26). This prevents major increases in mean pulmonary artery pressure (mPAP) at high flow states, thus preserving right ventricular (RV) function and energy expenditure. Pulmonary hypertension (PH) is a devastating disease where mPAP is abnormally high at rest (≥25 mmHg) and further markedly increases on exercise, resulting in increased RV work and hydraulic power (6, 8, 22–26, 33). This leads to impaired functional capacity and decreased RV function, both of which are related to prognosis and are used as end points in therapeutic trials in PH (6, 26). Thus, numerous studies have been aimed at understanding the pathophysiology of exercise PAP in PH patients. Our study focused on the hemodynamic correlates of PAP in exercising PH.

The mPAP-CO relationship is reasonably well fitted by a linear function in various forms of PH, and it is admitted that most of the mPAP variance on exercise is explained by CO (4, 20, 26, 27, 32). A linear relationship exists between exercise workload, heart rate (HR), and O2 uptake, and increases in HR play a key role in CO increases (27, 32, 38).

In the catheterization laboratory, exercise is usually performed in subjects while in the supine position, a condition associated with slight increases in stroke volume (SV) in normotensive controls (15) but with either unchanged SV (15, 19, 22, 23) or even decreased SV (28) in PH patients. This suggests a contributory role of HR on pulmonary hemodynamics in exercising PH, as also suggested by the relationship between the 6-min walked distance and the chronotropic reserve (30). Recent studies (1, 12, 15, 16, 18, 32) have focused on HR in PH, and pharmacological manipulation of HR has been also studied (3, 11, 31). However, the relationship between mPAP and HR remains to be precisely documented in exercising PH.

The limitations of the hemodynamic approach based on the mPAP-CO relationship have been acknowledged (25, 26, 34). This so-called steady model neglects pulsatile arterial load while the pulmonary circulation is highly pulsatile (25, 26). It is generally admitted that PA pulse pressure [PApp; PApp = systolic PAP (sPAP) – diastolic PAP (dPAP)] is a valuable estimate of pulsatile load and that resting PApp is mainly influenced by SV and PA compliance (5, 6, 37, 43). The
hemodynamic correlates of PAp on exercise remain poorly documented.

The present high-fidelity pressure, retrospective study aimed to document the link between PAP and HR in PH patients who performed incremental-load exercise while in the supine position. The main hypothesis tested was that most of the mPAP and PAp variance was explained by HR.

**MATERIALS AND METHODS**

**Patients**

This study was approved by the ethics board of Paris-Sud University (approval no. 9708, CCPRBR de Bicêtre, Le Kremlin Bicêtre, France), and informed consent was obtained from all patients. From December 1996 to February 1998, 16 patients with precapillary PH [mPAP ≥ 25 mmHg and pulmonary artery occlusion pressure (PAop) ≤ 15 mmHg] had their PAP recorded at rest and on exercise using a high-fidelity pressure catheter (Cordis/Sentron, Roden, The Netherlands) according to our previously described protocol (4). All patients had severe precapillary PH (mPAP ≥ 45 mmHg). Thermodilution CO (in triplicate) and PAP were measured at rest and at each workload up to the maximum tolerated level. Data were first obtained at rest. RV pressure was obtained at baseline and after a 1-min equilibrium period. The catheter was then advanced into the main pulmonary artery, and pressures were recorded after a 1-min equilibrium period. After nitric oxide challenge and after a 5-min washout period, PAPs were obtained on exercise.

Exercise tests were performed in the supine position on an electronically braked cycle ergometer (Cycline 100, Tecmachine, Andezieux-Boutheon, France) secured to the catheterization table. Hae-

modynamic values were first measured at a rate of 60 rpm, with the workload being increased stepwise by 15 W every 3 min from 0 W to a maximum workload of 60 W, depending on the patient’s functional tolerance. The number of steps was determined for each individual by the operator’s judgement based on the patient’s functional tolerance, age, and comorbidities. Hemodynamic parameters were measured during the last minute of each exercise level. All measures were obtained at steady state (i.e., unchanged mPAP and HR). To enter the present retrospective analysis, patients had to have their full mPAP-CO data set recorded at rest and over at least three exercise levels. Four patients with only two to three mPAP-CO points or with missing data were excluded, such that twelve patients entered the final analysis (8 men and 4 women, age: 45 ± 14 yr). The final diagnosis was pulmonary arterial hypertension (PAH) for seven patients and chronic pulmonary thromboembolism (CTEPH) for five patients.

The fundamental law of hemodynamics indicates that mean flow is the product of the mean pressure gradient driving mean flow through the pulmonary circulation times the vascular conductance (1/resistance) (33). In the pulmonary circulation, the mean pressure gradient is the mPAP minus PAop difference. PAop was not obtained at each exercise level for all patients, either for technical reasons (i.e., not possible to obtain reliable PAop) or because the operator considered that the maneuver involved undue risk to the patient. Thus, the mPAP-CO relationship was studied instead of the (mPAP – PAop)-CO relationship. For clinicians interested in understanding the correlates of elevated mPAP in PH, CO is most often treated as the independent variable and mPAP is treated as the dependent variable. In various forms of PH, the mPAP-CO relationship is reasonably well fitted by a linear function, thus implying that mPAP is a flow-dependent variable and that most of the mPAP variance is explained by CO.

The mPAP-CO relationship may diverge from linearity in subgroups of PH patients (20). A curvilinear function has been previously used in some studies to fit the mPAP-CO relationship, and this helps quantify PA elastic properties (26, 34). Curvilinearity (concave-down flattening) is expected to be more marked in PH patients that reach a high CO value at peak exercise. Thus, in the subgroup of our PH patients in whom the mPAP-CO relationship diverged from linearity, the patterns of individual pressure-flow plots were visually analyze to test if outliers came at random values or at high flow values. Only qualitative data analysis was thus performed, and not quantitative data analysis, as the mathematical curvilinear fit requires PAop measurements at each workload (26, 34), which were not available in our study, as previously indicated.

**Pressure Waveform Analysis**

Pressure data were computed on a Toshiba 3200 SX with home-made software, and we used a sampling frequency of 1,000 Hz (4, 9). Time intervals were manually determined. The onset of the systolic pressure pulse and corresponding dPAP was manually identified as the time when the pressure derivative (dP/dt) increased steeply. This also allowed us to determine the pulse interval, HR (in beats/min) was calculated as 60,000/pulse interval (in ms). Maximum HR was esti-

mated using the following formula: 220 = age (in yr). sPAP was automatically calculated by the computer software as the PAP at the time when dP/dt = 0 in systole (systolic zero crossing). mPAP was automatically calculated as the area under the pressure curve divided by the pulse interval. PAop was calculated as the sPAP – dPAP difference. SV was calculated as CO/HR. Pressures and time parameters were averaged out over 15 consecutive sinus rhythm beats. Input resistance (Rin) was calculated as mPAP/CO (in mmHg·min·l⁻¹) to quantify the major part of arterial load resisting to RV ejection, i.e., the input impedance at zero frequency (25). Rin is equivalent to total peripheral resistance (25), and a value of >3 mmHg·min·l⁻¹ was considered abnormal (24). mPAP and HR were determined using the same PAp data analysis obtained from the same catheter, and, thus, a form factor may well underlie the potential relationship between mPAP and HR. In an attempt to test this hypothesis, the PAop area per beat was also calculated as mPAP times the heart period product (in mmHg·s).

**Statistical Analysis**

Data are presented as means ± SD. Comparisons between data at rest and at the highest workload under study were performed using ANOVA. Relative changes in mPAP, PAop, CO, HR, and SV were compared using ANOVA followed by a t-test with the Bonferroni correction. Simple linear regressions were performed using the least-squares method, and the coefficient of determination (r²) was pre-

sented. The Fisher’s exact test was used to compare the proportion of patients with significant mPAP-CO linear fits between PAH and CTEPH patients and between men and women. Statistical significance was assumed for two-sided P < 0.05.

**RESULTS**

Five pressure-flow points were obtained in 5 of 12 patients, and 4 points were obtained in the remaining 7 of 12 patients. Thus, 53 pressure-flow points were analyzed in the study population (mean number of pressure-flow points per patient: 4.4).

**Hemodynamic Data at Rest and at Peak Exercise**

Table 1 shows the individual data at rest and at the highest workload for mPAP (range: 47.5–99.5 mmHg), PAop (range: 32.0–84.5 mmHg), CO (range: 2.4–11.1 l/min), HR (range: 71–152 beats/min), and SV (range: 27–99 ml). At the highest workload, HR corresponded to 71 ± 10% of the maximum HR (range: 57–84%). Compared with individual resting values, mPAP, PAop, CO, and HR increased throughout the protocol in all PH patients, whereas individual SV responses on exercise
Table 1. Individual hemodynamic variables at rest and peak values recorded during exercise

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age, yr</th>
<th>Diagnosis</th>
<th>Number of P-Q Plots</th>
<th>Rest (mPAP, mmHg)</th>
<th>Exercise (mPAP, mmHg)</th>
<th>Rest (PApp, mmHg)</th>
<th>Exercise (PApp, mmHg)</th>
<th>Rest (CO, l/min)</th>
<th>Exercise (CO, l/min)</th>
<th>Rest (HR, beats/min)</th>
<th>Exercise (HR, beats/min)</th>
<th>Rest (SV, ml)</th>
<th>Exercise (SV, ml)</th>
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<td>Female</td>
<td>63 PAH</td>
<td>5</td>
<td>53.9</td>
<td>65.4</td>
<td>48.7</td>
<td>59.0</td>
<td>3.90</td>
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<td>113</td>
<td>133</td>
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<td>50.5</td>
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<td>51.6</td>
<td>3.00</td>
<td>4.19</td>
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<td>121</td>
<td>36</td>
<td>35</td>
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<td>36 PAH</td>
<td>5</td>
<td>66.2</td>
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<td>67.0</td>
<td>82.3</td>
<td>3.98</td>
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<td>57.5</td>
<td>67.5</td>
<td>46.1</td>
<td>61.8</td>
<td>4.98</td>
<td>7.14</td>
<td>90</td>
<td>107</td>
<td>55</td>
<td>67</td>
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<tr>
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<td>4</td>
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<td>68.7</td>
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<td>68.1</td>
<td>5.54</td>
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<td>86</td>
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<td>64</td>
<td>66</td>
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<tr>
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<td>46.8</td>
<td>64.0</td>
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<tr>
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<td>72.6</td>
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<tr>
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<td>67.6</td>
<td>46.7</td>
<td>62.1</td>
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<tr>
<td>Patient 11</td>
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<td>30 CTEPH</td>
<td>4</td>
<td>79.0</td>
<td>92.9</td>
<td>70.4</td>
<td>84.5</td>
<td>4.80</td>
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<td>109</td>
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<tr>
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<td>57 CTEPH</td>
<td>4</td>
<td>52.2</td>
<td>78.4</td>
<td>64.4</td>
<td>81.8</td>
<td>2.78</td>
<td>11.1</td>
<td>71</td>
<td>112</td>
<td>109</td>
<td>99</td>
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</tbody>
</table>

mPAP, mean pulmonary artery pressure (PAP); PApp, pulmonary artery pulse pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; PAH, pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension. HR has been corrected to the nearest whole number. For comparison between rest and exercise values, all comparisons were *P < 0.05 except where indicated [*not significant (NS)].

differed between patients, with SV being increased, unchanged, or decreased. On average, compared with resting values, mPAP, PApp, CO, and HR increased at peak exercise, whereas SV was unchanged (Table 1). At peak exercise, there were no significant differences between the relative increases in mPAP, PApp, CO, and HR (Fig. 1). The relative increase in mPAP at peak exercise was positively related to the relative increase in HR (r² = 0.74; Fig. 2, top) but not to the relative increase in CO (r² = 0.10, *P = not significant; Fig. 2, bottom). The relative increase in HR was negatively related to the relative changes in SV (r² = 0.51; Fig. 3). Rm in at rest was >3 mmHg-min⁻¹ in every PH patient (Table 2). On average, compared with resting values, Rm and the pressure area per beat did not change at peak exercise (Table 2).

Individual Pressure-Flow Point Analysis

The mPAP-CO relationship. There was a significant linear mPAP-CO relationship in 8 of 12 patients (67%), whereas there was no significant relationship in the remaining 4 patients. The r² value ranged from 0.66 to 0.99 (median r² = 0.83; Table 3). The slope and intercept of the mPAP-CO relationship were scattered and ranged from 3.9 to 19.0 mmHg-min⁻¹ and from −33 to 40 mmHg, respectively. The proportion of patients with a significant mPAP-CO linear fit was similar in PAH and CTEPH patients (P = 0.22) and in men and women (P = 0.21).

Based on visual inspection, curvilinearity was ruled out in the 8 of 12 patients with a significant linear mPAP-CO fit. In the 4 of 12 patients in whom the linear fit did not apply, 1 patient (patient 12) exhibited curvilinearity with concave-down flattening of the mPAP-CO relationship. In this patient, the corresponding CO at peak exercise (11.1 l/min) was the highest CO documented in the study population (Table 1). Deviation from linearity occurred at random in the remaining three patients (patients 5, 10, and 11).

mPAP-HR relationships. There was a significant positive linear relationship between mPAP and HR in every patient (Table 3). A typical example is shown in Fig. 4. Overall, HR explained >90% of the mPAP variation in every patient (r² range: 0.91–0.99, median r² = 0.985). In 5 of 12 patients (patients 3, 4, 6, 7, and 9; Table 3), >95% of the mPAP variation was explained by either HR or CO. The slope and intercept of the mPAP-HR relationship were scattered and ranged from 0.39 to 1.10 mmHg-min⁻¹ and from −33 to 31 mmHg, respectively (Table 3). There was no relationship between the slope of the mPAP-HR relationship and that of the mPAP-CO relationship.

Correlates of sPAP and dPAP

Similar results were observed for sPAP and dPAP (Table 4). sPAP increased in all patients (from 89 ± 15 to 115 ± 15 mmHg, P < 0.05, relative increase: 1.30 ± 0.10). sPAP was linearly related to mPAP in 12 of 12 patients (each r² = 0.99), to HR in 11 of 12 patients (r² range: 0.88–0.99, median r²: 0.985), to CO in 8 of 12 patients (r² range: 0.68–0.99, median r²: 0.86), and to SV in 3 of 12 patients. dPAP increased in all patients (from 38 ± 6 to 49 ± 6 mmHg, P < 0.05, relative increase: 1.31 ± 0.18). dPAP was linearly related to mPAP in
12 of 12 patients ($r^2$ range: 0.89–0.99, median $r^2$: 0.99), to HR in 12 of 12 patients ($r^2$ range: 0.89–0.99, median $r^2$: 0.975), to CO in 7 of 12 patients ($r^2$ range: 0.58–0.99, median $r^2$: 0.82), and to SV in 3 of 12 patients.

Fig. 2. Top: positive linear relationship between the relative increase in mPAP and the relative increase in HR at peak exercise ($n = 12$). Bottom: lack of relationship between the relative increase in mPAP and the relative increase in CO. NS, not significant.

12 of 12 patients ($r^2$ range: 0.89–0.99, median $r^2$: 0.99), to HR in 12 of 12 patients ($r^2$ range: 0.89–0.99, median $r^2$: 0.975), to CO in 7 of 12 patients ($r^2$ range: 0.58–0.99, median $r^2$: 0.82), and to SV in 3 of 12 patients.

Fig. 3. Negative relationship between the relative increase in HR and the relative changes in SV at peak exercise ($n = 12$).

Correlates of PApp

PApp and mPAP were linearly related both at rest ($n = 12$, $r^2 = 0.52$) and in the full data set ($n = 53$, $r^2 = 0.74$, each $P < 0.05$). Individual pressure-flow point analysis documented significant linear relationships between PApp and mPAP in 12 of 12 patients, with $r^2$ ranging from 0.91 to 0.99 (median $r^2 = 0.985$; Table 5). A typical example is shown in Fig. 5. Significant linear relationships were documented between PApp and HR in 10 of 12 patients (83%, $r^2$ range: 0.77–0.99, median $r^2$: 0.97) and between PApp and CO in 7 of 12 patients (58%, $r^2$ range: 0.76–0.99, median $r^2$: 0.875). A significant linear relationship between PApp and SV was documented in 1 of 12 patients only.

DISCUSSION

This study focused on the hemodynamic correlates of PAP in severe precapillary PH patients who performing incremental-load exercise while in the supine position. Four to five PAP-CO points were obtained for every patient. The first new result was that there was a strong linear relationship between HR and mPAP in every patient, and the contribution of HR as the main hemodynamic correlate of mPAP in exercising PH may have important implications. The second new result was that mPAP explained most of the PApp variance, thus unexpectedly suggesting that the mean and pulsatile PAP components share similar pathophysiological mechanisms on exercise. It must be stressed that the sample size was small, and further studies are needed to confirm our findings in other forms of PH.

While only 8 of 12 PH patients exhibited a linear mPAP-CO relationship, a strong linear relationship between mPAP and HR was consistently documented in 12 of 12 patients. The portion of mPAP variance that could not be explained by HR was 1.5% (median), thus making it questionable to enter other variables in the model. The relatively small sample size and the study design made it hazardous to statistically compare CO and HR as predictors of exercise mPAP (42). However, considering the portion of mPAP variance explained by HR (98.5%) versus that explained by CO (83%), and considering the
Consistency With Previous Studies

The principles that underlie scientific modeling caution against favoring the complex models over the simple ones (the parsimony principle or Occam’s razor). In this respect, using HR rather than CO (= HR × SV) to predict mPAP has the major advantage of halving the number of independent variables. Thus, in the 5 of 12 patients in whom >95% of the mPAP variation was explained either by HR or by CO (patients 3, 4, 6, 7, and 9; Table 3), the parsimony principle favors the use of HR to predict mPAP. Finally, at peak exercise, the relative increase in mPAP was related to the relative increase in HR, not in CO (Fig. 2), and this confirmed that the changes in mPAP and HR were tightly coupled. Overall, as far as the amount of information contained in the database is concerned, our study supports the use of HR to predict mPAP in populations similar to ours.

Methodological Considerations

Both the use of high-fidelity pressure recordings and the high sampling rate (1,000 Hz) may contribute to explain the unusual strength of the mPAP-HR relationship in all patients (median $r^2 = 0.985$). Linear regression considers variation in the dependent variable (mPAP) and fits a line to minimize the difference between the mPAP observed and mPAP predicted from the independent variable value (CO or HR). The thermodilution method is the most commonly used method for measuring CO in the catheterization laboratory. Sizable precision errors amount to ±10–20% with the thermodilution method (44), and this contrasts with the high precision of our
HR measurements. This may contribute to explain our findings. However, it must noted that using fluid-filled catheters, Janicki et al. (20) failed to document a linear mPAP-CO relationship in 31% of their patients, although these authors used the Fick principle to measure CO. Although both the extremely high $r^2$ value of the mPAP-HR relationship in every patient and the parsimony principle may well imply that HR suffices to track mPAP changes on exercise, further high-fidelity pressure studies measuring CO with more precise methods are needed in an attempt to further compare mPAP-HR and mPAP-CO relationships in PH. Finally, the high precision of the HR measurement is also valuable as the commonly used linear regression procedure generally does not allow for uncertainty in the independent variable (13).

Pressure-flow curves are commonly used to describe the functional status or tone of pulmonary vessels. They assume that tone is maintained constant during the measurements. This assumption may not be true in the presence of large flow changes such as those seen at peak exercise, with CO $> 10$ l/min, and distensible models of the pulmonary circulation may be used (26, 34). Such models rely on a curvilinear fit with concave-down flattening of the mPAP-CO relationship. In our study, this could explain “less good” mPAP-CO fit in one PH patient (patient 12). The curvilinear model has been mainly developed in an attempt to quantify pulmonary artery elastic properties, namely, the fractional pulmonary arter diameter change per mmHg pressure ($\alpha$). To this end, the model fits mPAP using three variables (left atrial pressure, SV, and HR) and two constants (total peripheral resistance at zero-load and $\alpha$). If one is not interested in quantifying PA elastic behavior but simply wants to predict exercise mPAP, the parsimony principle implies that the linear mPAP-HR fit must be favored whenever possible, as it uses only one variable (HR) and two constants (slope and intercept of the relationship).

### Pathophysiologic Hypotheses

Exercise is associated with parasympathetic withdrawal and marked sympathetic stimulation leading to a positive chronotropic effect at the sinus node level (35). The HR at each workload reflects the intensity of exercise and O2 uptake (26, 38). It has been suggested that the exercise-related humoral and neural sympathetic stimulation (as reflected in HR) may increase mPAP through both flow-dependent mechanisms and flow-independent mechanisms.

mPAP is a flow-dependent variable (4, 26, 27, 32, 33, 36), and tachycardia is the main mechanism by which CO increases in exercising PH (19, 23, 28–32). Although the PA wall is viscoelastic, with mechanical properties potentially modulated by frequency, the intrinsic effects of HR on mPAP is unlikely as there is no change in mPAP with increasing HR in anesthe-

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**Table 4.** $r^2$ values for the linear relationships between sPAP and dPAP and CO, HR, SV, and mPAP

<table>
<thead>
<tr>
<th>Patient</th>
<th>CO</th>
<th>HR</th>
<th>SV</th>
<th>mPAP</th>
<th>dPAP</th>
<th>CO</th>
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<td>Patient 1</td>
<td>0.52*</td>
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<td>0.97</td>
<td>0.28*†</td>
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<td>0.81*</td>
<td>0.90</td>
<td>0.21*†</td>
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<tr>
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<td>0.97</td>
<td>0.81*†</td>
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<td>0.99*</td>
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<td>0.85*†</td>
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<td>0.93</td>
<td>0.72*†</td>
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</table>

All comparisons were $P < 0.05$ except where indicated (*NS). All relationships were positive except where indicated (†negative relationship).
tized paced animals where CO remains unchanged (14). In our study, both mPAP and HR were determined using the same PAP data analysis obtained from the same catheter, and a form factor may well underlie, at least in part, the mPAP-HR relationship. In our study, the peaking and narrowing of the pulmonary artery pulse-contour from rest to peak exercise occurred without significant changes in the corresponding PAP area on average. As SV was also unchanged, the unchanged PAP area (mPAP × heart period) and unchanged Rm ([mPAP × heart period]/SV) may be viewed as reflecting the same hemodynamic pattern. It must be noted that Rm decreases in exercising controls (22), whereas the PAP area remains to be documented.

This study documented that HR and CO are not interchangeable correlates of mPAP, as mPAP was not consistently related to CO. In an attempt to explain this finding, one hypothesis is that some exercising patients exhibited unchanged or decreased SV, and this buffered the increase in CO at a given exercise HR value. Another hypothesis is that besides increasing CO, the exercise-related humoral and neural sympathetic stimulation may also increase mPAP through flow-independent additional mechanisms, e.g., decreased pulmonary arterial compliance and enhanced pulmonary artery smooth muscle tone increasing both the resistance to flow and the zero-flow pressure. As RV ejection in a stiff vasculature results in disproportionate increases in PAP (5, 37, 43), decreased pulmonary arterial compliance induced by both the exercise-related sympathetic stimulation and increased mPAP could contribute to the PApp-mPAP and PApp-HR relationships. The pulmonary arterial stiffening could also be caused by the higher HR itself (21). Sympathetic stimulation also increases pulmonary artery smooth muscle tone. During exercise, neurohumoral changes are present and probably do affect pulmonary vascular tone (25, 26, 34, 41), and this may cause deviations from linearity. Finally, increased tone of pulmonary vessels is expected to impact on the zero-flow downstream pressure (25, 26, 27), which mathematically modifies mPAP and may cause deviations from linearity too.

**Correlates of PApp, sPAP, and dPAP**

mPAP accounts for ~80% of the RV hydraulic afterload (steady load), and a complementary approach based on the pulsatile arterial load and elastic properties of the pulmonary circulation needs to be discussed. PApp is a valuable estimate of pulsatile load. At rest, PApp is mainly influenced by SV and pulmonary arterial compliance (5, 6, 37, 43). In our study, mPAP explained the vast majority of PApp variance on exercise (mean $r^2 = 0.985$), thus implying that the mean and pulsatile components of PAP share essentially similar pathophysiological mechanisms, including marked dependence on HR. This finding was unexpected on the basis of classic vascular physiology (5, 6, 25), and the implications for modeling the pulsatile component of arterial load deserve further studies.

On exercise, the individual sPAP and dPAP values were most strongly related to mPAP in every PH patient, and this extends to every individual the property previously described in the population as a whole using essentially the same database at rest (7) or another database on exercise (39). In our exercising PH patients, it was thus expectable that both sPAP and dPAP were strongly related to the same variables as was mPAP, namely, HR (Table 4).

**Limitations**

Our findings should be interpreted with great caution due to the following limitations. The number of subjects in this high-fidelity pressure study was small, and this could result in type II errors, such that the observed nonsignificant relationships must be carefully discussed. On the other hand, the fact that significant mPAP-HR relationships were observed in every patient, with unusually high $r^2$ values, is worth noting. Our findings remain to be confirmed in a large patient population and in patients with less severe disease (e.g., mild to moderate PH or PH studied after an effective therapy). Indeed, one may argue that the finding that HR predicts mPAP is mainly a consequence of the remarkably unchanged SV during exercise in these patients with severe pulmonary vascular disease. However, this hypothesis is questionable for the following reasons. First, increases in SV of >20% were documented in two patients (patients 1 and 4) in whom the $r^2$ coefficients of the mPAP-HR were 0.98 and 0.96, respectively. Second, using fluid-filled catheters and conventional measurements of HR, preliminary results from our group indicated that HR also predicts mPAP in normotensive subjects (see Ref. 29 and unpublished observations). The results pertain strictly to precapillary PH, and further validation is also needed in patients with other forms of PH (e.g., PH associated with left heart disease). Moderately loaded exercise cycling is currently performed in our laboratory as it reflects daily life RV workload more accurately than maximal exercise. Despite moderate workload ($\leq 60$ W), the patient’s HR at the highest workload corresponded to 71% of the maximum HR, thus indicating moderate to vigorous exercise. Thus, the results may not necessarily apply to maximal exercise. It must be acknowledged that CO and O$_2$ uptake responses may exhibit different patterns during maximal exercise (24, 40). It must be also acknowledged that the curvilinearity of the mPAP-CO relationship may be observed in the presence of large flow changes, such as those seen during maximal exercise, as previously documented (26, 34). This may contribute to explaining why the mPAP-CO relationship was not statistically significant in 1 of 4 patients only (patient 12), but it is worth noting that a strong linear mPAP-HR relationship was still documented in this patient ($r^2 = 0.91$). Finally, as far as the mPAP-CO relationship is concerned, it must be noted that it was not our aim to compare the respective value of the linear fit versus the curvilinear fit and that the latter one could not be precisely analyze in the present study as PAop was not available at each workload.

**Perspectives**

The role of HR is too often neglected in exercise analysis as well as in followup studies. Increased sympathetic activity has been documented in PH and may be related to disease severity and clinical deterioration (10, 41). Recent PH studies have focused on HR (1, 12, 15, 16, 18, 32) as well as on pharmacological manipulation of HR (3, 11, 31). HR is easy to record in a reliable way, and the results of the present study strongly encourage the development of clinical and experimental studies on HR in PH. Further studies involving a larger number of
PH subjects are needed to determine the main correlates of the slope of the mPAP-HR relationship, the clinical interest of the relationship, and its pathophysiological implications for designing future trials with HR-lowering drugs. Finally, the described relationship may be utilitarian with regard to precisely predicting exercise mPAP from HR or to cross-check the hemodynamic database on exercise, and this also deserves further confirmation.

In conclusion, exercise mPAP is undoubtedly a flow-dependent variable, and the study confirmed that the mPAP-CO relationship was linear in the majority of our severe precapillary PH patients who performed incremental-load cycling while in the supine position. However, a strong linear relationship between HR and mPAP was consistently documented, thus implying that mPAP may be also treated as a HR-dependent variable and that HR sufficed to predict exercise mPAP. Favoring HR over CO to predict mPAP had methodological advantages: 1) this fulfills the parsimony principle by halving the number of independent variables used in the model; 2) HR is by far easier to measure than CO, and it can be easily monitored; and 3) the higher precision of HR measurement is valuable as linear regression generally does not allow for uncertainty in the independent variable. The limited value of thermodilution CO to predict mPAP could be explained by the following hypotheses: 1) CO measurement carries unavoidable precision errors; 2) unchanged or decreased SV on exercise tends to buffer the increase in CO at a given HR; 3) curvilinearity of the mPAP-CO relationship may be observed at high flow states; and 4) besides increasing CO, the exercise-related sympathetic stimulation (as reflected in HR) could also increase mPAP through flow-independent additional mechanisms. Our results apply strictly to the relatively small population under study, and further studies are needed to confirm our findings in other populations.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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PULMONARY ARTERY PRESSURE-HEART RATE RELATIONSHIP IN PH

43. Wang Z, Chesler NC. Pulmonary vascular wall stiffness: an important contributor to the increased right ventricular afterload with pulmonary hypertension. Palm Circ 1: 212–223, 2011.