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Characterization of Patients With Borderline Pulmonary Arterial Pressure

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BACKGROUND: Resting mean pulmonary artery pressure (mPAP) values between 20 and 25 mm Hg are above normal but do not fulfill the criteria for pulmonary hypertension (PH). The clinical relevance of such borderline hemodynamics is a matter of discussion.

METHODS: We focused on patients who underwent right-sided heart catheterization during rest and exercise for symptoms indicative of PH or due to underlying disease associated with an increased risk for pulmonary arterial hypertension and characterized the patients according to their resting mPAP. Patients with manifest PH (mPAP $\geq$ 25 mm Hg) were excluded.

RESULTS: We included 141 patients, 32 of whom presented with borderline hemodynamics (20 $<$ mPAP $<$ 25 mm Hg). Borderline patients were older (65.8 $\pm$ 12.5 years vs 57.3 $\pm$ 12.5 years, $P = .001$) and more often had cardiac comorbidities (53% vs 15%, $P < .001$) or decreased lung function (47% vs 16%, $P < .001$) as compared with patients with resting mPAP $<$ 21 mm Hg. After correction for age, borderline patients had significantly increased pulmonary vascular resistance (2.7 $\pm$ 0.7 Wood units vs 1.8 $\pm$ 0.8 Wood units, $P < .001$) and mPAP/cardiac output (CO) and transpulmonary gradient/CO slopes (both $P < .001$) as well as lower peak oxygen uptake (16.9 $\pm$ 4.6 mL/min/kg vs 20.9 $\pm$ 4.7 mL/min/kg, $P = .009$) and 6-min walk distance (383 $\pm$ 120 m vs 448 $\pm$ 92 m, $P = .001$). During follow-up (4.4 $\pm$ 1.4 years), the mortality rate of borderline patients vs patients with resting mPAP $<$ 21 mm Hg was 19% vs 4%.

CONCLUSIONS: In patients undergoing right-sided heart catheterization with exclusion of manifest PH, borderline elevation of pulmonary arterial pressure is associated with cardiac and pulmonary comorbidities, decreased exercise capacity, and a poor prognosis.

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ABBREVIATIONS: CO = cardiac output; mPAP = mean pulmonary artery pressure; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; TPG = transpulmonary gradient

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Pulmonary hypertension (PH) is a progressive disease characterized by a mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg at rest. It may lead to right ventricular failure and eventually death.[1] According to some studies, the development of PH may be predicted by pulmonary arterial pressures (PAPs) derived from right-sided heart catheterization (excessive increase of PAP during exercise,[2-4] borderline resting mPAP [21-24 mm Hg])[5] and an increased transpulmonary gradient (TPG).[5] In addition, some studies suggested that these conditions may overlap.[6,7] Although these hemodynamic conditions may be of great clinical interest and potentially represent new targets for therapy,[8,9] there are limited long-term follow-up data, and comorbidities have not been analyzed systematically. We aimed to compare data from a real-life patient population with borderline mPAP values with data from patients with normal resting mPAP and historical data from healthy control subjects. A further objective was to describe the relation between resting and exercise hemodynamics in the examined patients.

Materials and Methods

We retrospectively analyzed all consecutive patients of our clinic between 2006 and 2011who underwent right-sided heart catheterization with hemodynamics during rest and exercise. Patients with mPAP ≥ 25 mm Hg were excluded. Patients were eligible for the study when PH was suspected due to disease associated with an increased risk for pulmonary arterial hypertension (collagen vascular disease, myelodysplastic syndrome, or liver cirrhosis) or when complaints such as dyspnea on exertion could not be explained by heart or lung disease. Right-sided heart catheterization at rest and during exercise with cycle ergometry was routinely performed as described earlier.[10] The zero reference line was placed at the anterior axillary line in all supine measurements. Hemodynamic measurements were available at rest, 25 W, 50 W, and peak exercise. As part of the routine workup, 6-min walk distance and N-terminal pro-brain natriuretic peptide level were assessed; transthoracic echocardiography and pulmonary function tests were performed. Patients unable to exercise were excluded from this analysis.

A relevant cardiac comorbidity was predefined as the presence of confirmed coronary heart disease or previous myocardial infarction, chronic atrial fibrillation, arterial hypertension with left ventricular hypertrophy, or impaired systolic left ventricular function (ejection fraction < 50%). A relevant respiratory impairment was predefined as $FEV_1/FVC < 70\%$ or $FEV_1 < 65\%$ or the presence of OSA treated by CPAP or noninvasive ventilation. A historical control group comprising 51 healthy subjects aged < 50 years with available mPAP, cardiac output (CO), and pulmonary artery wedge pressure (PAWP) values at rest and at least at two different exercise levels was used to compare the study patients with completely asymptomatic subjects without any risk factors for PH.[11]

Data are presented as mean ± SD for continuous variables and absolute and relative frequency for categorical data. Patient characteristics were compared with *t*, χ^2, and Fisher exact tests. Correlations with mPAP and PAWP values at various exercise levels were sought by using partial correlations controlling for age. Between-group differences were evaluated with age-adjusted analysis of variance. To compare changes in CO related to changes in mPAP and pulmonary vascular resistance (PVR) between patients with normal resting mPAP or borderline resting mPAP and the control group, means with 95% CIs were calculated and plotted. Multiple testing *P* value adjustment was not performed because this was an exploratory analysis of retrospectively collected data. $P < .05$ was considered significant. Statistical analysis was performed with SPSS version 20.0.0. (IBM Corporation) software. The study was approved by the local Committee on Biomedical Research Ethics (NR: 25-408 ex 12/13).

Results

This analysis is based on resting and exercise hemodynamics data of 141 patients (107 women) from our center (age, 59.2 ± 13.0 years; height, 166 ± 8 cm; weight, 72 ± 15 kg). Seventy-three patients were included due to dyspnea, 60 due to collagen vascular disease, and eight due to myelodysplastic syndrome or liver cirrhosis with or without dyspnea. Of the 141 patients, 109 had mPAP < 21 mm Hg and 32 had mPAP between 21 and 24 mm Hg at rest. Eighty-nine patients had no cardiac or pulmonary disease, whereas 52 had a relevant pulmonary or cardiac comorbidity; these patients were generally characterized by higher mPAP and decreased exercise capacity compared with patients with no relevant pulmonary or cardiac comorbidities (Table 1).

Age was positively correlated with resting and exercise mPAP (rest, $r = 0.32$; 25 W, $r = 0.48$; 50 W, $r = 0.43$; maximal exercise, $r = 0.34$; all $P < .001$) and with exercise PAWP (25 W, $r = 0.31$ [$P < .001$]; 50 W, $r = 0.29$ [$P = .001$]; maximal exercise, $r = 0.20$ [$P = .02$]) but not with resting PAWP ($P = .41$). All the following correlations were corrected for age.

Patients With Borderline vs Normal Resting mPAP

Patients with borderline resting mPAP (21-24 mm Hg) compared with patients with normal resting mPAP (≤ 20 mm Hg) were older (65.8 ± 12.5 years vs 57.3 ± 12.5 years, $P = .001$) and more often presented with a cardiac comorbidity (53% vs 15%, $P < .001$) or a respiratory limitation (47% vs 16%, $P < .001$). Patients with borderline resting mPAP had elevated resting PVR (2.7 ± 0.7 Wood units vs 1.8 ± 0.8 Wood units, $P < .001$), resting PAWP (9.6 ± 3.2 mm Hg vs 6.8 ± 2.5 mm Hg, $P < .001$), and TPG (12.5 ± 3.3 mm Hg vs 8.4 ± 2.8 mm Hg, $P < .001$) but similar CO compared with patients with normal resting mPAP (Table 2).

During exercise, the mPAP/CO slope in the borderline resting mPAP group was steeper than in the normal