Exercise Pathophysiology in Patients With Primary Pulmonary Hypertension

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Background—Patients with primary pulmonary hypertension (PPH) have a pulmonary vasculopathy that leads to exercise intolerance due to dyspnea and fatigue. To better understand the basis of the exercise limitation in patients with PPH, cardiopulmonary exercise testing (CPET) with gas exchange measurements, New York Heart Association (NYHA) symptom class, and resting pulmonary hemodynamics were studied.

Methods and Results—We retrospectively evaluated 53 PPH patients who had right heart catheterization and cycle ergometer CPET studies to maximum tolerance as part of their clinical workups. No adverse events occurred during CPET. Reductions in peak O_2 uptake ($\dot{V}O_2$), anaerobic threshold, peak O_2 pulse, rate of increase in $\dot{V}O_2$, and ventilatory efficiency were consistently found. NYHA class correlated well with the above parameters of aerobic function and ventilatory efficiency but less well with resting pulmonary hemodynamics.

Conclusions—Patients with PPH can safely undergo noninvasive cycle ergometer CPET to their maximal tolerance. The CPET abnormalities were consistent and characteristic and correlated well with NYHA class. **(*Circulation*. 2001;104: 429-435.)**

Key Words: oxygen ■ hypertension, pulmonary ■ ventilation ■ exercise ■ hemodynamics

Primary pulmonary hypertension (PPH) is a progressive and usually fatal disease of unknown etiology[1–3] that leads to increased pulmonary vascular resistance and loss of the pulmonary vasodilator response to exercise. Because of inefficient lung gas exchange and the inability of the right ventricle to adequately increase pulmonary blood flow (cardiac output [CO]) for the O_2 exercise demand, dyspnea and/or fatigue ensues. The increased right ventricular work eventually causes pulmonary hypertension at rest, at which time cardiac catheterization and/or echocardiography is used to establish the diagnosis and to grade the severity.

Cardiopulmonary exercise testing (CPET) with gas exchange has the potential of noninvasively grading the severity of exercise limitation, quantifying the hypoperfusion of the lung and systemic circulation, and assessing responses to therapy[4,5] before overt right ventricular failure and pulmonary hypertension are evident at rest.

The objective of the present study was to quantify the exercise abnormalities in aerobic function and ventilatory efficiency in PPH patients and to relate them to traditional measurements, such as resting hemodynamics and New York Heart Association (NYHA) symptom class.

Methods

Patients and Normal Control Subjects

The medical records of 53 patients with PPH who systematically underwent echocardiography, right heart catheterization, and CPET for clinical evaluation were retrospectively studied. The diagnosis of PPH was based on clinical and laboratory data, which included right heart catheterization to satisfy diagnostic criteria described by a National Institutes of Health registry of PPH and by the World Health Organization.[3,6] Patients with other disorders were excluded. For comparison purposes, the CPET findings of 20 normal subjects of similar age, sex, and body size were also analyzed. The institution's Human Subjects Committee approved the project.

Measurements

Right heart catheterization with standard hemodynamic measurements was performed within 1 month of each patient's CPET study. Just before their CPET studies, patients had standard pulmonary function tests.

Each patient performed a physician-supervised, standard, progressively increasing work rate (WR) CPET to maximum tolerance on an electromagnetically braked cycle ergometer. Gas exchange measurements (Cardiopulmonary Metabolic Cart, Medical Graphics) were made during 3 minutes of rest, 3 minutes of unloaded leg cycling at 60 rpm followed by a progressively increasing WR exercise of 5 to 15 (10 ± 3) $W \cdot min^{-1}$ to maximum tolerance, and 2 minutes of recovery.[7] Pulse oximetry (SpO_2), heart rate (HR), 12-lead ECG, and cuff blood pressure were monitored and recorded.

Minute ventilation ($\dot{V}E$, BTPS), O_2 uptake ($\dot{V}O_2$, STPD), CO_2 output ($\dot{V}CO_2$, STPD), and other exercise variables were computer-calculated breath by breath, interpolated second by second, and averaged over 10-second intervals.[7,8] The anaerobic threshold (AT), ratio of O_2 uptake to WR increase ($\Delta\dot{V}O_2/\Delta WR$), and oxygen pulse ($O_2$ pulse) were determined as previously described.[7] Ventilatory efficiency during exercise was expressed as the ratio of ventilation to CO_2 output at AT ($\dot{V}E/\dot{V}CO_2$@AT)[7] and the slope of $\dot{V}E$ versus $\dot{V}CO_2$ over the linear component of the plot of $\dot{V}E$ versus $\dot{V}CO_2$.[9] The rate

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TABLE 1. Summary of Demographics, Resting Hemodynamics, and CPET in 53 PPH Patients

Demographics	
Age, y	42±12
Sex, %	
Female	89
Male	11
Height, cm	164±10
Weight, kg	73±19
Race, %	
White	68
Hispanic	15
Asian	9
Black	8
NYHA class	2.8±0.6
Resting hemodynamics	
mRAP, mm Hg	11±5
mPAP, mm Hg	64±18
mPWP, mm Hg	9±4
CO, $L \cdot min^{-1}$	3.9±1.3
Cardiac index, $L \cdot min^{-1} \cdot m^2$	2.2±0.8
PVR, $mm\ Hg \cdot L^{-1} \cdot min^{-1}$	15±7
PVRI, $mm\ Hg \cdot L^{-1} \cdot min^{-1} \cdot m^2$	28±14
TPVR, $mm\ Hg \cdot L^{-1} \cdot min^{-1}$	18±7
mBP, mm Hg	87±10
SVR, $mm\ Hg \cdot L^{-1} \cdot min^{-1}$	22±8
SVRI, $mm\ Hg \cdot L^{-1} \cdot min^{-1} \cdot m^2$	38±14
TSVR, $mm\ Hg \cdot L^{-1} \cdot min^{-1}$	25±9
LVEF, %	62±6
CPET	
Peak $\dot{V}O_2$	
$L \cdot min^{-1}$	0.78±0.27*
% Pred	44±14
AT	
$L \cdot min^{-1}$	0.60±0.19*
% Pred	59±16
Peak work rate	
W	46±25†
% Pred	35±16
Peak O_2 pulse	
$mL \cdot beat^{-1}$	5.82±1.95*
% Pred	58±17
Peak HR	
bpm	135±23*
% Pred	76±12
Peak ventilation	
$L \cdot min^{-1}$	45±16*
As % MVV	49±14
MRT, s	48±17*
$\dot{V}E/\dot{V}CO_2$@AT	
Ratio	50±14*
% Pred	172±52
$\dot{V}E$ vs $\dot{V}CO_2$ slope	
Ratio	47±20*
% Pred	164±76
$\Delta\dot{V}O_2/\Delta WR$, $mL \cdot min^{-1} \cdot W^{-1}$	6.34±1.41*
AT/Peak $\dot{V}O_2$	
Ratio	0.79±0.09*
% Pred	138±18

mRAP indicates mean right atrial pressure; mPAP, mean pulmonary artery pressure; mPWP, mean pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; PVRI, PVR index; TPVR, total PVR; mBP, mean systemic artery pressure; SVR, systemic vascular resistance; SVRI, SVR index; TSVR, total SVR; LVEF, left ventricular ejection fraction; peak $\dot{V}O_2$, peak exercise O_2 uptake; % Pred, percentage of predicted value; AT, anaerobic threshold; MVV, maximal voluntary ventilation; MRT, mean response time of $\dot{V}O_2$ during unloaded cycling; $\dot{V}E/\dot{V}CO_2$@AT, ratio of ventilation to CO_2 output at AT; and $\Delta\dot{V}O_2/\Delta WR$, increase in $\dot{V}O_2$ per increase in work rate.

*$P<0.0001$ vs predicted value for CPET parameters.

of $\dot{V}O_2$ increase during unloaded cycling was expressed as the mean response time (MRT) for a monoexponential curve fit to the second-by-second $\dot{V}O_2$ measurements during the 3 minutes of unloaded cycling.[10] If the first breath $\dot{V}O_2$ equaled the 3-minute $\dot{V}O_2$, the MRT was considered equal to the duration of the first breath.

Statistical Analysis

Standard equations were used to predict actual and percent predicted (%Pred) values for maximal voluntary ventilation and CPET parameters.[7,11] The predicted value for $\dot{V}E/\dot{V}CO_2$@AT was calculated as $24.71-4.04\times$sex (female=0, male=1)$+0.115\times$age (data from 41 normal subjects). Resting CPET values were compared with their predicted values by using paired 2-tailed *t* tests. A significant change was defined as an α level of $P<0.05$. Correlation and regression analyses were performed by ANOVA. Simple individual linear regression analyses were performed by the Pearson correlation coefficient (*r*) between individual variables and each of the other variables. Multicolinearity analyses were performed to predict NYHA class by using stepwise regression with an α level of $P=0.05$ for tolerance level.[12,13]

Results

Pulmonary Hemodynamics and Cardiopulmonary Exercise Analyses

Most of the 53 PPH patients were middle-aged women (Table 1) of NYHA class 3. Their symptoms were dyspnea (87%), fatigue (42%), lower extremity edema (21%), syncope (13%), light-headedness (11%), chest pain or tightness (8%), and palpitations (6%).

At cardiac catheterization, all patients had resting pulmonary hypertension (mean pulmonary artery pressure 64±18 mm Hg), increased mean right atrial pressure and pulmonary vascular resistance, reduced CO and cardiac index, and normal left ventricular ejection fraction (Table 1). On echocardiography, all patients had an enlarged right ventricle and/or right atrium, 89% had tricuspid valve regurgitation, and approximately one third had a patent foramen ovale.

All patients completed CPET without incident. Two patients completed only 2 to 3 minutes of unloaded pedaling; the duration of exercise in all others averaged 8±2 (range 3.5 to 14) minutes. All subjects exercised above their ATs; this finding and their high end-exercise respiratory exchange ratio (1.23±0.11)

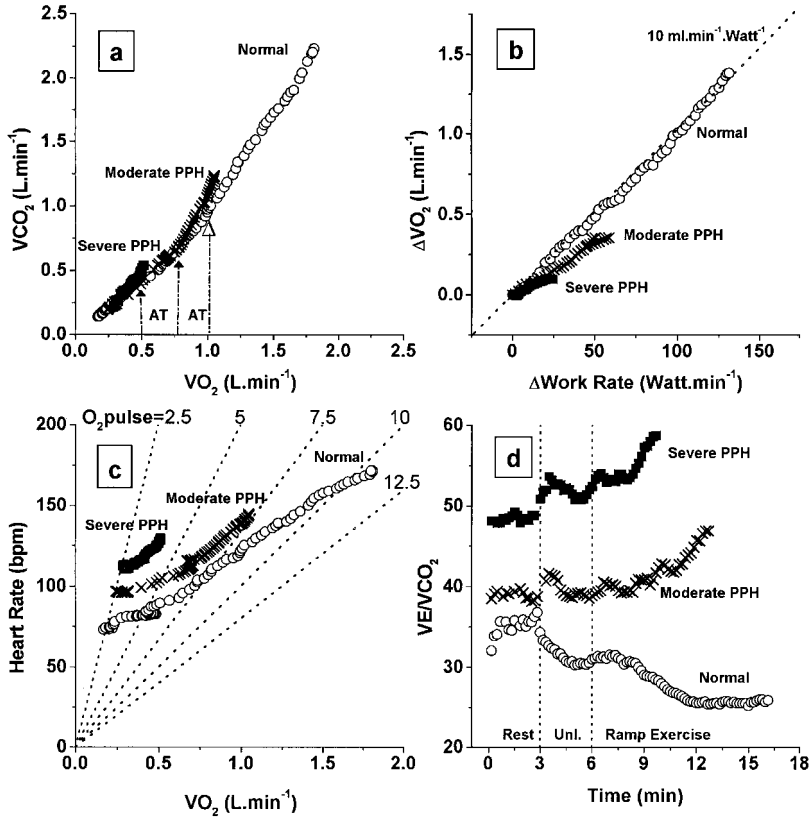

Figure 1. CPET measurements of 2 PPH patients and normal control subject (open circles; female, aged 28 years, height 162 cm, and weight 55 kg). Patients with moderate PPH (×; female, aged 35 years, height 161 cm, and weight 84 kg) and severe PPH (solid squares; female, aged 27 years, height 160 cm, and weight 58 kg) are illustrated. All have similar predicted values. Protocol consisted of 3 minutes of rest, 3 minutes of unloaded cycling at 60 rpm (Unl.), and ramp WR of 15, 10, and 5 W · min^{-1}, respectively, to maximal tolerance. a, $\dot{V}CO_2$ vs $\dot{V}O_2$ with arrows at the respective AT of each subject. b, Change in $\dot{V}O_2$ vs change in WR, with dotted line indicating normal slope of 10 mL · min^{-1} · W^{-1}. c, HR vs $\dot{V}O_2$, with diagonal dotted lines indicating O_2 pulse in mL · $beat^{-1}$. d, Ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) vs time, with vertical dashed lines separating rest, unloaded, and ramp exercise. Characteristic abnormalities of PPH patients depicted are low values for peak $\dot{V}O_2$, AT, peak WR, $\Delta\dot{V}O_2/\Delta WR$, peak HR, and peak O_2 pulse. With PPH, resting $\dot{V}E/\dot{V}CO_2$ values are elevated and tend to remain relatively constant or increase during exercise, contrasting with lower resting and decreasing $\dot{V}E/\dot{V}CO_2$ during exercise in normal control subject.

indicate that they had developed a significant metabolic acidosis and had exercised to a heavy, if not maximal, work intensity. The dominant symptoms described for stopping cycle exercise were leg fatigue (49%), dyspnea (43%), palpitations (4%), and light-headedness (2%).

Pattern of Exercise Gas Exchange

The parameters of exercise gas exchange were systematically abnormal in the PPH patients (Table 1). Peak $\dot{V}O_2$, peak WR, peak O_2 pulse or $\dot{V}O_2$/HR, the ratio of $\dot{V}O_2$ increase to WR increase ($\Delta\dot{V}O_2/\Delta WR$), AT, and MRT were all moderately to severely reduced. There was a marked increase in the slope of $\dot{V}E$ versus $\dot{V}CO_2$ and a moderate decrease in peak HR in all patients. Compared with the control group, the differences between actual and predicted values for all of these variables were significant ($P<0.0001$) (Table 1). The typical abnormal pattern of CPET findings for 2 PPH patients, 1 with moderate and 1 with severe exercise limitation, and a normal control subject are shown in Figure 1. The exercise pathophysiology is reflected in the reduced peak $\dot{V}O_2$, AT, $\Delta\dot{V}O_2/\Delta WR$, and peak O_2 pulse and high $\dot{V}E/\dot{V}CO_2$.

Correlations

Table 2 summarizes multiple correlations between CPET and other variables. NYHA class was significantly correlated with exercise parameters of aerobic function and ventilatory efficiency and better with %Pred values than either per kilogram or absolute values. NYHA class was significantly, but weakly, correlated with resting CO and pulmonary vascular resistance but not with pulmonary artery pressure. Peak WR, AT, and O_2 pulse ($\dot{V}O_2$/HR), slope of $\dot{V}E$ versus $\dot{V}CO_2$, and $\dot{V}E/\dot{V}CO_2$@AT were also significantly correlated with NYHA class ($P<0.01$ to $P<0.0001$ for all) (Table 2).

Peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$@AT correlated well with NYHA class ($P<0.0001$) (Figure 2). Peak $\dot{V}O_2$ and $\dot{V}O_2$/HR also correlated well with AT ($P<0.0001$, Figure 2), showing that the latter can be used as a submaximal parameter for grading aerobic function. The good correlation between peak $\dot{V}O_2$/HR and AT suggests that the latter is highly influenced by stroke volume (SV).

The MRT of $\dot{V}O_2$ for PPH patients during unloaded cycling exercise averaged 48±17 seconds versus 14±9 seconds for the control subjects ($P<0.0001$) (Figure 3). MRT was positively correlated with NYHA class and negatively correlated with peak $\dot{V}O_2$, AT, and peak O_2 pulse (all $P<0.001$).

By use of stepwise regression analysis of multiple factors, NYHA class could be estimated from peak $\dot{V}O_2$ (%Pred) and the slope of $\dot{V}E$ versus $\dot{V}CO_2$ (%Pred) ($R=0.64$, $P<0.0001$).

Physiological Severity of PPH

The physiological responses to exercise were abnormal in all patients. Table 3 categorizes the PPH patients into 4 groups on the basis of the severity of reduction in their %Pred peak $\dot{V}O_2$ rather than the less discriminating gradations in NYHA class or pulmonary hemodynamic data. By use of this method of grading disease severity, there is virtually no overlap in any of the key parameters of aerobic function (peak $\dot{V}O_2$, AT, $\Delta\dot{V}O_2/\Delta WR$, peak O_2 pulse, and MRT of $\dot{V}O_2$) or ventilatory efficiency ($\dot{V}E/\dot{V}CO_2$@AT and slope of $\dot{V}E$ versus $\dot{V}CO_2$) when the control subjects and the PPH patients of mildest severity are compared. Peak $\dot{V}E$ became a lesser fraction of the actual maximal voluntary ventilation as disease severity increased.

TABLE 2. *r* Matrix of Selected Simple Regressions for Multiple Factors in Patients With PPH

Variable	Peak $\dot{V}O_2$, % Pred	Peak $\dot{V}O_2$, mL · min^{-1} · kg^{-1}	Peak $\dot{V}O_2$, L · min^{-1}	AT, % Pred	AT, mL · min^{-1} · kg^{-1}	AT, L · min^{-1}	Peak WR, W	$\dot{V}E/\dot{V}CO_2$ @AT	$\dot{V}E/\dot{V}CO_2$ Slope	Cardiac Index, L · min^{-1} · m^2	PVRI, U Index
NYHA	−0.54*	−0.49*	−0.44†	−0.45*	−0.44†	−0.39‡	−0.35‡	0.44†	0.37‡	0.26§	0.23

	NYHA (class)	Peak $\dot{V}O_2$, % Pred	AT, % Pred	Peak WR, % Pred	Peak O_2 Pulse, % Pred	$\Delta\dot{V}O_2/\Delta WR$, mL · min^{-1} · W^{-1}	$\dot{V}E/\dot{V}CO_2$ @AT, % Pred	$\dot{V}E$ vs $\dot{V}CO_2$ Slope, % Pred	AT/ Peak $\dot{V}O_2$, % Pred	Peak HR, % Pred	Peak $\dot{V}E$, As %MVV	MRT, s	CO, L · min^{-1}
Selected exercise parameters													
Peak $\dot{V}O_2$	−0.54*												
AT	−0.45*	0.92*											
Peak WR	−0.42†	0.78*	0.77*										
Peak O_2 pulse	−0.43†	0.86*	0.82*	0.56*									
$\Delta\dot{V}O_2/\Delta WR$	−0.24	0.56*	0.42†	0.52*	0.46†								
$\dot{V}E/\dot{V}CO_2$@AT	0.49*	−0.49*	−0.44†	−0.36‡	−0.46*	−0.30§							
$\dot{V}E$-vs-$\dot{V}CO_2$ slope	0.39‡	−0.30§	−0.26§	−0.23§	−0.34‡	−0.15	−0.92*						
AT/peak $\dot{V}O_2$	0.35*†	−0.52*	−0.15	−0.37‡	−0.39‡	−0.39‡	0.35‡	0.26§					
Peak HR	−0.31§	0.38‡	0.33‡	0.47§	−0.12	0.18	−0.19	−0.04	−0.28§				
Peak $\dot{V}E$	−0.05	0.41†	0.36‡	0.38‡	0.28§	0.12	−0.14	0.28§	−0.24§	0.25§			
MRT	0.41†	−0.62*	−0.61*	−0.50*	−0.44†	−0.25§	0.15	0.13	0.25§	−0.45†	−0.26§		
Selected resting hemodynamics													
CO	−0.31§	0.32§	0.33§	0.27§	0.36‡	0.28§	−0.23	−0.08	−0.14	0.02	0.08	−0.24	
PVR	0.27§	−0.25§	−0.29§	−0.19	−0.27§	−0.25§	0.13	0.04	−0.02	0.07	0.09	0.05	−0.69*

U index indicates Wood unit index (mm Hg · L^{-1} · min^{-1} · m^2).
*$P<0.0001$, †$P<0.001$, ‡$P<0.01$, and §$P<0.05$.

Discussion

Basis for CPET Abnormalities in PPH

The breathlessness of PPH patients during exercise can be related to the relative hypoperfusion of their well-ventilated alveoli (increased "dead space"). In normal subjects, the ventilatory response ($\dot{V}E$) to exercise is tightly related to CO_2 output ($\dot{V}CO_2$).[9,11,14,15] In PPH, the ventilation of underperfused alveoli causes an increase in dead space ventilation, manifested by a hyperbolic increase in $\dot{V}E$ relative to the $\dot{V}CO_2$

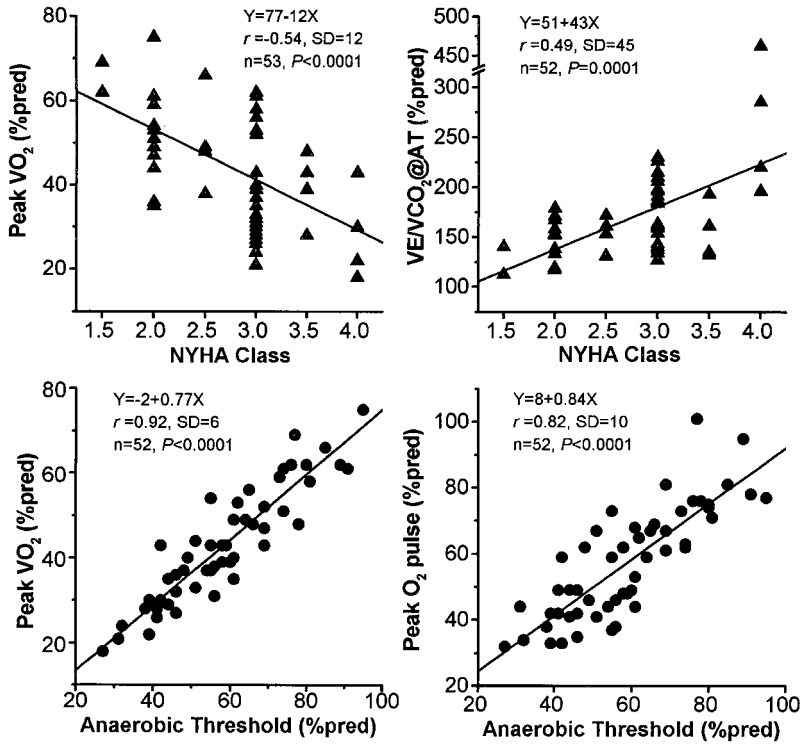

Figure 2. Correlations of peak $\dot{V}O_2$ (%pred) and ventilatory equivalent for CO_2 at AT ($\dot{V}E/\dot{V}CO_2$@AT) vs NYHA symptom class (top panels) and peak $\dot{V}O_2$ and peak O_2 pulse vs AT (bottom panels) in PPH patients during CPET. All correlations are highly significant.

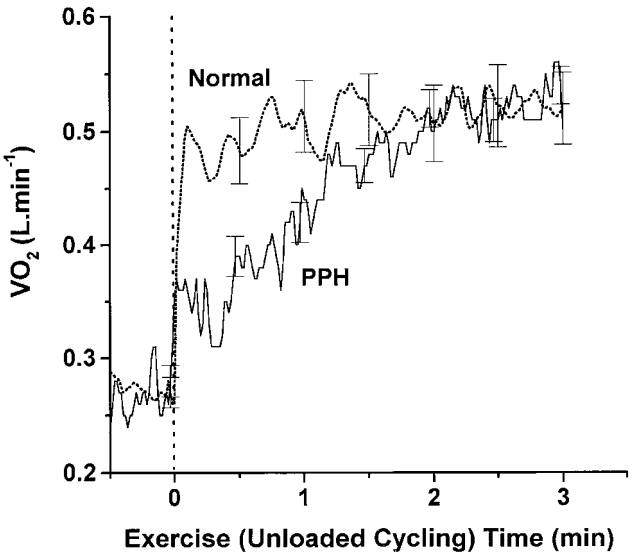

Figure 3. $\dot{V}O_2$ kinetics in response to 3 minutes of unloaded cycling exercise in PPH patients and normal control subjects. Data are averaged second by second during unloaded cycling for 50 PPH patients and 20 control subjects. Mean±SE values are shown at half-minute intervals. Kinetics of PPH patients are markedly slower, but by 3 minutes, they reach the same average $\dot{V}O_2$.

increase during exercise. In addition, the lactic acidosis at low WRs and hypoxemia can act as additional stimuli to breathing[7] and contribute to the sensation of dyspnea in PPH patients, even though their peak $\dot{V}E$ was well below their maximal voluntary ventilation. Concurrently, the inability to adequately increase pulmonary (and therefore systemic) blood flow during exercise results in the failure to meet the exercise O_2 requirement.

A brief description of 5 parameters of aerobic function (peak $\dot{V}O_2$, peak O_2 pulse, AT, $\Delta\dot{V}O_2/\Delta WR$, and MRT) that reflect the inability of pulmonary blood flow to increase adequately in PPH patients follows.

Peak $\dot{V}O_2$

Peak $\dot{V}O_2$ assesses the subject's maximal work ability and the maximal ability of the circulatory system to increase CO. In PPH, this relates to the pulmonary vasculopathy, which limits blood flow through the lung (and thus through the body).

Peak O_2 Pulse

From the Fick principle, $\dot{V}O_2$ equals $CO\times C(a-\bar{v})O_2$. $C(a-\bar{v})O_2$ denotes content difference between arterial and mixed venous blood. Because CO is the product of HR and SV, dividing both sides of the Fick equation by HR discloses that the O_2 pulse ($\dot{V}O_2$/HR) at any given time equals $SV\times C(a-\bar{v})O_2$. As noted previously,[16–18] a low peak O_2 pulse usually indicates a low peak SV.

Anaerobic Threshold

The AT, which describes the highest $\dot{V}O_2$ that the patient can sustain without developing a lactic acidosis, appears to be an independent marker of PPH severity.

$\Delta\dot{V}O_2/\Delta WR$

$\Delta\dot{V}O_2/\Delta WR$ also characterizes PPH severity[7] (Table 3). Values progressively lower than 10 mL/min per watt disclose a higher than normal dependence on anaerobic metabolism and,

TABLE 3. Resting and Exercise Values in Normal Subjects and PPH Patients Categorized According to Severity of Reduction in CPET Aerobic Capacity

	Normal* (n=20)	Mild PPH (n=3)	Moderate PPH (n=14)	Severe PPH (n=22)	Very Severe PPH (n=14)
Peak $\dot{V}O$ range, % pred	82–132	65–79	50–64	35–49	<35
Peak $\dot{V}O_2$, % pred	101±19	70±4	58±4	42±5	27±4
Peak $\dot{V}O_2$, mL · min^{-1} · kg^{-1}	29.5±6.6	14.5±3.3	12.5±2.2	11.2±2.6	8.1±1.7
AT, % pred	104±16	85±7	75±10	57±9	41±7
AT, mL · min^{-1} · kg^{-1}	16.3±3.9	10.4±2.3	9.7±1.3	8.7±2.2	6.8±1.3
Peak O_2 pulse, % pred	108±25	86±11	73±8	56±11	39±5
Peak HR, % pred	96±13	83±12	80±8	77±12	70±13
$\Delta\dot{V}O_2/\Delta WR$, mL · min^{-1} · W^{-1}	9.6±0.9	8.3±0.5	7.0±1.5	6.0±1.0	5.6±1.3
$\dot{V}E/\dot{V}CO_2$@AT, % pred	99±12	142±22	149±21	161±25	219±76
$\dot{V}E/\dot{V}CO_2$@AT, absolute	29±4	43±6	45±7	46±8	62±20
$\dot{V}E$-vs-$\dot{V}CO_2$ slope, % pred	88±11	164±49	148±27	141±32	215±123
$\dot{V}E$-vs-$\dot{V}CO_2$ slope, absolute	25±3	49±14	45±9	40±10	60±32
Peak $\dot{V}E$, as % MVV	70±15	63±19	54±9	47±11	43±16
MRT, s	12±10	34±9	37±14	47±13	64±15
mPAP, mm Hg	...	48±17	63±14	70±18	57±17
CO, L · min^{-1}	...	5.1±1.1	4.4±1.4	3.5±1.0	3.8±1.2
PVR, mm Hg · L^{-1} · min^{-1}	...	8±4	15±8	18±5	14±6
NYHA class	...	2.0±0.4	2.5±0.5	2.8±0.6	3.3±0.4

*Each CPET parameter of all PPH patients is significantly different from that of normal control subjects ($P<0.001$).

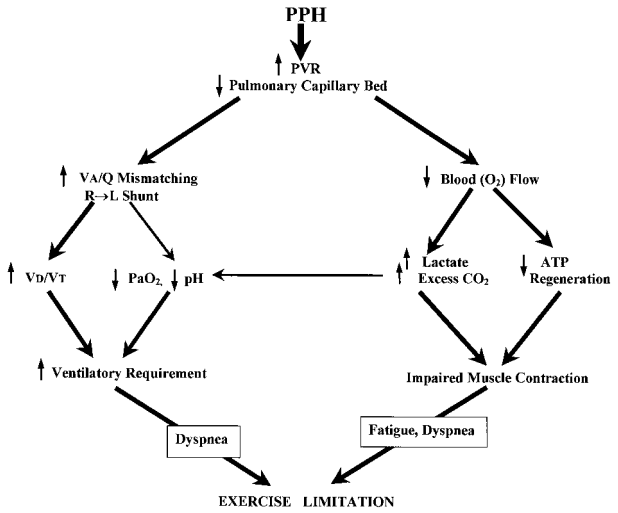

Figure 4. Pathophysiology of exercise limitation of PPH patients. Longer arrows show pathways leading to dyspnea and fatigue with exercise. Shorter arrows indicate how each response differs from normal. PVR indicates pulmonary vascular resistance; V_A/Q, alveolar ventilation/perfusion ratio; R, right; L, left; V_D/V_T, dead space volume/tidal volume ratio; and Pa_{O_2}, arterial O_2 pressure.

therefore, a decreased ability to aerobically satisfy high-energy phosphate requirements.

Mean Response Time

The MRT of $\dot{V}_{O_2}$ for constant WR exercise depends on the rate of increase of pulmonary blood flow at the start of exercise.[10] Because our patients were so exercise limited, the kinetics, even for unloaded cycling, were markedly slower than that for our normal subjects, with the latter achieving steady-state $\dot{V}_{O_2}$ values within 15 seconds on average (Figure 3).

Abnormalities in Exercise Physiology in PPH Patients and Basis of Symptoms

On the basis of our CPET findings, the mechanisms that might account for the most common symptoms in PPH patients (dyspnea and/or fatigue with exercise) can be better understood (Figure 4).

Dyspnea

The finding of an increased ventilatory response to exercise appears to be a uniform finding in PPH patients (Table 3). Their dyspnea can be attributed to at least 3 mechanisms that increase ventilatory drive relative to metabolism (Figure 4, left branch).

The first is ventilation/perfusion mismatching, resulting in an increased ratio of dead space volume to tidal volume that is due to hypoperfusion of ventilated alveoli.[1,15,19] The second mechanism is the increased hydrogen ion (H^+) stimulus to ventilation resulting from a low WR lactic acidosis (low AT). This stimulates $\dot{V}_E$, not only from the increase in H^+ that is due to the decrease in HCO_3^- but also from the increase in $\dot{V}_{CO_2}$ that is due to the dissociation of a large amount of HCO_3^- as it buffers the newly formed lactic acid. The third mechanism, present in many of our patients, is arterial hypoxemia, which is due to a reduced pulmonary capillary bed with shortened red blood cell transit times or to a right to left shunt through a patent foramen ovale. The hypoxemic (shunted) blood entering the systemic arterial circulation stimulates ventilation profoundly because it has not only a low P_{O_2} but also a high P_{CO_2} and high H^+ concentration.

Fatigue

In PPH, aerobic regeneration of ATP is impaired, with more work being done anaerobically at relatively low WRs, as reflected by the reduced peak $\dot{V}_{O_2}$, AT, and $\Delta\dot{V}_{O_2}/\Delta$WR in our patients (Figure 4, right branch). Because the mechanism of anaerobic ATP regeneration stimulates anaerobic glycolysis, a prominent lactic acidosis results. Probably the most important mechanism leading to muscle fatigue in PPH is the reduction in the rate of aerobic regeneration of ATP.

Light-Headedness

The light-headedness with exercise that some PPH patients experience is probably related to their inability to adequately maintain CO and systemic blood pressure with exercise and/or sudden arterial hypoxemia via a patent foramen ovale.

Resting Pulmonary Hemodynamics in PPH Patients

There were significant but modest correlations between resting CO and pulmonary vascular resistance with NYHA class and several of the CPET measures of aerobic function (Table 2). Cardiac catheterization is invasive and carries a significant risk of morbidity and mortality in PPH,[3,4,20] although it is essential in making the diagnosis. In contrast, CPET measures of aerobic function and gas exchange efficiency might be better for determining disease severity and tracking the clinical course, especially in view of the better correlations of these measures with NYHA symptom class.

Grading of Physiological Impairment in PPH

All of the CPET parameters of aerobic function and gas exchange efficiency in our patients correlated well with their NYHA symptom class. Because NYHA class correlated best with %Pred peak $\dot{V}_{O_2}$, we chose the latter parameter to physiologically grade the impairment in PPH (Table 3), as did Weber et al[18] for chronic heart failure. The absence of overlap in the predicted peak $\dot{V}_{O_2}$ of our PPH patients (18 to 75 %Pred) and our 20 control subjects (82 to 132 %Pred) (Table 3) indicates the discriminating power of CPET even in "mild" PPH. Two thirds of our PPH patients had peak $\dot{V}_{O_2}$ levels of $<$50% predicated value**,** a level associated with a 60% 2-year mortality in patients with chronic left heart failure.[21]

Peak O_2 pulse and AT decreased in parallel fashion within the grading established by the peak $\dot{V}_{O_2}$ in our patients (Table 3). Because O_2 pulse equals $SV\times C(a-\bar{v})O_2$, the progressively decreasing peak O_2 pulse likely reflects a progressive reduction in peak SV paralleling disease severity. The AT becomes a higher fraction of peak $\dot{V}_{O_2}$ as disease severity (peak $\dot{V}_{O_2}$) worsens, suggesting a decrease in cardiovascular reserve as PPH worsens (Table 3).

Conclusions

The pathophysiological CPET findings that we have described in PPH appear to be consistent and characteristic. CPET is of great potential value for evaluating patients with dyspnea and fatigue safely, reproducibly, and noninvasively.[8,22,23] It may become as useful in assessing the prog-

nosis of PPH patients as it has been in patients with chronic heart failure,[11,23] or it may be used for the purpose of prioritizing patients for lung transplantation and for evaluating drug therapy.[4,5] The need to categorize disease severity accurately and noninvasively in PPH patients makes it desirable that physicians responsible for diagnosis and management of these patients become familiar with CPET and the information that can be derived from it.

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