Gas Exchange Detection of Exercise-Induced Right-to-Left Shunt in Patients With Primary Pulmonary Hypertension

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Background—Because of high pulmonary vascular resistance in patients with primary pulmonary hypertension (PPH), right atrial pressure may exceed left atrial pressure during exercise, resulting in a right-to-left shunt via a patent foramen ovale (PFO). This shunting would disturb arterial P_{CO_2} and H^+ homeostasis if the pulmonary blood were not simultaneously hyperventilated to compensate for the high CO_2 and H^+ in the shunted blood. This article first hypothesizes and then describes unique changes in gas exchange when right-to-left exercise-induced shunting (EIS) occurs.

Methods and Results—Retrospectively, the cardiopulmonary exercise tests of 71 PPH patients were studied. Criteria postulated to document hyperventilation of the pulmonary blood flow due to a right-to-left EIS were (1) an abrupt and sustained increase in end-tidal O_2 with a simultaneous sustained decrease in end-tidal CO_2; (2) an abrupt and sustained increase in the respiratory exchange ratio; and (3) usually, an associated decline in pulse oximetry saturation. Each patient was evaluated for a PFO with resting echocardiography. The investigators interpreting the gas exchange evidence of EIS were blinded to the echocardiographic readings. Forty-five percent of the patients had demonstrable EIS by gas exchange criteria. Almost all were also positive for a PFO by echocardiography. Using the resting echocardiograph as the reference, the sensitivity, specificity, positive and negative predictive values, and accuracy were all between 90% to 96%.

Conclusions—Exercise-induced right-to-left shunting can be detected by noninvasive, cardiopulmonary exercise testing in patients with PPH. **(*Circulation*. 2002;105:54-60.)**

Key Words: shunts ■ echocardiography ■ exercise ■ hypertension, pulmonary

Patients with right-to-left intracardiac shunts regulate arterial P_{CO_2} and pH by hyperventilating unshunted lung blood flow to compensate for the high CO_2 content in shunted blood.[1] During clinical cardiopulmonary exercise testing (CPET) of patients with primary pulmonary hypertension (PPH), we frequently observed gas exchange patterns indicating acute hyperventilation of pulmonary blood flow, suggesting shunting via a patent foramen ovale (PFO).

In normal persons, right-to-left shunting via a PFO is unlikely because left atrial pressure exceeds right atrial pressure. However, with abnormally high pulmonary vascular resistance (as in PPH), right atrial pressure can exceed left atrial pressure, especially during exercise, and force venous (low P_{O_2} and high P_{CO_2} and H^+) blood through a PFO directly into the systemic circulation, stimulating systemic arterial chemoreceptors and causing hyperventilation of the unshunted pulmonary blood flow. This compensatory hyperventilation increases CO_2 unloading, thereby maintaining arterial P_{CO_2} and H^+ homeostasis, despite the presence of an exercise-induced right-to-left shunt (EIS).

The objective of the present study was to describe the specific gas exchange changes that can be used to identify those patients with PPH who develop an EIS.

Methods

The Institutional Review Board at Harbor-UCLA approved this protocol. We evaluated the clinical records and gas exchange evidence for or against EIS in 71 PPH patients[2] and compared these determinations, in a blinded fashion, with the evidence for PFO found during resting echocardiography. The majority of patients were in New York Heart Association (NYHA) class III. None had other significant concurrent disorders.

CPET Protocol, Measurements, and Data Display

Each patient performed standard, physician-supervised, progressively increasing work rate (WR) CPET on an electromagnetically braked cycle ergometer.[2,3] Breath-by-breath gas exchange measurements (Cardiorespiratory Diagnosis System, Medical Graphics), and recordings of ECG, systemic blood pressure, and pulse oximeter saturation (Sp_{O_2}) were made during 3 minutes of rest, 3 minutes of unloaded cycling, progressively increasing WR exercise, and 2 minutes of recovery.[2–4] WR was increased at 5 to 15 W/min (mean, 10 ± 3 W/min), depending on the physician evaluation of patient fitness. Data were interpolated second-by-second, averaged every 10 seconds, and then printed in a table and on a single-page 9-panel plot with 15 graphic displays of the patient's responses to CPET (Figure 1).[2–6] For this investigation, only the first CPET of each patient was analyzed.

Concurrently, CPET studies were obtained from a control group of 20 normal subjects with a similar age, sex, and body size.

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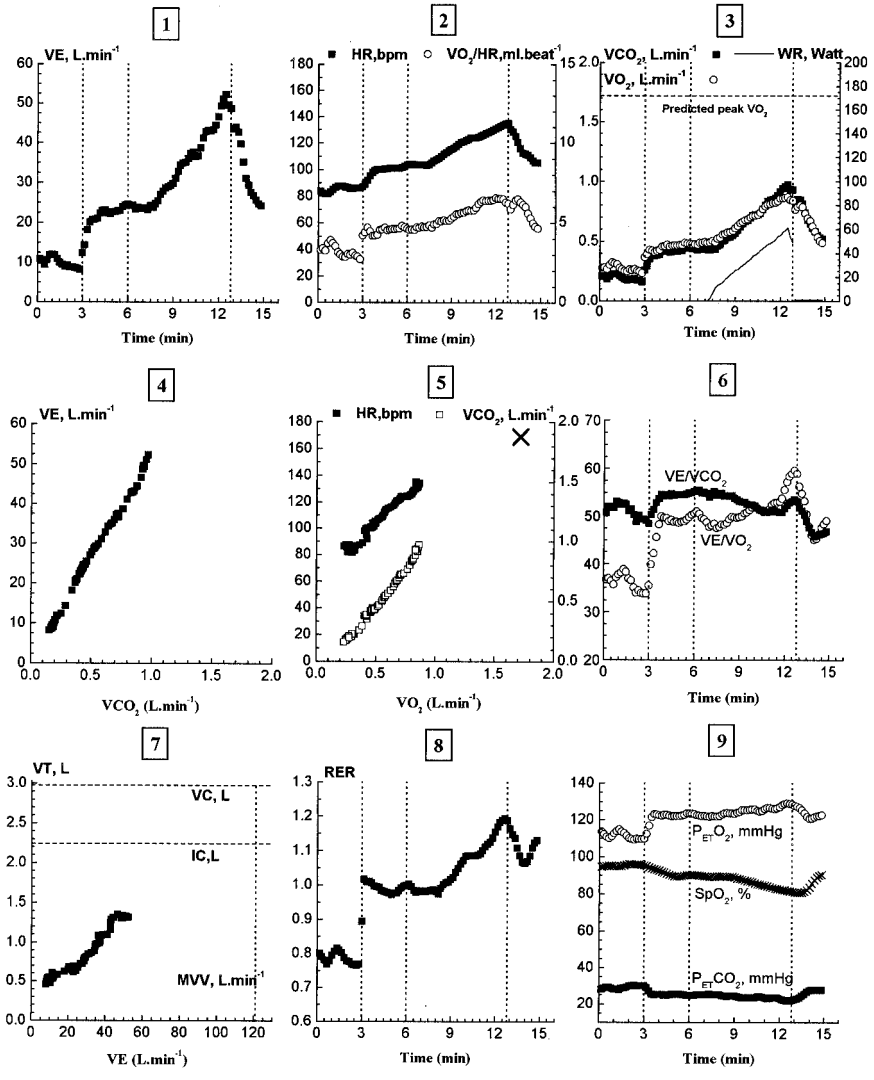

Figure 1. Exercise gas exchange responses to progressively increasing cycle CPET in a 51-year-old woman with PPH who manifests a right-to-left shunt at the start of unloaded cycling. Points are 10-second averages. The vertical dashed lines separate the periods of rest, unloaded cycling, incremental work, and recovery, respectively. In panel 3, the diagonal line shows the increasing cycle resistance. In panel 5, the "X" depicts the predicted peak $\dot{V}O_2$ and peak heart rate (HR). $\dot{V}E$ indicates minute ventilation; $\dot{V}O_2$/HR, oxygen pulse; $\dot{V}O_2$, oxygen uptake; $\dot{V}CO_2$, carbon dioxide output; $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$, ventilatory equivalents for O_2 and CO_2; VT, tidal volume; VC, vital capacity; IC, inspiratory capacity; MVV, maximal voluntary ventilation; RER, respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); $P_{ET}O_2$ and $P_{ET}CO_2$, end-tidal pressures of O_2 and CO_2; and SpO_2, pulse oximeter values for oxyhemoglobin saturation. The low and flattened peak $\dot{V}O_2$ and peak O_2 pulse and high ventilatory equivalents are typical of PPH, with or without a shunt. The typical and dominant evidences for a right-to-left shunt are an abrupt decrease in $P_{ET}CO_2$ and concurrent increases in$P_{ET}O_2$ (panel 9), RER (panel 8), and $\dot{V}E/\dot{V}O_2$ more than $\dot{V}E/\dot{V}CO_2$ (panel 6). SpO_2 (panel 9) declines soon thereafter.

Detection of EIS by Gas Exchange Criteria

Three author-investigators (graders), who were blinded regarding all identifying patient information and echocardiographic findings, independently reviewed the 9-panel CPET plots using the following criteria to identify an EIS at the start of unloaded cycling exercise: (1) an abrupt and sustained increase in end-tidal O_2 ($P_{ET}O_2$), with a simultaneous, sustained decrease in end-tidal CO_2 ($P_{ET}CO_2$) (Figure 1, panel 9); (2) an abrupt and sustained increase in the respiratory exchange ratio (RER=carbon dioxide elimination/oxygen consumption [$\dot{V}CO_2/\dot{V}O_2$; Figure 1, panel 8), and (3) usually, an associated SpO_2 decline (Figure 1, panel 9).

Echocardiography

All patients underwent resting transthoracic echocardiography with Valsalva maneuvers and bubble studies.[7–10] The great majority had >1 echocardiogram on different days. In addition, ≈1 of 10 had transesophageal echocardiography. If an atrial right-to-left shunt was detected during any echocardiographic study, the patient was categorized as PFO-positive (PFO+); if not, the patient was categorized as PFO-negative (PFO−).

Separation of PPH Patients into Groups

Using the above criteria applied to the 9-panel CPET graphic array, the 71 CPET studies were independently graded as either EIS-positive (EIS+) or EIS-negative (EIS−) by 3 graders. Two graders also used tabular data to aid in their decision-making when the changes in the graphic data were less obvious. Patients who were PFO+ by echocardiography and unanimously EIS+ were placed in the shunt group; those who were PFO− by echocardiography and unanimously EIS− were placed in the no-shunt group. Any PFO+ patient categorized as EIS− or any PFO− patient categorized as EIS+ by any grader was placed in the discordant group. During this process, all 3 graders independently identified 3 patients who were EIS− during unloaded cycling but converted to EIS+ near the end of their CPET; these were excluded from the grouping.

Statistical Analyses

Data are expressed as mean±SD, except where specifically noted. Most CPET values are expressed as a percent of predicted value.[2,3,11,12] Repeated ANOVA with 2-tailed Scheffe tests were used to identify differences between groups; paired *t* tests were used to identify changes from rest.[13,14] $P<0.05$ was considered significant. Sensitivity, specificity, and predictive values of EIS detection of shunt were calculated,[14] despite knowing that a PFO induced during exercise might be unrecognizable during resting echocardiography.

Results

Similarities of PPH Groups at Rest and Peak Exercise

All CPET studies were completed without adverse events. The demographics of the shunt, no-shunt, discordant, and

TABLE 1. Demographics and CPET Parameters in PPH Patients and Control Subjects

	PPH Patients			Control Subjects (n=20)
	Shunt (n=18)	No Shunt (n=39)	Discordant (n=11)	
Age, y	42±12	44±12	38±14	42±13
Sex, female/male	16/2	33/6	11/0	17/3
Height, cm	161±9	164±9	164±10	165±7
Weight, kg	73±21	73±17	70±16	64±12
NYHA class	3.0±0.6	2.7±0.6	2.8±0.4	...
Peak $\dot{V}O_2$, %pred	40±12	46±14	43±13	104±16*
Peak WR, %pred	32±13	40±18	37±15	108±25*
Peak HR, %pred	76±8	77±13	74±11	96±13*
Peak $\dot{V}E$, %MVV	52±12	45±14	48±12	70±15*
AT, %pred	53±15	61±16	58±16	101±19*
$\dot{V}E/\dot{V}CO_2$ at AT, %pred	205±71†	151±22	176±40	98±13*
$\dot{V}E$ vs $\dot{V}CO_2$ slope, %pred	210±110†	137±27	164±46	88±11*

Values are mean±SD. $\dot{V}O_2$ indicates exercise oxygen uptake; %pred, percentage of predicted value; $\dot{V}E$, minute ventilation; MVV, directly measured maximal voluntary ventilation; AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$ at AT, ratio of ventilation to carbon dioxide output at anaerobic threshold.

*$P<0.001$, control group vs each group of PPH patients; †$P<0.05$, shunt group versus no-shunt group; all other comparisons, $P>0.05$ using 2-tailed repeated ANOVA.

control groups were similar (Table 1). Except for a higher ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) at the anaerobic threshold and a higher slope of $\dot{V}E$ versus $\dot{V}CO_2$, all of the peak exercise CPET findings of the 3 PPH patient groups were similar to each other (Table 1) but dissimilar from findings in the control group.

Differences in Gas Exchange Between Shunt and No-Shunt Groups

Figure 2 contrasts key CPET measurements that distinguish 2 representative PPH patients (one EIS+ and one EIS−) from a normal subject. Figure 3 describes the second-by-second mean values at rest and during the 3 minutes of unloaded cycling exercise for the same variables in the shunt, no-shunt, and control groups. In the PPH groups, gas exchange was impaired at rest (low $PETCO_2$ with high ventilatory equivalent for O_2 [$\dot{V}E/\dot{V}O_2$], $\dot{V}E/\dot{V}CO_2$, and $PETO_2$), with the $PETCO_2$ lowest in the shunt group (Figures 2 and 3). After beginning unloaded cycling, the shunt group abruptly decreased their $PETCO_2$, while the $PETO_2$, $\dot{V}E/\dot{V}O_2$, and RER concurrently abruptly increased (Figures 2 and 3). Shortly thereafter, the SpO_2 declined in most of the shunt patients. In contrast to the shunt group, the no-shunt group showed lesser changes in $PETO_2$, $PETCO_2$, RER, $\dot{V}E/\dot{V}O_2$, and SpO_2.

Table 2 summarizes the changes in $PETO_2$, $PETCO_2$, $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, RER, $\dot{V}E$, and SpO_2 from rest to the end of unloaded cycling that distinguish the shunt group from the no-shunt group and the statistical significance of these changes. However, by the end of unloaded cycling, all groups had normal and similar increases in $\dot{V}O_2$ and $\dot{V}CO_2$.

The Late-Developing EIS

Figure 4 depicts 1 of 3 patients who developed unmistakable gas exchange evidence of a late-developing EIS during CPET, just before stopping. As with an EIS during unloaded cycling, a late-developing EIS is characterized by abrupt and striking decreases in $PETCO_2$ and SpO_2, with concurrent striking increases in $PETO_2$, RER, and $\dot{V}E/\dot{V}O_2$ more than $\dot{V}E/\dot{V}CO_2$. This patient was PFO− on repeated echocardiography. Her CPET pattern persisted until 2 years after starting epoprostenol therapy, at which time no further CPET evidence of EIS was noted, reflecting her improvement. The second patient had a similar late-developing EIS, but was PFO− by echocardiography at the time of CPET. Two years previously, before treatment, she had been PFO+ by echocardiography. The third patient with CPET changes typical of a late-developing EIS was PFO− on repeated echocardiography.

Grouping of PPH Patients

Excluding the 3 patients with a late-developing EIS, Figure 5 shows the distribution of the 68 patients among the shunt (n=18) and no-shunt (n=39) groups (all 3 graders agreed) and the discordant group (n=11).

If the resting echocardiograph was used as a reference for PFO detection, the overall sensitivity and specificity for CPET EIS detection would be 90% and 96%, respectively (Table 3). Overall, PFO+ PPH patients would also be CPET EIS+ 94% of the time, whereas PFO− PPH patients would be EIS− 95% of the time. Within the discordant group, echocardiography documented a PFO in 6 patients (Figure 5), but 2 of them had been PFO− on one or more other echocardiographic studies, illustrating the inconstant nature of shunting, even at rest.

Considering all 71 PPH patients, 18 were early EIS+ (by all 3 graders) and PFO+, 6 others were PFO+ and EIS+ by the evaluations of 1 or 2 graders (Figure 5), and 3 others were late EIS+ by all 3 graders. Thus, 38% [(18+6+3=21)/71=38%] had convincing evidence for right-to-left shunting during CPET. Five others (Figure 5), although PFO−, had

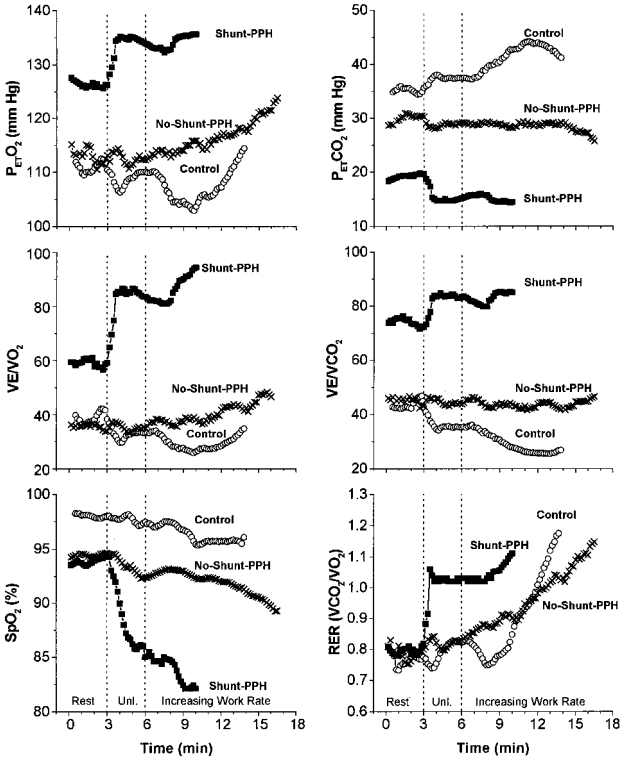

Figure 2. CPET responses in 3 women: one normal (Control; aged 52 years; height, 178 cm; weight, 54 kg), one with PPH without development of a right-to-left shunt (No-Shunt-PPH; aged 45 years; height, 167 cm; weight, 65 kg) and one with PPH with development of a right-to-left shunt (Shunt-PPH; aged 41 years; height, 166 cm; weight, 87 kg) at the start of unloaded cycling exercise. Points are 10-second averages for 3 minutes of rest followed by 3 minutes of unloaded cycling, followed by progressively increasing exercise to maximum. WR was incremented at 10 W/min in the PPH patients and at 20 W/min in the control. In the Shunt-PPH patient, shunted venous blood with high P_{CO_2} and H^+ and low O_2 reaches the systemic arterial chemoreceptors and stimulates ventilation, with rapid increases in $\dot{V}_E/\dot{V}_{O_2}$ and P_{ETO_2} and a decrease in P_{ETCO_2}. The concurrent increase in $\dot{V}_E/\dot{V}_{CO_2}$ is considerably less than that of $\dot{V}_E/\dot{V}_{O_2}$, because unshunted blood passing through the pulmonary circulation continues to unload CO_2 but is unable to load more O_2 after its hemoglobin becomes fully saturated. In the No-Shunt-PPH patient, the $\dot{V}_E/\dot{V}_{CO_2}$ and $\dot{V}_E/\dot{V}_{O_2}$ do not increase as in the Shunt-PPH patient or decrease as much during mild and moderate exercise as in the control patient. Near the end of maximum exercise, the hyperventilation accompanying metabolic acidosis causes P_{ETO_2}, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$, and RER to rise and P_{ETCO_2} to decrease in all individuals with good chemoreceptor sensitivity.

evidence suggesting that they were EIS+. Thus, up to 45% ([27+5=32]/71=45%) of our patients may have had right-to-left shunting during exercise.

Discussion

In the presence of a PFO and increased pulmonary vascular resistance, exercise-induced increases in venous return cause right atrial pressure to increase. When it exceeds left atrial pressure, venous return can shunt through a PFO, diverting deoxygenated, acidemic, CO_2-rich blood to the systemic circulation. This stimulates arterial chemoreceptors (carotid bodies) to maintain arterial H^+ and Pa_{CO_2} homeostasis, causing an immediate increase in ventilation, as manifested by rapid increases in alveolar P_{O_2} (reflected in a P_{ETO_2} increase) and decreases in alveolar P_{CO_2} (reflected in a P_{ETCO_2} decrease) (Figures 1 through 4). Consequently, CO_2 unloading from the unshunted pulmonary blood flow increases as alveolar P_{CO_2} falls, but O_2 loading increases less because pulmonary capillary P_{O_2} reaches the flat part of the oxyhemoglobin dissociation curve. Thus, ventilation increases more steeply relative to $\dot{V}_{O_2}$ than $\dot{V}_{CO_2}$, resulting in a greater increase in $\dot{V}_E/\dot{V}_{O_2}$ than $\dot{V}_E/\dot{V}_{CO_2}$ and a stepwise increase in RER (Figures 1 through 4).

Even at rest, there are distinctly more gas exchange abnormalities (higher $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$, and P_{ETO_2} and lower P_{ETCO_2} and Sp_{O_2}) in the shunt than no-shunt groups (Figures 2 and 3). These pre-exercise abnormalities can be attributed to hypoperfusion of well-ventilated lung and probable chronic hyperventilation.[2,15]

With unloaded cycling, the group differences become more obvious (Figures 2 and 3 and Table 2). In the shunt group, $\dot{V}_E/\dot{V}_{O_2}$, P_{ETO_2}, and RER all increased and P_{ETCO_2} decreased (indicating an acute ventilatory increase disproportionate to metabolism), and Sp_{O_2} decreased. In the no-shunt group, Sp_{O_2} declined slightly. In contrast, $\dot{V}_E/\dot{V}_{O_2}$ and P_{ETO_2} decreased and P_{ETCO_2} increased in the control group. An abrupt increase in $\dot{V}_E/\dot{V}_{CO_2}$ always indicated an EIS in our study.

Figure 4 illustrates the concurrent, dramatic, unambiguous gas exchange findings seen when shunting abruptly begins and ends at the end of exercise rather than earlier. Near the end of exercise, the stimuli to the chemoreceptors (and oximeter probe) are robust because the shunted mixed-venous blood is more acidemic, hypercarbic, and hypoxemic; thus, it more strikingly alters ventilation to maintain arterial homeostasis.[1]

Pitfalls in Detection of a PFO and EIS

Because a PFO may be so small or the interatrial pressure differences so trivial, shunt blood flow may not be demonstrable by echocardiography, even with Valsalva maneuvers.[8–10]

During CPET, the shunt fraction may be so small or the data so noisy that interpretation of EIS criteria are ambiguous. Other potential problems for clinicians using CPET to detect an EIS include a delayed or imperfect response of the Sp_{O_2} signal, a poorly scaled graphic data display, or a too-brief period of pre-exercise CPET data.

Two exercise-induced conditions that might lead the clinician to identify an EIS incorrectly are anxiety-induced hyperventilation or a very low anaerobic threshold .

Acute hyperventilation decreases P_{ETCO_2} while increasing P_{ETO_2}, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$, and RER. However, hyperventilation without shunting of venous CO_2 into the systemic circulation is rarely sustained with a stable RER for more than a minute or two during exercise because these patients become CO_2-unloaded and acutely alkalemic. With hyperventilation and no other disease, Sp_{O_2} does not decrease and MRT for $\dot{V}_{O_2}$ is normal, in contrast to PPH.[2,3]

With a low anaerobic threshold , the development of lactic acidosis at a low WR causes P_{ETO_2}, $\dot{V}_E/\dot{V}_{O_2}$, and RER to

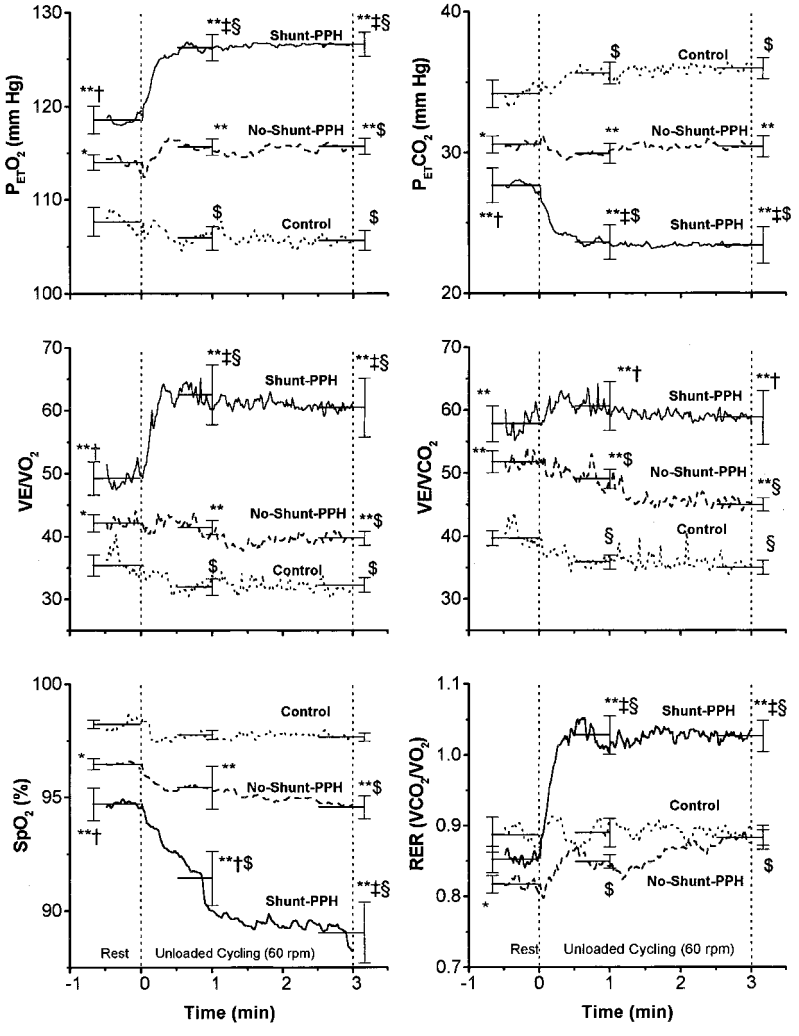

Figure 3. Average CPET responses in the control (n=20), no-shunt-PPH (n=39), and shunt-PPH (n=18) groups during rest and unloaded cycling. Changes in mean P_{ETO_2}, P_{ETCO_2}, $\dot{V}_E/\dot{V}O_2$, $\dot{V}_E/\dot{V}CO_2$, SpO_2, and RER are plotted second-by-second from rest to the end of unloaded exercise. SEE values for the last minute of rest and the periods from 0.5 to 1 minute and 2.5 to 3 minutes of unloaded cycling are also shown. At rest, the $\dot{V}_E/\dot{V}CO_2$ for the PPH groups differ strikingly from the values in the control group; at the end of unloaded cycling, the P_{ETO_2}, P_{ETCO_2}, $\dot{V}_E/\dot{V}O_2$, SpO_2, and RER of the shunt and no-shunt groups differ strikingly from each other. *$P<0.05$ and **$P<0.001$ for differences from control group; †$P<0.05$ and ‡$P<0.001$ for differences between shunt and no-shunt groups for each time period using a 2-tailed repeated ANOVA; \$$P<0.05$ and §$P<0.001$ for differences from each group's resting values using a paired *t* test.

continue to increase, in contrast to the abrupt but stable increases seen with an EIS. Evidence that the anaerobic threshold is reached later during exercise confirms that the earlier changes are due to an EIS.

Validity of Patient Groupings

As demonstrated in Figures 4 and 5, the absence of a detectable PFO at rest does not preclude right-to-left shunting during exercise. Because shunting is a dynamic process

TABLE 2. Changes in CPET Parameters From Rest to End of Unloaded Cycling in PPH Patients and Controls

	PPH Patients			
	Shunt (n=18)	No Shunt (n=39)	Discordant (n=11)	Control Subjects (n=20)
ΔP_{ETO_2}, mm Hg	8.1±3.3*†	1.5±4.0*‡	6.1±2.5*†	−1.9±6.1
ΔP_{ETCO_2}, mm Hg	−4.3±2.4*†‡	−0.1±1.8*‡	−2.6±1.0*†	1.8±2.5
$\Delta\dot{V}_E/\dot{V}O_2$	12.2±10.9*†‡	−2.3±6.8‡	4.9±4.5*†	−4.2±7.1
$\Delta\dot{V}_E/\dot{V}CO_2$	1.8±11.0*	−6.6±9.3	−3.5±7.9	−4.9±3.7
ΔRER	0.18±0.07*†	0.07±0.08‡	0.14±0.08*†	0.01±0.14
ΔSpO_2, %	−6±5*†‡	−1.7±2*	−1.5±2*	−0.4±0.6
$\Delta\dot{V}O_2$, L/min	0.22±0.14	0.24±0.10	0.22±0.07	0.24±0.10
$\Delta\dot{V}CO_2$, L/min	0.28±0.15	0.23±0.09	0.25±0.07	0.22±0.09
$\Delta\dot{V}_E$, L/min	16.9±8.2*†	9.1±3.9*‡	12.6±4.1*†	6.7±3.5

Values are mean±SD. Δ denotes the changes from rest to the end of unloaded cycling exercise.
*$P<0.05$ vs control group; †$P<0.05$ vs no-shunt PPH group; ‡$P<0.05$ vs discordant PPH group using 2-tailed repeated ANOVA.

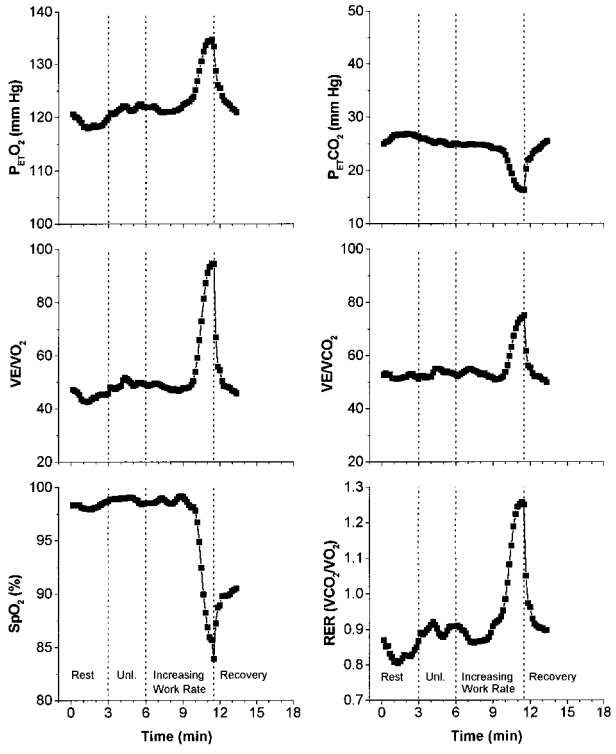

Figure 4. Cycle CPET in a PPH patient who developed an EIS just before the end of exercise. Symbols indicate 10-second averaged values. Three minutes of rest was followed by 3 minutes of unloaded cycling (left vertical line), increasing WR (10 W/min) exercise to peak tolerance (middle vertical line), and 2 minutes of recovery (right vertical line). During the 11th minute of the study, the patient developed sudden dyspnea with abrupt and marked gas exchange findings of a right-to-left shunt (increasing P_{ETO_2} and RER, decreasing P_{ETCO_2} and Sp_{O_2}, and $\dot{V}E/\dot{V}O_2$ increasing more $\dot{V}E/\dot{V}CO_2$). These changes abruptly returned toward their pre-shunt values when exercise stopped. All 3 patients with a late exercise-induced right-to-left shunt had an increase in $\dot{V}E/\dot{V}CO_2$ as their shunt opened.

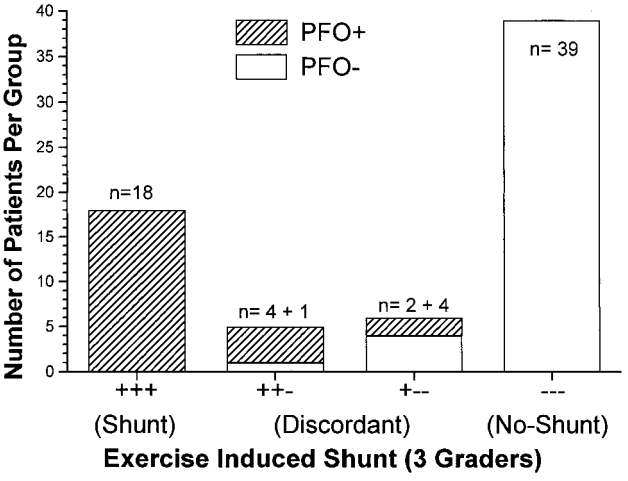

Figure 5. Concordant and discordant findings in determination of shunt or no-shunt groups in 68 PPH patients. The bars quantify the independent decisions of 3 graders (investigators) who were blinded to the results of the resting echocardiography. The presence or absence of an EIS during CPET is marked by + or −, respectively. Hatched bars depicts the presence (+) and open bars depicts the absence (−) of a demonstrable PFO during resting echocardiography. A total of 18 patients were described as having a shunt and 39 patients were described as having no shunt by all 3 graders, and resting echocardiography concurred in these grades. The 11 patients in the 2 center columns are placed in the discordant group because one or more of the investigators' grades differed from the resting echocardiography findings.

dependent on transient pressure differentials, we did not expect to find an absolute concordance between the resting echocardiograph and CPET evidence of an EIS. It is unlikely that even the most sensitive echocardiographic methods at rest would detect PFOs in the 39 patients who were graded as EIS− or that the 18 patients who had a detectable PFO by echocardiography would not also have right-to-left shunting during exercise. Therefore, we used both CPET and echocardiographic findings to define and compare the shunt and no-shunt groups.

Incidence of Right-to-Left Shunting

The high sensitivity, specificity, positive and negative predictive values, and accuracy comparing CPET with echocardiography (Table 3) demonstrate the utility of the gas exchange method in EIS detection. With respect to intraobserver variability, it seems that using tabular data to detect small changes increased sensitivity but slightly decreased specificity.

Ultimately we found, using both the resting and exercise measurements of our 71 PPH patients, that in addition to the 18 patients who were both PFO+ and EIS+ by all graders, 9 more patients (6 by echocardiography and 3 by distinctive late-exercise changes) had convincing evidence of a right-to-left shunt either at rest or during exercise (Figures 4 and 5). Five more may have had right-to-left shunting by CPET criteria (Figure 5). Thus, the incidence of right-to-left shunting through a PFO in our PPH patients during exercise seems to be 38% to 45%.

An autopsy study of 965 "normal" hearts showed a PFO incidence of 20% to 34%, with decreasing PFO frequency but increasing size with advancing age.[16] Using Valsalva maneuvers during echocardiography, the incidence of PFO in normal subjects is reported at just 5% to 18%,[7–10] in part because most normal adults do not shunt blood through their PFO and also because the Valsalva maneuver does not always produce sufficient interatrial pressure differences to cause shunting. An 18% echocardiographic incidence of PFO or interatrial defects was detected in a recent

TABLE 3. Analysis of Grading of Exercise-Induced Right-To-Left Shunt Assuming PFO Detected By Resting Echocardiography Is "Gold Standard"

	Graders			
	A*	B	C	Average
Sensitivity, %	75	100	96	90
Specificity, %	100	95	93	96
PV+, %	100	92	89	94
PV−, %	88	100	98	95
Accuracy, %	91	97	94	94

PV+ indicates positive predictive value; PV−, negative predictive value.
*Did not use CPET tabular data.

series of untreated PPH patients.[17] Stroke patients have a higher incidence of PFO (as high as 78% in young patients with cryptogenic strokes, possibly due to paradoxical emboli).[8–10] The relatively high EIS+ incidence in our series argues that chronic pulmonary hypertension also increases the potential for shunting through foramina ovale that might otherwise remain undetected and that such shunting may favor an increased survival.

Implications

CPET is a safe, noninvasive, cost-effective, and easily repeatable method for assessing PPH patients[2] and detecting an EIS. The 9-panel graphic array (Figure 1) not only helps in the general interpretation of CPET studies, but also assists in the recognition of the distinctive gas exchange pattern of an EIS.

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