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Exercise oscillatory ventilation in heart failure and in pulmonary arterial hypertension☆

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ABSTRACT

Background: Patients with pulmonary arterial hypertension (PAH) and with heart failure (HF) have increased ventilatory responses to exercise in proportion to disease severity. Exercise-associated oscillatory ventilation (EOV) predicts poor outcome in HF. Whether EOV occurs in PAH is unknown.
Methods: We analyzed the initial cardiopulmonary exercise tests (CPETs) and right heart catheterization data of 109 patients with PAH and in 107 patients with HF consecutively referred to our center.
Results: The PAH patients were aged 54 ± 16 years and their NYHA functional class was 2.8 ± 0.5. The HF patients were aged 53 ± 13 years and NYHA 2.4 ± 0.6. Hemodynamic data were obtained in only 36 of them. The patients with PAH compared to those with HF had a lower peak VO_2 (13 ± 5 vs 17 ± 5 mL/kg/min, $p < 0.001$) and a higher ventilatory equivalent for CO_2 (V_E/VCO_2) slope (55 ± 21 vs 34 ± 7, $p < 0.001$). Mean pulmonary artery pressure was higher (50 ± 10 vs 29 ± 11 mmHg) and wedge pressure lower (10 ± 3 vs 19 ± 5 mm Hg) in PAH patients, but cardiac output was not different (4.0 ± 1.3 vs 4.2 ± 1.2 L/min). EOV was present in 22 patients (21%) with HF and in no patient with PAH.
Conclusions: Patients with PAH compared to HF with slightly better functional class have a lower aerobic exercise capacity and higher ventilatory responses, but no EOV. An increase in pulmonary artery wedge pressure rather than a low cardiac output may be necessary condition of EOV in HF.
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1. Introduction

Dyspnea and fatigue during exercise and eventually at rest, are prominent symptoms in chronic heart failure (HF) as well as in pulmonary arterial hypertension (PAH). Aerobic exercise capacity is decreased in both conditions, with similarly altered cardiopulmonary exercise test (CPET) profile. Both HF and PAH patients present with decreased peak oxygen uptake (VO_2), anaerobic threshold and O_2 pulse, and increased ventilation (V_E) to CO_2 output (VCO_2) relationships [1–6]. At comparable functional state, peak VO_2 is lower and V_E/VCO_2 higher in PAH compared to HF [6]. Decreased peak VO_2 and increased V_E/VCO_2 are predictors of decreased survival in HF [7–12] and in PAH [13–16].

In addition to decreased aerobic exercise capacity and increased ventilatory responses, a proportion of patients with HF also presents with ventilatory oscillations during exercise (EOV) [17–21]. This particular ventilatory pattern is an additional CPET variable associated with decreased survival in HF [22–24].

Oscillatory ventilation is thought to result from the combination of prolonged circulatory time, overactivity of chemoreceptors and ergoreceptors and arterial baroreflex impairment [19,21,25,26] with insufficient buffering by hypocapnia and increased alveolar volume [27]. However, why patients with the same severity of HF may or not present EOV remains incompletely understood. PAH is a right heart failure syndrome with circulatory and autonomic nervous system disturbances similar to those reported in HF [6,28,29]. EOV therefore could occur in PAH, and possibly emerge as a marker of disease severity.

The purpose of this study was to answer the question whether EOV occurs in PAH versus HF at comparable functional impairment, and whether it relates to decreased exercise capacity, increased ventilatory responses or severity of pulmonary hypertension.

2. Methods

2.1. Patients

We retrospectively analyzed the CPET of PAH or HF patients performed between June 2000 and June 2012 at the Erasmus University Hospital in Brussels. The study was approved by the local Institutional Review Board (ref num: P 2012/352). The diagnosis of PAH and HF rested on compatible clinical signs and symptoms, electrocardiogram, chest

☆ Every author has taken responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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roentgenogram, lung function tests, echocardiography, ventilation/perfusion (V_A/Q) scintigraphy and right heart catheterization following current expert consensus recommendations [30,31]. The inclusion criteria consisted in compatible diagnosis and CPET and right heart catheterization within six months.

The study included 44 men and 65 women with PAH aged 54 ± 16 yrs (mean ± SD), body mass index (BMI) 26 ± 6 kg/m^2. PAH was idiopathic in 56 patients and associated in 53. Eighty patients (73%) were treatment naive. The other PAH patients were treated, with an endothelin receptor antagonist in (n = 15), a phosphodiesterase-5 inhibitor (n = 5), and parenteral prostacyclins (n = 13). Diuretics were taken by 47 of the PAH patients.

The study also included 107 patients (76 male) with HF aged 52 ± 13 yrs, BMI 27 ± 5 kg/m^2. HF was systolic in 102 patients and diastolic in 5, idiopathic in 26, ischemic in 36, associated with valvular disease in 10 and of miscellaneous origins in 35. Treatments included angiotensin converting enzyme inhibitors in 73 patients, angiotensin receptor blockers in 17, β-blockers in 86 and diuretics in 78. Five HF patients were treatment naive.

2.2. Cardiopulmonary exercise testing

Each patient underwent standard cycle ergometer incremental CPET as previously reported [6,15]. The load increments varied between 5 and 15 W/min such as to obtain an 8 to 12 min duration test. All ventilation and gas analysis were performed using a Vmax, (Sensormedics, Yorba Linda, CA). Gas analysers and pneumotachograph were calibrated prior to each test. Heart rate and blood pressure were obtained via an automatic standard electrocardiogram and sphygmomanometer.

EOV was defined by the presence of 3 or more ventilatory oscillations of more than 5 l and with a duration of 40 to 140 s [22–24]. Anaerobic threshold (AT) was determined using the V-slope method.

2.3. Right heart catheterisation

Right heart catheterization was performed in all the PAH patients and in 36 HF patients without premedication with the patient lying supine and breathing room air. A balloon-tipped, flow-directed thermodilution 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp; Irvine, CA) was inserted under local anesthesia into an internal jugular or femoral vein and was floated under continuous pressure-wave monitoring into a pulmonary circulation to measure pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), right atrial pressure (RAP), and cardiac output (CO). Systemic arterial pressure was determined intermittently by sphygmomanometry. Heart rate (HR) was determined from a continuously monitored ECG lead. Pulmonary vascular pressures were measured using disposable transducers (TruWave; Baxter Healthcare Corp) zero-leveled at midchest, and pressures read at non-forced end-expiration. Cardiac output was determined by thermodilution as a mean of at least three successive measurements (COM-2; Baxter Healthcare Corp).

2.4. Statistics

Data are presented as mean ± standard deviation (SD). PAH and HF groups and HF subgroups were compared by unpaired t tests.

3. Results

The PAH and HF patient populations were comparable in age and BMI, with male predominance in HF and female predominance in PAH, and moderately more advanced New York Heart Association (NYHA) functional class in PAH (2.36 ± 0.60 vs 2.75 ± 0.46 in HF patients, $p < 0.001$). The CPET and right heart catheterizations had been performed within the same week in 82% of the PAH patients and 74% of the HF patients.

The results of the CPET are presented in Table 1. The maximum achieved respiratory exchange ratios (RER) show that the patients exercised until exhaustion at levels equal or very close to maximum VO_2. Peak workload, VO_2, VO_2 at AT, O_2 pulse, VO_2/workload (W) slope and end-tidal PCO_2 ($P_{ET}CO_2$) were decreased and V_E/VCO_2 slope was increased, more in PAH than in HF patients. Patients with PAH compared HF had slightly higher respiratory rates but no different tidal volumes. EOV was identified in 22 HF patients. No PAH patient presented with EOV.

A comparison of CPET data of HF patients with and without EOV is shown in Table 2. The HF patients with EOV had a lower $P_{ET}CO_2$ and greater O_2 pulse at peak exercise, and larger tidal volume at rest. No other differences were found between HF with and without EOV.

The relationship between V_E/VCO_2 slope as a function of $P_{ET}CO_2$ in patients with PAH and in HF patients with and without EOV is shown in Fig. 1. The PAH patients had a higher V_E/VCO_2 at lower $P_{ET}CO_2$ than the HF patients ($p < 0.001$). The V_E/VCO_2 vs $P_{ET}CO_2$ relationships were not different in HF patients with or without EOV (P NS).

The right heart catheterization measurements are presented in Table 3. Patients with PAH had more severe pulmonary hypertension, with higher mean PAP (PAPm) and PVR, but PAWP was higher in HF. RAP, CO, HR and SV were not different.

A comparison, of hemodynamic data of HF patients with and without EOV is shown in Table 4. There were no differences between patients with or without EOV.

Table 1
Cardiopulmonary exercise tests in PAH and in HF patients.

	IPAH–APAH (n = 56–53)	HF (n 107)	p
Peak RER	1.17 ± 0.09	1.16 ± 0.11	NS
Peak workload, W	51 ± 26	85 ± 35	<0.001
VO_2, mL/kg/min			
@AT	9.5 ± 3.0	11.6 ± 3.2	<0.001
Peak	12.8 ± 4.7	16.7 ± 5.0	<0.001
$P_{ET}CO_2$, mm Hg			
Rest	26 ± 4	33 ± 4	<0.001
@AT	25 ± 5	35 ± 5	<0.001
Peak	21 ± 5	32 ± 5	<0.001
V_E/CO_2			
@AT	51 ± 12	35 ± 7	<0.001
Slope	55 ± 21	34 ± 7	<0.001
Peak HR, bpm	133 ± 26	126 ± 25	0.04
Peak SBP, mm Hg	161 ± 33	152 ± 42	NS
O_2 pulse, mL/beat	6.8 ± 2.5	10.5 ± 3.3	<0.001
VO_2/workload slope, L/min/W	7.1 ± 3.1	9.2 ± 2.8	<0.001
EOV, yes (%)	0 (0)	22 (20.6)	<0.001
Tidal volume, L			
Rest	0.72 ± 0.23	0.67 ± 0.13	NS
Peak	1.52 ± 0.42	1.62 ± 0.40	NS
Respiratory rate			
Rest	20 ± 5	19 ± 3	<0.05
Peak	36 ± 7	34 ± 5	<0.01

Legend: PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; APAH: associated PAHHF: chronic heart failure RER: respiratory exchange ratio; VO_2: oxygen uptake; @AT: at anaerobic threshold; V_E/VCO_2: ventilatory equivalent for carbon dioxide; SBP: systolic blood pressure; EOV: exercise oscillatory ventilation; and HR: heart rate.

Table 2
Cardiopulmonary exercise tests in HF patients with and without exercise oscillatory ventilation (respectively EOV+ and EOV−).

	EOV− (n 85)	EOV+ (n 22)	p
Peak RER	1.16 ± 0.11	1.16 ± 0.09	NS
Peak workload, W	83 ± 36	90 ± 32.	NS
VO_2, mL/kg/min			
@AT	11.5 ± 3.4	11.6 ± 2.8	NS
Peak	16.5 ± 5.2	17.2 ± 4.6	NS
$P_{ET}CO_2$, mm Hg			
Rest	33 ± 4	32 ± 4	NS
@AT	35 ± 5	34 ± 5	NS
Peak	32 ± 5.	30 ± 4	0.02
V_E/CO_2			
@AT	35 ± 7	35 ± 6	NS
Slope	33 ± 7	36 ± 6	NS
Peak HR, bpm	128 ± 25	120 ± 26	NS
Peak SBP, mm Hg	151 ± 41	157 ± 46	NS
O_2 pulse, mL/beat	10.2 ± 3.3	11.7 ± 2.8	0.02
VO_2/workload slope, L/min/W	9.3 ± 2.9	8.8 ± 2.4	NS
Tidal volume, L			
Rest	0.66 ± 0.18	0.73 ± 0.16	0.04
Peak	1.60 ± 0.51	1.74 ± 0.41	NS
Respiratory rate, bpm			
Rest	18 ± 4	20 ± 5	NS
Peak	34 ± 6.	35 ± 5	NS

Abbreviations: see Table 1.

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