Sex difference in response to cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease

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Background

Cardiopulmonary exercise testing is an important clinical tool to evaluate exercise capacity and to predict the outcome in patients with chronic obstructive pulmonary disease (COPD).

Aim

To evaluate exercise tolerance and pulmonary function in COPD patients in relation to sex.

Patients and methods

This prospective cross-sectional analytic study has been conducted in Assiut University Hospital, Chest Department from May, 2017 to January, 2019. Sixty patients with clinical and functional diagnosis of COPD were subjected to: baseline dyspnea assessment assessed by modified Medical Research Council and COPD assessment test, arterial blood gas analysis preexercise and postexercise, pulmonary function test, and cardiopulmonary exercise testing. The patients were divided into two groups: each group included 30 men and 30 women.

Results

There were no significant differences between both sexes in response to exercise with the exception of significantly higher oxygen consumption (VO_2% predicted) in men (in men = 49.53 ± 9.08, in women = 44.83 ± 7.60, $P = 0.03$) and that women had significantly higher lactate threshold than men (lactate threshold = 55.46 ± 5.32 and 50.57 ± 7.74, respectively, $P = 0.02$). Female patients had significantly lower breathing reserve and significantly lower respiratory frequency ($P < 0.001$). Male patients had significantly lower heart $rate_{max}$, and significantly higher heart rate reserve than women ($P < 0.001$ and 0.04, respectively).

Conclusions

There were no significant differences between both sexes in response to exercise except that men with COPD had significantly higher oxygen consumption and exercise capacity (peak VO_2) than women with COPD.

Keywords:

cardiopulmonary exercise testing, chronic obstructive pulmonary disease, sex, peak VO_2, pulmonary function test

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Introduction

Cardiopulmonary exercise testing (CPET) is a methodology that has changed the approach to patients' functional evaluation, linking performance, and physiological parameters to the underlying metabolic substratum and providing exercise capacity descriptors, for example, peak oxygen uptake (peak VO_2). An accurate assessment of the exercise capacity of patients with chronic obstructive pulmonary disease (COPD) is important for exercise prescription and for determining response to therapy. CPET is useful for determining the causes of exercise limitation and for assessing the maximal exercise capacity of patients with COPD [1].

For the most part, women and men who participate in exercise training have similar responses in cardiovascular, respiratory, and metabolic functions (providing that size and activity level are normalized). Relative increases in $VO_{2\ max}$ are equivalent for women and men [2].

Several sex differences have been noted in acute response to exercise. At the same absolute rate of exercise, women have a higher heart rate response than men, primarily because of a lower stroke volume. This lower stroke volume is a function of smaller heart size and smaller blood volume [3].

CPET is clinically useful in the objective determination of exercise capacity (VO_2 peak) and limitations [4]. Thus, the current study aims to assess sex difference in response to exercise in COPD patients.

Patients and methods

This prospective cross-sectional analytic study has been conducted in Assiut University Hospital, Chest Department, Cardiopulmonary Exercise Testing Unit and Pulmonary Function Unit from May, 2017 to January, 2019. The study protocol was approved by the Faculty of Ethics Committee, Assiut University and patients signed an informed consent (IRB no: 17100985).

Sixty patients (30 men and 30 women) fulfilling the clinical and functional diagnosis of stable COPD (at least 3 months without exacerbations) according to GOLD criteria [5] were enrolled into this study. All patients were subjected to the following: careful history taking, full clinical examination, arterial blood gas analysis preexercise and postexercise, pulmonary function test (PFT), and CPET.

Inclusion criteria

Stable COPD patients aged 40–70 years were included. All patients were with clinical features of COPD and associated spirometry compatible with the GOLD criteria. Patients were selected randomly in crossover 1: 1.

Exclusion criteria

Patients with primary cardiac diseases, orthopedic, or neurological conditions affecting the ability of exercise, patients with previous lung resection or malignancies, acute pulmonary embolism, acute exacerbation of COPD, and severe arterial hypertension were excluded.

Methods

(1) Medical history included:
   (a) Name, age, sex, smoking history, and other comorbidities
   (b) Assessment of baseline dyspnea based on the modified Medical Research Council (mMRC) dyspnea scale. An mMRC score more than or equal to 2 is included as threshold for separating less breathlessness from more breathlessness [5]
   (c) COPD assessment test (CAT): eight self-reported questions to evaluate the health status in COPD patients [5]

(2) Resting pulmonary function:
   Spirometry (P/N Co9035–12–99; Cosmed SrL, Quark PFTs Ergo, Italy, Milano). including forced expiratory volume in the 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, maximal expiratory flow at 25–75% of FVC (MEF_{25-75}), and maximal voluntary ventilation testing was performed in the pulmonary function lab. Results were expressed in liter and liter/second and as percent predicted

(3) Arterial blood gases analysis:
   Blood samples were taken from the radial artery at room air and were analyzed using a blood gas analyzer (Rapid lab 850; C hiron Diagnostics (Made in USA, Bedford), Critical Care Systems). Measurements including pH, arterial oxygen tension PaO_2, arterial carbon dioxide tension $PaCO_2$, and arterial oxygen saturation SaO_2 were recorded. Arterial blood gases were done before and directly after CPET

(4) CPET
   CPET was performed for all patients using a treadmill (Cosmed SrL, Quark PFTs ergo, P/N Co9035–12–99). We prepared an incremental treadmill exercise protocol in which the work rate increased at 1-min intervals. The unloaded VO_2 was estimated from the patient's body weight [6].

The following parameters were recorded:

(1) Metabolic response: oxygen consumption VO_2 (ml/min), VO_2 (ml/kg/min), and anerobic threshold
(2) Ventilatory response: minute ventilation (VE), breathing reserve, tidal volume (VT), and respiratory frequency
(3) Cardiovascular response: heart rate (HR), oxygen pulse (VO_2/HR), HR reserve, and systolic and diastolic blood pressure
(4) Gas exchange response: oxygen saturation (SpO_2), ventilatory equivalent for VO_2 (VE/VO_2), and ventilatory equivalent for VCO_2 (VE/VCO_2).

All patients stopped the test due to dyspnea. No cardiovascular complications or primary cardiac reasons for termination were observed during the exercise test.

Statistical analysis

These nonparametric data were collected and were analyzed using the Statistical Package for the Social Sciences (version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range) while nominal data were expressed in the form of frequency (percentage). c^2 test was used to compare the nominal data of different groups in the study while Student's t test was used to compare the mean of two different groups and paired t test was used to compare data of the same group before and after exercise. Different correlations of continuous variables in the study were determined with Pearson's correlation. The level of confidence was kept at 95% and hence, the P value was significant if less than 0.05.

Results

Sixty patients with COPD were recruited in this study, 30 (50%) patients were women and 30 (50%) were men.

Patient characteristics in Table 1 shows that the male and female patients had insignificant differences as regards age, BMI, number of exacerbation and hospital admission, mMRC scale, and CAT assessment tool.

On comparison of gasometric parameters before and after exercise (Table 2) it was seen that there was significant decrease in pH, PaO_2, and SaO_2 and significant increase in $PaCO_2$ and lactic acid after exercise with no significant difference between both sexes.

As regards PFT, male patients had significantly higher MEF_{50} in comparison to female patients with no significant difference in FEV_1, FVC, FEV_1/FVC, MEF_{75}, and MEF_{25-75} as shown in Table 3.

Table 4 shows that VO_2 (% predicted) was significantly higher in male patients than female patients and that women had significantly higher lactate threshold (LT) than men. Also, female patients had significantly lower breathing reserve and respiratory frequency in comparison to male patients ($P < 0.001$). Regarding gas exchange response, there were no significant differences between male and female COPD patients. As regards cardiovascular response there was significant decrease in HR_{max}, and significant increase in HR reserve in men in comparison to female patients ($P < 0.001$ and 0.04, respectively).

In male patients, it was seen from Table 5 that FEV_1 (% predicted) had positive significant correlation with VO_2 (% predicted), VT (l), and VO_2/HR. In female patients, it was noticed that FEV_1 had positive significant correlation with VO_2 (% predicted), VE (min), VT (l), and VO_2/HR and it had negative significant correlation with HR reserve.

Table 6 shows that CAT had positive significant correlation with $petCO_2$ (mmHg), and negative significant correlation with VT (l), VO_2/HR, and $petO_2$ (mmHg). In male patients, CAT had negative significant correlation with VT (l). In female patients, CAT had negative significant correlation with VE (min), VT (l), and VO_2/HR.

Discussion

Exercise intolerance is a common symptom in COPD, and reflects both cardiorespiratory status, and global disease severity and prognosis [7]. Evaluating exercise capacity allows monitoring of disease and response to intervention. Hence, the current study aimed to assess the difference in lung function and exercise performance and parameters in COPD patients in both sexes.

The main finding in the study was on comparing arterial blood gas, the values at rest and postexercise, the level of pH, PaO_2, and SaO_2 had decreased and $PaCO_2$ and lactic acid increased significantly after exercise but with no difference in men and women (pH postexercise was significantly lower in women).

These results come in agreement with those of Dantzker and D'Alonzo [8] who examined the effect of low-level, steady-state exercise on pulmonary gas exchange in seven patients with severe COPD and pulmonary hypertension. They reported that exercise led to a significant fall in arterial PaO_2 from 76 ± 10 to 63 ± 8 mmHg, a rise in arterial $PaCO_2$ from 56 ± 6 to 62 ± 8 mmHg, and a fall in mixed venous PO_2 from 38 ± 2 to 32 ± 2 mmHg. Thus, exercise on

Table 1 Demographic and clinical data of chronic obstructive pulmonary disease patients in both sexes

	Male (*n*=30)	Female (*n*=30)	*P*
Age (years)	57.86±12.79	53.53±11.45	0.17
GOLD class			
I, II	18 (60)	16 (53.3)	0.50
III, IV	12 (40)	14 (46.7)	
BMI (kg/m²)	25.96±3.84	25.27±4.06	0.42
Smoking status			
Smoker	9 (30)	0	
Nonsmoker	1 (3.3)	30 (100)	**<0.001**
Exsmoker	20 (66.7)	0	
Smoking index, pack Year	37.13±18.02	0	**<0.001**
mMRC dyspnea scale	2.60±0.49	2.70±0.46	0.42
CAT assessment	20.33±4.65	22.06±3.76	0.11
Number of exacerbations in the last year	5.33±3.49	6.80±3.23	0.09
Number of hospital admissions in the last year	1.46±1.07	2.03±1.37	0.08

Data were expressed in the form of *n* (%) and mean±SD. GOLD class I: FEV_1% predicted more than or equal to 80%; class II: 50% less than or equal to FEV_1 less than 80%; class III: 30% less than or equal to FEV_1 less than 50%; class IV: FEV_1 less than 30%. CAT, chronic obstructive pulmonary disease assessment test; FEV_1, forced expiratory volume in the 1 s; mMRC, modified Medical Research Council. $P<0.05$; Bold items mean *P* value is less than 0.05 (statistically significant).

Table 2 Gasometric parameters of patients based on sex before and after exercise

	Male (*n*=30)	Female (*n*=30)	*P*1
pH^+			
Before	7.38±0.02	7.38±0.01	0.86
After	7.36±0.03	7.33±0.02	0.05
*P*2	<0.001	<0.001	
$PaCO_2$ (mmHg)			
Before	48.83±6.30	41.50±5.14	0.19
After	53.33±7.27	46.33±5.69	0.81
*P*2	<0.001	<0.001	
PaO2 (mmHg)			
Before	72.50±7.62	69.38±8.14	0.13
After	62.26±2.26	61.64±8.50	0.01
*P*2	<0.001	<0.001	
SaO_2 (%)			
Before	93.01±2.26	93.07±1.93	0.90
After	88.80±3.10	88.90±2.20	0.60
*P*2	<0.001	<0.001	
HCO^{-3} (mmol/l)			
Before	33.40±4.25	31.85±3.45	0.71
After	32.23±4.95	31.67±3.41	0.88
*P*2	0.31	0.81	
Lactic acid (mmol/l)			
Before	1.36±0.45	1.13±0.28	0.60
After	2.10±0.51	2.30±0.47	0.28
*P*2	<0.001	<0.001	

Data were expressed in the form of mean±SD. $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of arterial oxygen; SaO2, arterial oxygen saturation; HCO_3, bicarbonate. *P*1 compared between both groups; *P*2 compared data before and after exercise in the same group. $P<0.05$.

Table 3 Pulmonary function in chronic obstructive pulmonary disease patients in both sexes

	Male (*n*=30)	Female (*n*=30)	*P*
FEV_1 (l)	1.40±0.53	1.34±0.44	0.06
FEV_1 (% predicted)	51.22±10.59	51.03±8.39	0.93
FVC (l)	2.04±0.61	1.86±0.47	0.21
FVC (% predicted)	78.20±7.75	80.43±11.59	0.38
FEV_1/FVC PB	56.40±7.18	55.43±7.07	0.60
MEF_{75} (l)	3.54±0.60	3.37±0.53	0.24
MEF_{75} (% pred.)	75.60±16.53	79.80±9.68	0.23
MEF_{50} (l)	2.53±0.59	2.07±0.61	**<0.001**
MEF_{50} (% pred.)	74.23±16.67	76.26±13.40	0.60
MEF_{25-75} (l)	1.33±0.65	1.40±0.58	0.63
MEF_{25-75} (% pred.)	61.53±17.76	67.53±15.67	0.17

Data were expressed in the form of mean±SD. FEV_1, forced expiratory volume in the 1 s % predicted; FVC, forced vital capacity; MEF_{25-75}, mean expiratory flow at 25-75% of the forced vital capacity; MEF_{50}, mean expiratory flow at 50% of the forced vital capacity; MEF_{75}, mean expiratory flow at 75% of the forced vital capacity; PB, postbronchodilator. $P<0.05$.

a bicycle ergometer resulted in PaO_2 reduction and $PaCO_2$ increment, and the authors concluded that exercise-induced hypoxemia in patients with COPD was the result of a fall in mixed venous PO_2 and an insufficient increase in overall ventilation [8].

Wagner [9] suggested that patients with advanced COPD can exhibit almost any pattern of arterial blood gas changes from resting values, suggesting that an additional contributing factor to the hypoxemia of exercise is an inadequate ventilatory response, such that VE does not rise as much as does CO_2 production or O_2 uptake, causing arterial PCO_2 to increase and the alveolar-arterial PO_2 difference to fall.

Table 4 Cardiopulmonary exercise test parameters in chronic obstructive pulmonary disease patients in both sexes

	Males	Females	*P*
VO_2 (ml/min)	838.08±199.88	771.96±158.97	0.16
VO_2 (ml/min/kg)	12.25±1.35	11.63±1.18	0.06
VO_2 (% predicted)	49.53±9.08	44.83±7.60	**0.03**
RER at (LT)	1.31±0.21	1.28±0.36	0.44
Lactate threshold (%)	50.57±7.74	55.46±5.32	**0.02**
Ventilatory response			
VE (l/min)	44.39±6.24	42.06±6.84	0.33
BR (%)	29.53±4.21	26.01±3.87	**<0.001**
Tidal volume (l)	1.41±0.51	1.34±0.46	0.58
RF (breath/min)	33.13±3.74	31.80±3.38	**<0.001**
Gas exchange parameters			
$PetCO_2$ (mmHg)	40.10±5.71	42.16±4.62	0.12
$PetO_2$ (mmHg)	115.50±7.01	113.23±6.31	**0.19**
VE/VO_2	47.10±6.31	49.90±9.74	0.19
VE/VCO_2	35.90±5.31	36.01±1.80	0.90
Pre-SO_2 (%)	92.90±2.10	93.11±1.80	0.84
Post-SO_2 (%)	88.03±2.84	88.66±1.89	0.31
Cardiovascular response			
Resting HR (beat/min)	79.56±7.77	80.23±9.50	0.76
HR_{max} (beat/min)	129.43±9.22	136.86±12.39	**<0.001**
HR reserve (beat/min)	20.40±2.23	19.17±2.39	**0.04**
Oxygen pulse	10.23±1.68	10.87±2.45	0.24
Pre-SBP (mmHg)	132.86±6.53	133.03±6.16	0.92
Post-SBP (mmHg)	162.43±13.47	163.01±11.10	0.85
Pre-DBP (mmHg)	72.83±5.01	73.16±5.58	0.80
Post-DBP (mmHg)	80.73±4.91	79.80±3.51	0.41
MVV (% predicted)	46.93±11.66	47.30±10.13	0.89

Data were expressed in the form of mean±SD. BR, breathing reserve; DBP, diastolic blood pressure; HR, heart rate; HR_{max}, heart rate at maximum exercise; LT, lactate threshold; MVV, maximum voluntary ventilation % predicted; $PetCO_2$, end-tidal carbon dioxide tension; $PetO_2$, end-tidal oxygen tension; post-SO_2, posttest arterial oxygen saturation; pre-SO_2, pretest arterial oxygen saturation; RER, respiratory exchange ratio; RF, respiratory frequency; SBP, systolic blood pressure; VE, minute ventilation; VO_2, oxygen consumption. $P<0.05$; Bold items mean *P* value is less than 0.05 (statistically significant).

Table 5 Correlation between forced expiratory volume in the 1 s (% pred.) and exercise parameters in the studied groups

	Male		Female		All patients	
	r	*P*	*r*	*P*	*r*	*P*
VO_2 (% predicted)	0.50	<0.001	0.54	<0.001	0.50	<0.001
VE (min)	0.16	0.39	0.52	<0.001	0.31	<0.001
BR %	−0.30	0.09	Nil		−0.16	0.19
VT (l)	0.65	<0.001	0.77	<0.001	0.69	<0.001
HR reserve (beat/min)	−0.18	0.33	−0.67	<0.001	−0.37	<0.001
VO_2/HR	0.65	<0.001	0.78	<0.001	0.67	<0.001

Data were expressed in form of *r* value (strength of correlation), *P* (significance of correlation). BR, breathing reserve; HR, heart rate; $petCO_2$, end-tidal carbon dioxide tension; $petO_2$, end-tidal oxygen tension; VE, minute ventilation; VO_2, oxygen consumption; VT, tidal volume. $P<0.05$.

Table 6 Correlation between chronic obstructive pulmonary disease assessment test and exercise parameters in both groups

	Male		Female		All patients	
	r	*P*	*r*	*P*	*r*	*P*
VO_2 (% predicted)	–0.23	0.43	–0.21	0.26	–0.18	0.15
VE (min)	0.12	0.49	**–0.40**	**<0.001**	–0.08	0.51
BR %	–0.17	0.36	–0.43	0.34	–0.22	0.08
VT (l)	**–0.41**	**<0.001**	**–0.43**	**<0.001**	**–0.39**	**<0.001**
HR reserve	–0.10	0.59	0.35	0.06	0.14	0.37
VO_2/HR	–0.19	0.30	**–0.43**	**<0.001**	**–0.31**	**<0.001**

Data were expressed in the form of *r* value (strength of correlation), *P* (significance of correlation). BR, breathing reserve; HR, heart rate; $petCo_2$, end-tidal carbon dioxide tension; $petO_2$, end-tidal oxygen tension; VE, minute ventilation; VO_2, oxygen consumption; VT, tidal volume. $P<0.05$; Bold items mean *P* value is less than 0.05 (statistically significant).

Sex-specific differences in pulmonary function and exercise performance in normal individuals are recognized. We examined exercise performance in women and men, and the present study showed that in COPD patients both sexes had insignificant differences in exercise capacity represented at peak VO_2 (ml/min) and peak VO_2 (ml/kg/min). Men had significantly higher peak VO_2% predicted than women (P = 0.03). This was aligned with Thirapatarapong *et al.* [10] who reported that men had significantly higher VO_2% predicted than women (peak VO_2% predicted for males 52 ± 18, for females 37 ± 13, and $P < 0.001$).

Pinto-Plata *et al.* [11] studied 453 consecutive patients with COPD stages 1–4. Incremental CPET and PFTs were performed. They showed that women had significantly higher VO_2% predicted than men (mean VO_2% predicted for males 65 ± 24 and for females 71 ± 21, P = 0.003). However, in the same study after adjustment for sex, age, height, and COPD severity, there was no difference in exercise capacity and VO_2% predicted between women and men. This agrees with our finding. Also, after adjustment for weight, VO_2 (expressed in ml/kg/min) was significantly higher in men than women in all stages of COPD ($P > 0.05$ for all stages) [11].

As regards LT% predicted, the current study showed that women had significantly higher LT% predicted than men (LT% predicted for females 55.46 ± 5.32 and for males 50.57 ± 7.74). Similar results were reported by Pinto-Plata *et al.* [11] who found that LT% predicted was significantly higher in women (LT% predicted for females 55 ± 14, for males 48 ± 13 and $P > 0.0001$).

CPET is useful to measure the functional capacity in COPD patients by assessing the maximum oxygen uptake. Thus, it could be used as a good monitoring tool. In this study, we observed that FEV_1 (% predicted) had positive significant correlation with VO_2 (% predicted). These results are consistent with Hena *et al.* [12] who investigated 58 patients with stable COPD who performed the treadmill test using the Bruce protocol through CPET and categorized them into four groups based on the spirometric data following the GOLD guidelines. The authors observed a significant correlation (r = 0.47, P = 0.001) between FEV_1% predicted and maximum oxygen uptake ($VO_{2\,max}$, ml/kg/min).

Limitations

(1) Limited number of patients due to frequent exacerbations in patients followed up in the department
(2) No follow-up of exercise testing after rehabilitation.

Conclusion

The CPET is the gold-standard tool to evaluate dyspnea and exercise tolerance clinically in COPD. There were no significant differences between both sexes in response to exercise except that men with COPD had significantly higher oxygen consumption and exercise capacity (VO_2 peak) than women with COPD; FEV_1 (% predicted) had positive significant correlation with most of ventilatory and gas exchange and it had negative significant correlation with HR reserve and mMRC scale. There were no significant differences between both sexes regarding PFT variables.

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Conflicts of interest

There are no conflicts of interest.

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