Chronic obstructive pulmonary disease in women

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BACKGROUND: Little is known about the comparative impact of chronic obstructive pulmonary disease (COPD) between women and men and about women's response to pulmonary rehabilitation.
OBJECTIVES: To compare lung function, disability, mortality and response to pulmonary rehabilitation between women and men with COPD.
METHODS: In the present retrospective study, 68 women (mean age 62.5±8.9 years) and 168 men (mean age 66.3±8.4 years) were evaluated by means of pulmonary function testing and an incremental symptom-limited cycle exercise test. Forty women and 84 men also participated in a 12-week pulmonary rehabilitation program. A 6 min walking test and the chronic respiratory questionnaire were used to assess the effects of pulmonary rehabilitation. Survival status was also evaluated.
RESULTS: Compared with men, women had a smaller tobacco exposure (31±24 versus 48±27 pack-years, P<0.05), displayed better forced expiratory volume in 1 s (44±13 versus 39±14 % predicted, P<0.05), a higher functional residual capacity (161±37 versus 149±36 % predicted, P<0.05) and total lung capacity (125±20 versus 115±19 % predicted, P<0.001). Peak oxygen consumption was not different between women and men when expressed in predicted values but lower in women when expressed in absolute values. Pulmonary rehabilitation resulted in significant improvements in 6 min walking test and quality of life in both sexes, but women had a greater improvement in chronic respiratory questionnaire dyspnea. Survival status was similar between sexes, but predictors of mortality were different between sexes.
CONCLUSIONS: Women may be more susceptible to COPD than men. The clinical expression of COPD may differ between sexes with greater degree of hyperinflation in women, who also benefit from pulmonary rehabilitation.

Key Words: *COPD; Pulmonary rehabilitation; Survival; Women*

La maladie pulmonaire obstructive chronique chez les femmes

HISTORIQUE : On ne sait pas grand-chose des répercussions comparatives de la maladie pulmonaire obstructive chronique (MPOC) entre les femmes et les hommes et de la réponse des femmes à la réadaptation pulmonaire.
OBJECTIFS : Comparer la fonction pulmonaire, l'incapacité, la mortalité et la réponse à la réadaptation pulmonaire entre les hommes et les femmes atteints de MPOC.
MÉTHODOLOGIE : Dans le cadre de la présente étude rétrospective, 68 femmes (âge moyen de 62,5±8,9 ans) et 168 hommes (âge moyen de 66,3±8,4 ans) ont été évalués au moyen d'une exploration fonctionnelle respiratoire et d'un test de vélo d'exercice à symptômes limités incrémentiels. Quarante femmes et 84 hommes ont également participé à un programme de réadaptation pulmonaire de 12 semaines. Un test de marche de 6 minutes et le questionnaire sur la respiration chronique ont permis d'évaluer les effets de la réadaptation pulmonaire. On a également évalué le statut de survie.
RÉSULTATS : Par rapport aux hommes, les femmes étaient moins exposées au tabac (31±24 par rapport à 48±27 paquets-année, P<0,05), avaient un meilleur volume expiratoire maximal à la seconde (44±13 par rapport à 39±14 % prévus, P<0,05), une meilleure capacité résiduelle fonctionnelle (161±37 par rapport à 149±36 % prévus, P<0,05) et une meilleure capacité pulmonaire totale (125±20 par rapport à 115±19 % prévus, P<0,001). La consommation d'oxygène de pointe ne différait pas entre les hommes et les femmes lorsqu'elle était exprimée en valeurs prévues, mais elle était plus faible chez les femmes en valeurs absolues. La réadaptation pulmonaire a favorisé des améliorations considérables au test de marche de 6 minutes et à la qualité de vie dans les deux sexes, mais les femmes démontraient une plus grande amélioration de la dyspnée au questionnaire de respiration chronique. Le statut de survie était semblable entre les sexes, mais pas les prédicteurs de mortalité.
CONCLUSIONS : Les femmes sont peut-être plus susceptibles à la MPOC que les hommes. L'expression clinique de la MPOC peut différer entre les sexes, démontrée par un degré plus élevé d'hyperinflation chez les femmes, qui tirent également des bienfaits de la réadaptation pulmonaire.

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and mortality, affecting approximately 600 million people worldwide (1). Among the five most important causes of mortality, COPD is the only one whose age-adjusted mortality rate has continued to increase in recent years (2). It is also expected that the worldwide burden of COPD will continue to rise in the coming years (3). Recent years have also witnessed a major shift in the sex profile of the disease. Although earlier studies showed that men accounted for the majority of COPD-related deaths (4), the prevalence and mortality rate of COPD in women have more than doubled during the past 20 years in industrialized countries while they stabilized in men (5). In 2001, more women died from COPD than men in the United States (2), a trend also observed in other countries (6,7).

The increase in prevalence and mortality for COPD among women compared with men is usually attributed to the delayed rise of smoking prevalence in women (8). Another possibility

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is that the susceptibility to COPD risk factors, mainly tobacco, varies between sexes. This hypothesis has been difficult to prove because conflicting conclusions have been reached by different studies. For a given tobacco consumption, airflow obstruction is worse in women (9,10). Although this may be due to under-reporting in women, it nevertheless supports the idea that they are at greater risk to develop COPD than men. Studies investigating sex differences in the vulnerability to the deleterious effects of tobacco either reported greater susceptibility to tobacco in women (10-12) or failed to detect any sex disparities (13-15). Female smokers show greater bronchial responsiveness (16), lower baseline forced expiratory volume in 1 s (FEV_1) and faster decline in FEV_1 (10), although this is not always the rule.

Sex differences may also exist in the consequences of COPD because women report more respiratory symptoms (17) and physical impairment (18). Although not a uniform finding (19), lower quality of life has also been reported in women with COPD compared with men despite similar lung functions (20-23). Women may also respond differently to drug treatment (24) and pulmonary rehabilitation (25), although little information is available in this regard.

As a whole, the available information raises the possibility of sex differences in the susceptibility to the disease and related morbidity and mortality. We thus reasoned that women with COPD would demonstrate different patterns of lung impairment, response to pulmonary rehabilitation and mortality rate when compared with men. Accordingly, the aim of the present study was to compare lung function, disability, perceived handicap and the response to pulmonary rehabilitation and mortality rate between women and men with COPD.

PATIENTS AND METHODS

Subjects' selection

The present retrospective study included all consecutive patients diagnosed with COPD (26) who were evaluated at the exercise research laboratory at Hôpital Laval (Sainte-Foy, Quebec) between 1995 and 2002. The inclusion criteria were: a diagnosis of COPD based on current or past smoking history and irreversible airflow obstruction (26) (FEV_1 less than 80 % predicted, FEV_1/forced vital capacity [FVC] less than 70%); a maximal cycling exercise test performed in the exercise physiology laboratory of the research centre; and clinical stability at the time of exercise testing, ie, without symptomatic exacerbation or cardiovascular disease, uncontrolled hypertension (160/100 mmHg or higher), neurological disease, or any other condition that could impair capacity to perform the test or increase short-term mortality. Of the 236 patients identified, 124 patients had completed a 12-week pulmonary rehabilitation program. The consent to report this information was granted by the local ethics committee.

Pulmonary function tests and anthropometric data

Spirometry was performed according to the American Thoracic Society guidelines (26). Postbronchodilator FEV_1, FVC, FEV_1/FVC, functional residual capacity (FRC), total lung capacity (TLC) and residual volume (RV) values were then compared with the predicted values of Quanjer et al (27). Predicted inspiratory capacity (IC) was calculated by subtracting the predicted values of FRC from TLC (28). Height, weight, and past or present smoking history were obtained for all patients.

Maximal cycling exercise test

Following a 1 min resting period on the ergocycle, the maximum cycling exercise test (29) was initiated with work rate increments of 10 watts up to exhaustion. Peak oxygen consumption ($\dot{V}O_2$) was used as the index of maximal exercise capacity.

Survival

The medical chart of each patient was reviewed. The survival status and the date and cause of death were noted when available. When it could not be established from the medical chart, information was obtained from the Institut de la Statistique du Québec, an organization recording all deaths in the province of Quebec.

Pulmonary rehabilitation

The rehabilitation program included three-weekly exercise sessions for 12 weeks. Aerobic exercise consisted of 30 min on an ergocycle at 80% of maximal power output. Upper and lower body resistance exercises, breathing exercises and relaxation were also performed. This program has been previously described in detail (30). A 6 min walking test (6MWD) (31) and the chronic respiratory questionnaire (CRQ) (32) were completed at baseline and at the end of the rehabilitation program to assess its efficacy. The CRQ is a disease-specific instrument that measures dyspnea, fatigue, emotional function and mastery. A difference in score of 0.5 corresponds to the smallest difference in score that patients view as important (33).

Statistical analysis

Descriptive parameters were used to describe the study population at baseline, and data were compared using *t* tests or Mann-Whitney U test and Fisher's exact test. Age, the only non-disease-related personal characteristic that was different between the two groups, was used as a covariate in the analysis. Univariate analyses were conducted based on the Cox proportional hazards model using each of the potential predictors of mortality in patients, with COPD as independent variables (age, sex, body mass index (BMI), pack-years of smoking, FEV_1 % predicted, FVC % predicted, FRC % predicted, TLC % predicted, IC % predicted, IC/TLC and peak $\dot{V}O_2$) and the survival status as the dependent variable. Independent variables that were associated with mortality in the univariate analyses were then incorporated into a multivariate analysis also based on the Cox proportional hazards model. Correlations were established using the Pearson product moment. Statistical significance was set at the two-tailed 0.05 level. Values are reported as mean ± SD.

RESULTS

Patients

Between 1995 and 2002, 236 patients (68 women and 168 men) were evaluated at the research exercise physiology laboratory of the institution. The characteristics of the study population are shown in Table 1. Women were significantly younger and smoked notably less than men. Body mass index was similar between women and men. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) (34) classifications in disease severity were not significantly different between sexes: stage 0, none; stage I, none; stage II, 20 (29.4%) and 38 (22.6%); stage III, 37 (54.4%) and 79 (47.0%); stage IV, 11 (16.1%) and 51 (30.4%), in women and men, respectively.

TABLE 1
Patients characteristics (n=236)

	Women (n=68)	Men (n=168)
Age (years)	62.5±8.9*	66.3±8.4
Body mass index (kg/m^2)	24.5±6.2	25.7±5.0
Pack-years	31.0±24.2*	48.8±27.7
FEV_1 (L)	0.88±0.3*	1.12±0.46
FEV_1 (% predicted)	44.2±13.3†	39.6±14.7
FVC (L)	1.88±0.46*	2.58±0.75
FVC (% predicted)	78.6±17.3	72.6±23.2
FEV_1/FVC	48.1±11.2*	43.3±12.0
FRC (% predicted)	161.1±37.6†	148.9±36.8
RV (% predicted)	206.1±54.5	195.5±54.4
TLC (% predicted)	125.0±20.5‡	115.5±19.4
IC (% predicted)	77.4±18.4	75.3±19.4
IC/TLC	0.32±0.08	0.46±0.12
Peak $\dot{V}O_2$ (mL•kg^{-1}•min^{-1})	11.8±3.7‡	14.5±4.6
Peak $\dot{V}O_2$ (% predicted)	65.1±19.2	61.0±19.9
Maximum work capacity (watts)	40.8±20.7‡	63.2±32.4
Maximum work capacity (% predicted)	58.9±28.9‡	40.7±18.8

*Differences between sexes: *P<0.01; †P<0.05; ‡P<0.001. FEV_1 Forced expiratory volume in 1 s; FRC Functional residual capacity; FVC Forced vital capacity; IC Inspiratory capacity; RV Residual volume; TLC Total lung capacity; $\dot{V}O_2$ Oxygen consumption*

FEV_1 was higher in women. Women showed more hyperinflation than men with a greater FRC and TLC. Peak $\dot{V}O_2$ showed no differences between women and men when expressed in % predicted values, although women had a lower absolute peak $\dot{V}O_2$ when compared with men. The subgroup that enrolled in the rehabilitation program had similar age, sex distribution, pulmonary function tests and exercise capacity compared with the group as a whole (data not shown).

Survival

Among the 236 patients, there were 82 deaths. Mean follow-up time was 4.5±2.2 years. Women and men had a similar mortality rate of 34%. Specific mortality causes were available for 70 of the 82 reported deaths and are presented in Table 2. When both sexes were included in the analysis, predictors of mortality included age, smoking history, FEV_1 % predicted, FVC % predicted, FRC % predicted, IC % predicted, IC/TLC and RV % predicted (all P<0.05), but sex was not. Mortality analysis by sex (Table 3) show that the predictors of mortality differed between women and men. Body mass index, FRC % predicted, TLC % predicted, RV % predicted and peak $\dot{V}O_2$ (mL•kg^{-1}•min^{-1}) were significantly associated with mortality in women, while age, smoking history, FEV_1 % predicted, FVC % predicted, IC % predicted, peak (mL•kg^{-1}•min^{-1}) and peak $\dot{V}O_2$ % predicted were predictors in men.

The best predictive model for the multivariate analysis included age, smoking history, FVC % predicted and FRC % predicted. Unadjusted survival curves were similar between sexes (Figure 1, panel A). Survival curve adjusted for age, smoking history, FVC % predicted, FRC % predicted are provided in Figure 1, panel B. Although survival tended to be reduced in women, sex difference was not statistically significant.

TABLE 2
Specific causes of mortality

	Women, n (%)	Men, n (%)
Chronic obstructive pulmonary disease	8 (34.8)	23 (39.0)
Cancer	4 (17.4)	10 (16.9)
Cardiovascular diseases	2 (8.7)	14 (23.7)
Others	9 (39.1)	12 (20.3)
Total	23	59

Pulmonary rehabilitation

Fifty-eight per cent of women (n=40) and 50% (n=84) of men participated in pulmonary rehabilitation. Both sexes showed improvement in terms of 6MWD and CRQ scores following pulmonary rehabilitation. The improvement in the 6MWD was similar in women and men (47.8±59.9 m versus 43.6±40.2 m). The dyspnea, fatigue, emotion and control dimensions of the CRQ all demonstrated clinically significant improvements for both sexes. However, the improvement in the dyspnea domain was greater for women than for men (1.37±1.02 and 0.90±0.86, P<0.01) (Figure 2).

DISCUSSION

Results of the present study suggest higher susceptibility to COPD in women; women in the present study had a well-established COPD despite being younger and having smoked considerably less than men. Exercise tolerance and survival rate was comparable between sexes, but mortality predictors differed between women and men. Following pulmonary rehabilitation, the improvement in exercise tolerance was similar between sexes while the reduction in dyspnea was more pronounced in women.

Effects on lung impairment and disability

Consistent with a previous report (18), women in the present study showed severe COPD while being four years of age younger than men. An earlier development of COPD in women would imply the need for a sooner diagnosis and treatment. Unfortunately, the diagnosis of COPD is often missed in women (35) so that optimal treatment for this condition is delayed. Women in the present study had less severe airflow obstruction but more pronounced hyperinflation than men. While disease severity has traditionally been measured with FEV_1, patient disability can vary greatly for a given level of obstruction, and measures of hyperinflation may give further relevant information on patient condition (36). COPD may evolve differently in men and women, and the possibility for a sex-specific natural history of the disease cannot be excluded.

We found in women, compared with men, slightly higher FEV_1 but worsened hyperinflation. Whether this finding represents a mathematical artefact or a true difference in the phenotyping expression of the disease between sexes is difficult to resolve. One possibility is that these results could be explained by problems with the predicted values obtained from the regression equations. To minimize this potential bias, the predicted equations used for all pulmonary function variables come from the same study (27). This set of predicted equations included a large number of men and women and the precision of the estimates for the different predicted values is similar for

TABLE 3
Predictors of mortality: Univariate analyses by sex

	Women			Men		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age	1.027	0.979–1.078	0.27	1.076	1.033–1.121	0.0004
Body mass index	0.902	0.818–0.994	0.0381	0.997	0.923–1.035	0.43
Pack-years	1.014	0.996–1.032	0.12	1.009	1.000–1.018	0.0600
FEV_1 (% predicted)	0.982	0.948–1.019	0.34	0.962	0.941–0.983	0.0005
FVC (% predicted)	1.010	0.986–1.034	0.43	0.978	0.967–0.990	0.0002
FRC (% predicted)	1.018	1.004–1.032	0.0035	1.008	1.000–1.016	0.0380
TLC (% predicted)	1.027	1.005–1.049	0.0138	1.004	0.989–1.018	0.60
IC (% predicted)	0.986	0.964–1.008	0.20	0.972	0.956–0.987	0.0004
RV (% predicted)	1.027	1.001–1.018	0.0258	1.003	0.998–1.008	0.20
IC/TLC	0.013	0.013–0.013	0.12	0.006	0.006–0.006	0.0001
Peak $\dot{V}O_2$ (% predicted)	0.985	0.967–1.003	0.11	0.977	0.959–0.996	0.0169
Peak $\dot{V}O_2$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	0.997	0.995–0.999	0.0062	0.999	0.998–1.000	0.0036

FEV_1 Forced expiratory volume in 1 s; FRC Functional residual capacity; FVC Forced vital capacity; IC Inspiratory capacity; RV Residual volume; TLC Total lung capacity; $\dot{V}O_2$ Oxygen consumption

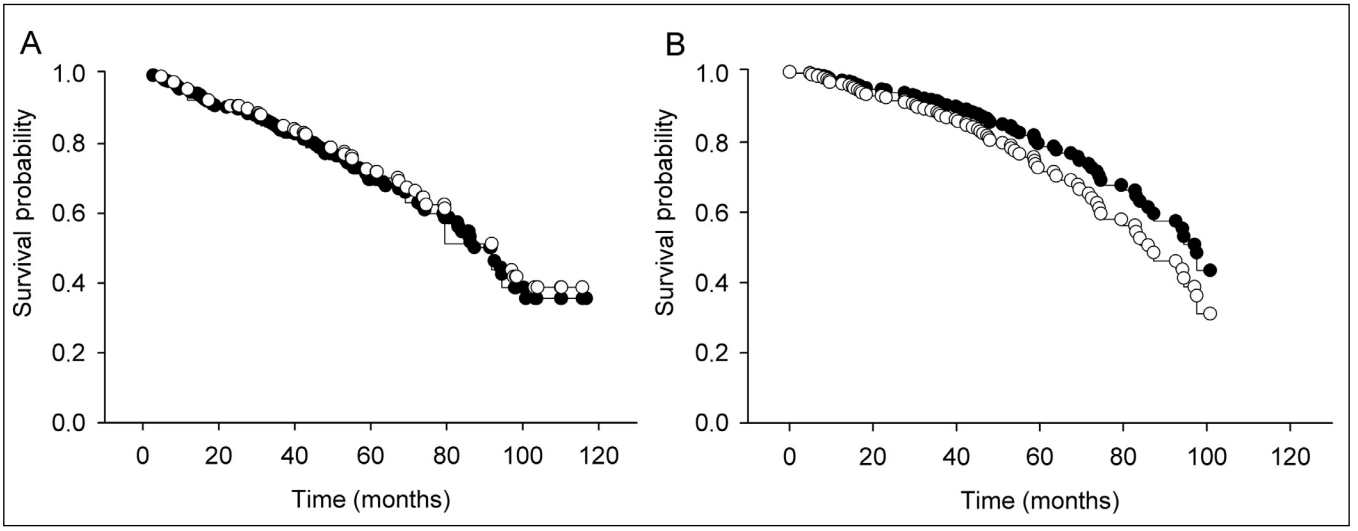

Figure 1) *Survival curves for men and women. Panel A are unadjusted curves. Panel B are curves adjusted for age, smoking history, functional residual capacity (%) predicted and forced vital capacity (%) predicted. Closed circles represent men and opened circles represent women*

both sexes. Dissociation between the severity of airflow obstruction and of hyperinflation could occur if the pathological process is predominantly located at the small airway and/or parenchyma levels, inducing more hyperinflation and less severe reduction in FEV_1. In fact, this possibility has been previously documented in patients with early COPD who showed emphysema and resting hyperinflation but normal expiratory flows (37). Furthermore, O'Donnell et al (38) clearly demonstrated that a volume effect can be induced with bronchodilators (ie, reduction in operating lung volumes) with little or no impact on FEV_1. Although it seems entirely plausible that changes in FEV_1 and lung volume can be dissociated, further studies are required before concluding on a specific sex-based susceptibility to hyperinflation.

The functional impact of this different disease pattern between men and women was assessed using an incremental symptoms-limited cycle exercise test. Although the interplay among airflow obstruction, lung volumes and exercise capacity is very complex (36), we found that, when expressed in % predicted value, women and men had similar peak $\dot{V}O_2$. Although this would suggest similar disability between sexes, the lower absolute $\dot{V}O_2$ value in women indicates a lower exercise reserve and women may indeed be at a disadvantage when performing activities of daily living.

Difference in tobacco susceptibility

The interpretation of the literature on sex difference in tobacco susceptibility is confounded by several potential biases. One bias is smoking under-reporting in women, particularly in older women in whom self-reported tobacco usage validity could be questioned due to social acceptability. Other studies nevertheless indicated that smoking self-reporting is reliable and that no difference between sexes is observed (39). The so-called healthy smoker selection biases (40), a bias that appears to be more important in women than in men, may also confound the interpretation about sex difference in tobacco susceptibility. According to this theory, only the healthiest women take up smoking, therefore leading to a greater underestimation of the health impact of smoking in women than in men. Despite these potential biases, the amount of evidence

points to the existence of a sex difference in the pulmonary effects of tobacco smoking. In several studies (10), including ours, the tobacco exposure was considerably less in women with COPD than in men, suggesting that lung function may be more affected by smoking in women than in men. On the other hand, once diagnosed with COPD, loss of lung function appears to be similar between sexes (41). It should be emphasized, however, that a loss in lung function of similar magnitude in both sexes should have greater impact in women because they have lower lung volumes than men. The final answer to the question of sex susceptibility to tobacco will only come from long-term longitudinal studies looking at the evolution of lung function in smokers of both sexes before the development of COPD.

We can not exclude that women who were younger than men may have received earlier medical attention than men in the course of their disease, perhaps because of a greater perception of dyspnea (12). However, at the time of study inclusion, women had a well-established COPD whose severity, despite different phenotypical expression, was not so dissimilar from that in men. It should also be considered that the diagnosis of COPD tends to be delayed in women compared with men (35). These observations suggest that women did not present themselves at a terribly different stage than men along the natural evolution of their disease.

All-cause mortality

A striking observation is that survival profiles were similar between sexes despite a younger age, lower exposition to tobacco and a higher FEV_1 % predicted in women than in men. When corrected for the important predictors of mortality, we found that survival tended to be poorer in women than men. Our study was underpowered to show that the mortality rate between women and men (1.3%) was statistically significant. This difference, if real, is probably clinically relevant and we calculated that approximately 600 subjects would have been required to reach a statistical threshold. According to epidemiological studies, COPD mortality is rising in women (7), and recently, Ringbaek et al (42) reported higher standardized mortality rates for women with COPD when compared with men. Another interesting finding of our study is that the physiological COPD profile differs between men and women and as a result, the predictors of mortality could differ between sexes, a topic for which little is known. Recently, lung hyperinflation (43) has been linked with increased mortality in COPD, and our results suggest that hyperinflation was more strongly associated with mortality. Also, a higher BMI seems to protect against mortality in women but not in men, probably because lower BMI was likely associated with muscle atrophy, a strong predictor of mortality in COPD (44). A reasonable explanation for the lack of protective effect of higher BMI on mortality in men is that, in contrast to women, the accumulation of the metabolically active visceral fat closely associated with cardiovascular mortality (45) may be more prevalent in men and may counterbalance any positive survival effects associated with higher BMI.

Pulmonary rehabilitation

Few studies have examined the effects of rehabilitation specifically in women. The positive impacts of rehabilitation on quality of life and functional status in women are reassuring. The finding that dyspnea improved to a greater extent in women than in men is also relevant because women often report greater dyspnea sensation than men (20,46). In our study, the use of the CRQ to assess dyspnea at baseline prevented between-sex comparisons to be made. We therefore cannot exclude that the larger improvement in dyspnea following rehabilitation could simply reflect that women had more dyspnea at baseline. However, Verrill et al (47) reported a trend for women to improve dyspnea to a greater extent than men following pulmonary rehabilitation despite similar dyspnea in both sexes at baseline. Foy et al (25) have shown that women do not benefit from long-term programs as much as men but this could not be addressed in the present study where only short-term effects of rehabilitation could be assessed.

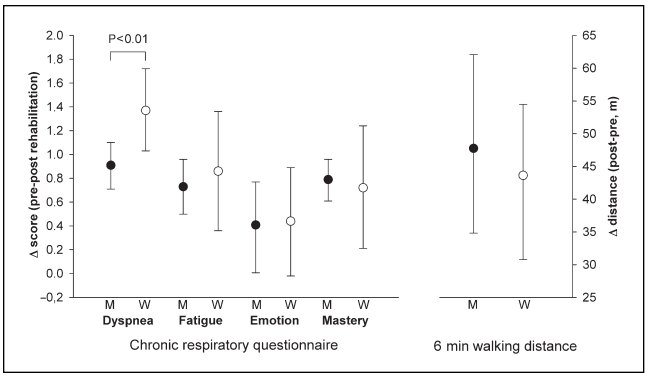

Figure 2) *Changes in the dyspnea, fatigue, emotion and mastery scales of the chronic respiratory questionnaire and 6 min walking distance test following pulmonary rehabilitation (mean ± 95% CI). Closed circles represent men (M) and opened circles represent women (W).*

The impact of the different physiological consequences of COPD on quality of life could not be compared between sexes in the present study because the CRQ was not designed to allow comparison among individuals (48). Previous studies have shown that health-related quality of life tends to be lower in women for a similar lung function (49).

CONCLUSION

The present study supports the concept that women may be more susceptible to tobacco smoke because they developed severe COPD at a younger age with less exposure to tobacco than men. We also found that the phenotypical expression of COPD differs between sexes, with women expressing a greater degree of hyperinflation than men. Survival rates tended to be lower in women but our study was underpowered to confirm the statistical significance of this finding. Furthermore, predictors of mortality varied according to sex, emphasizing the different impact of COPD in women when compared with men. Lastly, improvement in functional status, dyspnea and health-related quality of life has been obtained with rehabilitation in women with COPD. The present study therefore highlights the differential impact of COPD in women compared with men and the importance of continuing sex-based research in tobacco-related respiratory diseases.

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