

# Chronic obstructive pulmonary disease (COPD) and erectile dysfunction (ED): Results of the BRED observational study

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**Summary** Most patients with chronic obstructive pulmonary disease (COPD) share many risk factors and similar aetiological agents with erectile dysfunction (ED). Both conditions also cause serious interference with quality of life and sexual relationships. In general, ageing and chronic illness decrease sexual interest, sexual function, and testosterone levels. This observational study included 66 male patients referred to our centre with different grades of COPD. We studied the different correlations between COPD and ED. The data collected from each patient regarded the following features: demographic and social condition; smoking status; clinical status; spirometric measurements. In this group, COPD was diagnosed in 78.8% and ED was present in 83.3% with increased severity in presence of LUTS and nicotineism.

**KEY WORDS:** Chronic obstructive pulmonary disease (COPD); Erectile dysfunction; Endothelial dysfunction, Chronic inflammation.

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the persistent obstruction of airways (bronchiolitis) associated with the usually progressive destruction of lung areas (emphysema) associated with medical history of chronic inflammation, related to exposure to various pathogens including the prominent role attributed to cigarette smoking. Clinically it occurs with progressive shortness of breath, at first under stress and later – in severe cases – even at rest, cough and chronic catarrh (1).

Erectile dysfunction (ED), or the “persistent inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse” (2), not only implies a more or less severe deficit from a male biological functional point of view, but has also a particularly significant impact on relationships and the quality life of the man who is affected as well as on his partner. Currently epidemiological data still comply with the incidence values reported in the MMAS study, between 5 and 20% of men, with mild to severe medical history (3).

ED shares several risk factors (4-5) with hypertension (two-fold risk), chronic cardiovascular disease (four-fold risk) (6), diabetes (three-fold risk) (7) and the resulting predisposing factors such as hypercholesterolemia (8), obesity as well as a sedentary lifestyle with contextual nicotineism, irrespective of the abuse entity, further increase the weight of the cause/effect relationship.

In a consistently stable fashion, wider epidemiological studies reveal how men between 50 and 59 years are the most frequently represented category, while below 40 years of age, the prevalence of the disorder is between 1% and 10%, with an increase between 2 and 9% in the following decade, with a maximum of 15%, then up to 50-100%, from 70 years onwards. The association with various chronic conditions confirms an overall average increase of prevalence, which in the relationship between ED and diabetes, for example, is between 25 and 33%, with peaks up to 77% (9-10-11).

Other predominantly chronic conditions may be associated with erectile disorder both in terms of cause and maintenance: renal or hepatic impairment; endocrinopathies such as hypogonadism, hypothyroidism and hyperprolactinemia; various neurological diseases such as post-ischemic outcomes, multiple sclerosis or Parkinson's disease and psychiatric disorders with particular regard to anxious and depressive syndromes (12-13).

More recently, increasing importance has been attributed to the common association with obesity and metabolic syndrome (14), although it is not yet clear whether these two conditions are to be understood as a separate entity or an additional risk to diabetes or cardiovascular diseases and Lower Urinary Tract Symptoms (LUTS) (15), which in the results of the *Cologne Male Survey* correlate with ED at a rate of 72% (16).

COPD and ED are two conditions that apparently have little in common. Certainly it is virtually impossible to compare their consequences on overall health and long-term prognosis (*quod vitam*), the therapeutic commitment in drug, instrument, rehabilitation and – consequently – economical terms, inevitably involves the entire family sphere. In the face of all this, however, both of these conditions not only present numerous patho-

physiological mechanisms in common, and hence the possibility of shared approach. Furthermore, if we consider the population suffering from respiratory disease, what emerges is the constant demand for support in order to live a rewarding relationship and gratifying sexuality, which are extremely important in the early phases of the disease. In chronic disabling diseases, in fact, the sexual function can be otherwise altered, with negative consequences on the relationship, and more generally on the so-called quality of life (17-18). In men whose lives are often strongly affected by the disabling effects of chronic disease, sexuality can be a crucial moment of intimacy and a powerful source of pleasure, as well as of self-esteem and gratification and can help revive a positive affirmation of their role with their partner, whereas, in other contexts, such as work, sport, the social life, this role is limited or may have failed (19-21).

COPD is not a single nosological entity, but is rather a definition that gathers and describes chronic pulmonary conditions that cause a more or less important limitation of respiratory flow (22). Thus ED recognizes numerous aetiopathogenetic factors in common with chronic illnesses and, overall, an increased risk of incidence as has clearly emerged from various epidemiological investigations (23).

## MATERIALS AND METHODS

At the *Unit of Pathophysiology and Respiratory Rehabilitation at the IRCSS San Raffaele in Rome*, an observational study on Bronchopathy and Erectile Dysfunction –BRED was conducted from February 1 to July 30, 2015. 66 patients were studied in order to study the different correlations between COPD and ED. A database was designed and implemented in Visual Basic for Excel: data were then statistically evaluated using SPSS/v. 13.

Information gathered from each patient concerns the following features:

- *Demographic and social*: reason for visit, age, place of residence, marital status, type of work involving exposure or non-exposure to risk of respiratory diseases, perceived quality of life (St. George's scale);
- *Smoking habits*: active smoker, number of cigarettes smoked daily, years as smoker or ex-smoker;
- *Clinical*: co-morbidity/comorbidities, body mass index (BMI), blood glucose, total cholesterol, dyspnoea (MRC), COPD, erectile function (International Index of Erectile Function, IIEF), enlarged prostate (International Index symptoms of prostate, IPSS);
- *Spirometric measurements*: pH, CO<sub>2</sub>, O<sub>2</sub>, Forced expiratory volume (FEV<sub>1</sub>), forced total capacity (FVC), Tiffenau Index (TI), forced expiratory flow FEF<sub>75%</sub>, PEF, vital capacity (VC), total lung capacity (TLC). The reference ranges are summarized in Table 1.

COPD is expressed as a dichotomous categorical variable, while ED is also expressed as continuous. It should be specified that the latter is one of several fields of sexuality under investigation by the IIEF. The score obtained from particular applications allows to classify ED as shown in Table 2.

The distribution of absolute frequencies and percentages

**Table 1.**  
*Blood gas analysis and spirometric parameters and relative normality ranges.*

Parameters	Normality ranges
PH	7.35-7.45
CO <sub>2</sub>	35%-45%
O <sub>2</sub>	> 70%
FEV <sub>1</sub>	> 80%
FVC	> 80%
IT	> 80%
FEF <sub>75%</sub>	> 80%
PEF	> 80%
CV	> 80%
TLC	< 100%

**Table 2.**  
*Classification of ED.*

Score	Dysfunction
1-10	Severe
11-16	Moderate
17-25	Light
26-30	Absent

of categorical variables and descriptive statistics for continuous variables were used to summarize the characteristics of the sample as a whole, according to the severity of ED and COPD. To assess differences in the various characteristics of patients in the different groups, the Chi-square test (or Fisher's exact test) for categorical explanatory variables and non-parametric tests were used, given the non-normality of the data in question for the constant explanatory variables.

In particular, Kruskal-Wallis allowed the comparison of the various degrees of severity of the disease, while the Mann-Whitney test assessed the presence or absence of diagnosis of the disease. Both tests assess the function of divers variables.

These variables were further explored through Spearman nonparametric correlation coefficients, to identify possible relationships with the diagnosis and severity of ED and COPD. Correlations were calculated first for the entire sample and subsequently for the stratified sample according to the following category variables: active smoker, years smoked, years as former smoker, number of cigarettes per day, comorbidity/co-morbidities, BMI, dyspnoea.

Ultimately a logistic regression model was applied in order to identify possible predictors of ED and COPD. Critical limit for significance was set at 5%. The software used for the data analysis is SPSS/v 13.0.

## RESULTS

The sample from 39 to 72 year-olds, had a mean age of 62.4 ± 6.9. ED was present in 55 subjects (83.3%): 32 were severe (48.5%), 6 moderate (9.1%), 17 light (25.8%)

and the remaining 11 (16.7%) had a negative diagnosis. 40.9% (n = 27) of the patients had undergone medical examination for dyspnoea, 45.5% (n = 30), for cough, 12.1% (n = 8) for causes related to erectile functionality, one patient (1.5%) for a generic check up.

COPD was diagnosed in 52 patients (78.8%), among whom 10 (15.2%) had slight COPD, 19 (28.8%) moderate, 13 (19.7%) severe, 10 (15.2%) very serious and the remaining 14 (21.2%) were at risk. 13.6% (n = 9) of the patients had hypertension, 19.7% (n = 13), hypercholesterolemia, 15.2% (n = 10) suffered from several other diseases, and the remaining 51.5% did not have co-morbidities.

90.9% (n = 60) of the patients lived in cities while the rest of them lived in the country; 7 (10.6%) had a job that exposed them to lung disease risks; 56.1% (n = 37) were married or cohabiting, 31.8% (n = 21), were celibate, the remaining 12.2% were separated (n = 4) or widowed (n = 4).

According to the *St. Georges* questionnaire it was found that these patients perceived a low quality life ( $86.4 \pm 19.3$ ). The mean sample of patients had  $28.3 \pm 6.7$  BMI, 2 were underweight (3.0%) while 3 suffered severe obesity (4.5%).

Taking into account the smoking habits, 21.2% (n = 14) had never smoked, 24.2% (n = 16) were smokers and the remaining 54.5% (n = 36) had a history of smoking, including 30.6% (n = 11) who had stopped smoking for less than a year, and 16.7% (n = 6) for over five years.

Considering the sample as a whole, 12.1% (n = 8) smoked for less than ten years, and 28.8% (n = 19) for more than twenty years. Only one subject (1.5%) smoked less than 5 cigarettes a day, one-third of the remaining (30.8%) smoked between five and ten cigarettes a day, another third (34.6%) between ten and twenty, while the last third (32.7%) over twenty cigarettes per day.

24.2% (n = 16) had no dyspnoea, 39.4% (n = 26) light dyspnoea, 18.2% (n = 12) moderate, 16.7% (n = 11) severe and only one case (1.5%) suffered from extremely severe dyspnoea.

According to the IPSS scale, in the cases that showed lower urinary tract disorders, 39.4% (n = 26) of the cases had light symptoms, 10.6% (n = 7) of patients were seriously affected, while 50.0% (n = 33) were seriously compromised only under certain circumstances.

With regard to the spirometric parameters, 87.9% (n = 58) of the patients had normal values of pH, 3% (n = 2) lower than normal and 9.1% (n = 6) higher than the threshold of normality (average = 7.4; SD = 0.0).

Half of the patients had CO<sub>2</sub> levels above the normal range, while none had lower values (average = 47.8; SD = 12.9).

62.1% (n = 41) had normal oxygen levels while the remaining 37.9% (n = 25) had low levels (average = 73.8; ds 11.3).

Almost 70% (n = 46) of patients had low FVC, the remaining 30% (n = 20) had normal (average = 69.4; SD = 22.6).

84.8% (n = 56) were found to have too low FEV<sub>1</sub> values, while the remaining 15.2% (n = 10) had normal (average = 53.5; SD = 26.9).

Only 12.1% (n = 8) fulfilled the Tiffenau Index normali-

ty parameter, against 87.9% (n = 58) who were below the threshold (average = 57.7; SD = 21.3).

Slightly fewer than 30% (n = 19) had a normal vital capacity, compared with 71.2% (n = 47) (mean = 70.6; SD = 21.7).

Most patients, 51 (77.3%), had a total lung capacity that was higher than 100%, while only 22.7% (n = 15) was below the threshold (average = 145.4; SD = 64.5).

Studying the distribution of the subjects characteristics related to the severity degrees of ED and COPD, it was found that: 56.8% (n = 21) of married or cohabiting patients had severe ED, while the single men were affected by the disease only in 37.9% (n = 11) of the cases and in 41.4% (n = 12), the ED was light ( $X^2(3) = 7.9$ , p = 0.048); - 42.3% (n = 11) of the patients with absence or light urinary tract disorder suffered from light ED, while 63.6% (n = 21) of those who presented a median symptomatology, and 57.1% (n = 4) of those with severe symptoms, had severe ED ( $X^2(6) = 14.9$ , p = 0.021); - among subjects who had stopped smoking from less than a year, none had severe or very severe COPD, while among those who had stopped smoking for more than 5 years, 83.3% (n = 5) were suffering from severe COPD ( $X^2(12) = 33.2$ , p = 0.001); - there was no case of severe or very severe COPD among patients with FVC in the normal range, while an equal distribution of patients with FVC was observed to be below the normality threshold among the different degrees of COPD ( $X^2(4) = 15.5$ , p = 0.004).

The Kruskal-Wallis test has revealed a weak connection between ED and age, while COPD seems to be associated with most of the spirometric parameters, BMI, quality of life perception and ED expressed as absolute score (Table 3 shows the medians and statistics of the test).

According to the Mann-Whitney test, there is no statistical difference between the characteristics of patients without ED, or at risk of COPD and those who had already developed the disease.

The degree of ED has been correlated in a statistically significant way with the severity levels of COPD ( $\rho = -0.28$ , p = 0.024) and age ( $\rho = -0.33$ , p = 0.007), or rather a more serious form of COPD and at an older age corresponds to a more important ED.

As expected, COPD seems related to many spirometric parameters and quality of life. In particular, more severe COPD corresponds to poorer values of spirometric parameters, but a better sense of well-being.

The results are reported in Table 4.

In order to complete the study, a more thorough analysis of the stratified correlation for the main characteristics of the patients has been performed both for COPD as well as for ED.

Based on the logistic regression analysis none of the monitored parameters emerged as a predictor of the presence of ED. Statistical evidence has led to the identification of forced expiratory volume corruption as the sole predictor of COPD. Specifically, it has been estimated that patients with FEV<sub>1</sub> lower than 80% had about 5-fold higher odds of presenting pathology than patients with normal parameters (OR = 5.22, CI<sub>95</sub> = 1.25, 21.82, p = 0.023).

**Table 3.**

Distribution of the variable medians associated with erectile dysfunction and COPD, for the different severity degrees of the disease, and Kruskal-Wallis test ( $X^2$ , p-value).

		Absent (median)	Light (median)	Moderate (median)	Severe (median)	-	$X^2(3)$	p-value
<b>ED categorical</b>	Age	61	61	67	66	-	7.98	0.046
		At risk (median)	Light (median)	Moderate (median)	Severe (median)	Very serious (median)	$X^2(4)$	p-value
<b>COPD category</b>	BMI	27	29	25	31	23	13.0	0.011
	FVC	68	78	79	55	51	18.5	0.001
	FEV1	68	54	63	41	25	29.7	0.000
	IT	63	52	61	53	40	12.1	0.017
	FEF75%	39	44	29	16	10	27.4	0.000
	PEF	49	57	66	41	28	27.3	0.000
	CV	63	66	77	67	50	18.8	0.001
	St.George	97	100	93	73	74	15.8	0.003
	DE score	16	10	18	6	4	9.6	0.048

**Table 4.**

Variables associated with erectile dysfunction and COPD, both categorical ( $\rho$ , p-value).

		Variables	$\rho$	p-value
<b>ED category</b> (n = 66)	COPD category		-0.278(*)	0.024
	Age		0.327(**)	0.007
<b>COPD category</b> (n = 66)	O2		-0.244(*)	0.048
	FVC		-.359(**)	0.003
	FEV1		-.510(**)	0.000
	IT		-.254(*)	0.040
	FEF75%		-.490(**)	0.000
	PEF		-.394(**)	0.001
	Quality of life (St. George)		-.405(**)	0.001

## DISCUSSION

On the basis of an analysis of correlation, the severity degree of ED and COPD appear to be associated: severe levels of COPD correspond to poorer erectile function (24). However, it was not possible to identify the predictors of ED through the analysis of logistic regression, although it appeared that both married patients as well as those with medium to severe urinary disorders suffered from a higher level of dysfunction. Furthermore, patients with mild disease or absence of disease had a lower mean age. The only predictive parameter of COPD was found to be forced expiratory volume lower than 80%.

Many of the other spirometric parameters, although not predictive, resulted to be significantly correlated to a more severe form of COPD, as well as having a more positive perception of life quality. In addition to the previous results, the number of years as ex-smoker seems associated with the severity of COPD, or rather the greater part of those who had stopped smoking for more than 5 years had severe or very severe forms. Finally, according to the Kruskal-Wallis test, patients with varied degrees of

pathology differ significantly in many of the spirometric parameters, for body mass index, for the perception of quality of life and for ED, expressed as a continuous variable. The need to study the pathologies on the basis of certain characteristics of patients, such as smoking habits, requires subdividing them into small sample-sized groups.

This limits the efficacy of the study, as it does not allow generalization and the extension of the results to an entire population. A more appropriate study would provide for a stratified sample regarding both degrees of COPD severity, so as to obtain an equitable number of subjects suffering from the disease and at risk for COPD, as well as the different smoking habits.

At present, ED is increasingly establishing itself as the "sentinel symptom" of chronic diseases (hypertension, diabetes, ischemic heart disease): in this sense, it may paradoxically be a real "life saver" by which we can identify and eventually correct early phases of disease or hazardous lifestyles. It has also been emphasized how COPD is a "modifiable" condition before it becomes irreversible. Karadag (25) has shown how in patients with COPD, a high level of cytokines TNF- $\alpha$ , the recognized marker of chronic inflammation, is in turn correlated with body weight, chronic hypoxemia and cigarette smoking. In the relationship between the two pathological conditions, moderate and severe levels of TNF- $\alpha$  are particularly high in ED, suggesting that even chronic inflammation may play a causative role in the onset of ED in patients with COPD (26), resulting in alterations in the vascular endothelium (27-30).

However, the high levels of plasma cytokines related to the degree of obesity in patients with ED had already been evaluated by Giuliano (31). COPD, as other diseases of the lung, can result in a condition, shared with the ED, of vasoconstriction and microvascular occlusion. In the lung, this leads to changes in the ventilation/perfusion ratio, intrapulmonary shunting, arterial hypoxemia and pulmonary hypertension, especially in the later stages of the disease. In both primary and secondary pulmonary hypertension, there is a decreased expression of e-NOS

(endothelial nitric oxide synthase), pulmonary vascular endothelium.

The three aetiopathogenetic hypotheses are common in the two conditions: inflammatory, vascular and endocrine. Following sexual stimulation, non-adrenergic and non-cholinergic nerve endings (NANC) release NO, which through the second messenger, cGMP, induces the relaxation of the smooth muscles in the corpora cavernosa. The levels of cGMP are regulated by the action of PDE5, the enzyme responsible for the hydrolysis of cGMP in GMP. For the same functional cascade, this could also represent the rationale of treatment with PDE-5 inhibitors, aimed at improving the ventilatory lung flow (32).

## CONCLUSIONS

Both ED and COPD conditions share several risk factors and physiopathological mechanisms. These correlations can lead to some interesting assumptions of treatment, common to both diseases, although the importance of proper prevention, especially in younger patients, cannot be ignored.

ED and COPD may finally determine important ingravescence as well as often cause emotional, relational, social and sexual issues, with potentially depressive tendencies, not only in the patient but also, and especially, in the couple.

These conclusions confirm, once again, the need for a multi-speciality health policy for the prevention and management (33).

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