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ARTICLE ORIGINAL

Predictive factors of progressive decline in FEV1 in COPD subjects

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MOTS CLÉS

BPCO

Déclin du VEMS

Exacerbations

Tabagisme

Résumé

Introduction : La bronchopneumopathie chronique obstructive est une maladie inflammatoire chronique des voies aériennes définie par une obstruction bronchique pas ou peu réversible et caractérisée par un déclin progressif du VEMS

Méthodes : Afin d'évaluer le déclin évolutif du VEMS et d'identifier les facteurs prédictifs, nous avons réalisé une étude prospective épidémiologique et longitudinale étalée sur 03 ans, incluant des patients BPCO. Ces derniers, ont bénéficié à l'état stable d'une spirométrie par an durant cette période. **Résultats :** L'âge moyen des patients est de 61 ± 9 ans avec une prédominance masculine nette. La quantité de tabac cumulée est de 50 P/A. La majorité des BPCO sont de stade modéré 64,4 %. Durant les 36 mois de suivi, le déclin moyen annuel du VEMS de nos patients est de $39,7 \pm 23$ mL. Les fumeurs déclinent plus que les ex-fumeurs 51 mL vs 29 mL ($p:0,000$). Il existe une différence significative entre la décroissance annuelle du VEMS et les stades GOLD ; entre le stade II et III (44 mL vs 34 mL, $T:3,4$, $p < 0,05$) et entre III et IV (34 mL vs 22 mL, $T: -4,29$, $p < 0,05$). Le déclin du VEMS chez les exacerbateurs fréquents est plus important que celui des exacerbateurs moins fréquents (44 mL vs 34 mL, $T: -2,61$, ($p:0,000$)).

Conclusion : La persistance du tabagisme et la fréquence des exacerbations sont les principaux facteurs prédictifs du déclin du VEMS chez le sujet BPCO. Nous soulignons l'intérêt du sevrage tabagique et la prévention des exacerbations.

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KEYWORDS

COPD

Declin inFEV1

Exacerbations

Tobacco

Abstract

Introduction : Chronic obstructive pulmonary disease is a chronic inflammatory disease of the airways defined by bronchial obstruction that is not or only slightly reversible and characterized by a progressive decline in FEV1.

Methods . In order to evaluate the progressive decline in FEV and identify predictive factors, we carried out a prospective epidemiological and longitudinal

study spread over 3 years, including COPD patients. The latter benefited in a stable state from spirometry per year during this period

Results : The average age of patients is 61 ± 9 years with a clear male predominance . The cumulative quantity of tobacco is 50 P/ A. The majority of COPD is of moderate stage 64.4 %. During the 36 months of follow-up, the average annual decline in FEV of our patients was 39.7 ± 23 ml . Smokers declined more than ex-smokers, 51 ml vs. 29 ml ($p : 0.000$). There was a significant difference between the annual decrease in FEV1 and the GOLD stages; between stage II and III (44 mL vs 34 mL, $T : 3.4$, $p < 0.05$) and between III and IV (34 mL vs 22 mL $T : -4.29$, $p < 0.05$). The decline in FEV1 in frequent exacerbators is greater than that in less frequent exacerbators (44 ml vs 34,T:-2.61,($p : 0.000$)

Conclusion : Persistence of smoking and frequency of exacerbations are the main predictive factors of FEV1 decline in COPD subjects. We highlight the benefit of smoking cessation and the prevention of exacerbations.

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Introduction :

Age-related lung aging is expressed by an annual physiological decline in expiratory volume per second (FEV) which the authors estimate at 20-25ml per year in a subject with no respiratory history[1]. Lung maturity is reached around the age of 08 [2] and it is around the age of 20 that the decline in pulmonary function begins very slowly[3]. The physiological decline is linked to the disappearance of pulmonary elastic fibers with age, reducing the caliber of the distal bronchi and therefore their permeability and an increase in non-mobilizable air volume [4]. Chronic obstructive pulmonary disease is defined by little or no reversible bronchial obstruction secondary to the inhalation of gases or toxins. It evolves insidiously towards an inevitable progressive decline in respiratory function, assessed by measuring FEV1. Accelerated decline in FEV1 is a predictor of respiratory disability and in particular respiratory mortality and a high risk of hospitalization [5]

The objective of our study is to evaluate the annual decline in FEV1 in COPD subjects and to identify the predictive factors of this decline.

Patients and methods

This is a prospective analytical and longitudinal study involving a cohort of

COPD patients whose diagnosis is confirmed according to the GOLD criteria. A detailed interview was conducted in all patients meeting the eligibility criteria, including sociodemographic characteristics (sex, age, exposure to biomass, smoking: start, duration and quantity of smoking). of 03 years during which these patients were treated according to their stage of severity and evaluated each year by spirometry carried out after an exacerbation. We also recorded all episodes of exacerbations during the study period and retained a threshold of 3 exacerbations per year which characterizes a frequent exacerbator , by referring to the literature [6].

Inclusion criteria :

- Subjects over 40 years of age of both sexes.
- Smoker more than 10 packs/year and/or exposed to other risk factors (biomass, occupational factors)ventilator disorder not reversible or partially after bronchodilation test

Exclusion criteria

- Subjects with a history of bronchial asthma
- Subjects with a reversible obstructive ventilatory disorder; a gain in FEV of more than 12% and more than 200ml after a bronchodilation test

Data analysis

Data entry was carried out using SPSS 21 software. The descriptive analysis of qualitative and ordinal variables will include the number and frequency of each modality with its 95% confidence interval. That of the quantitative variables will include the mean, the standard deviation and their confidence intervals as well as the median, the percentiles and the extreme values . The comparison between the two qualitative variables is carried out by the Pearson chi-square test and between the quantitative variables by the Anova test.

The results

Our cohort is made up of one hundred and thirty-two men and three women, the average age is 61 years. The dominant risk factor is smoking, so 49% are smokers and 49% are ex-smokers. The notion of exposure to biomass is found in 35.5% with 10 years of average exposure. The majority of our patients suffered from moderate COPD (63.7%). (table 1) . During the 36 months of follow-up we recorded a frequency of 2.4 exacerbations per year on average.

The monitoring of COPD patients over the course of three years is done by evaluating the disease on a functional level, measuring spirometric parameters. All COPD patients in a stable state and at distance of exacerbation, benefited from an annual spirometry carried out according to the SPLF recommendations at time T1 1st year, T2 (2nd year) and T3 (3rd year). The maximum expiratory volume during the 1st second (FEV) is the gold standard parameter in monitoring the evolution of respiratory function.

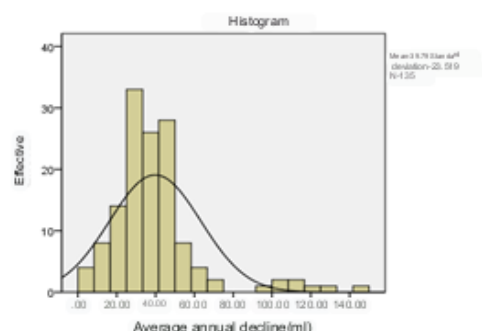
The average value of the annual decline in FEV1 represents the average difference in FEV1 values at T1, T2 and T3. According to our study, it is $39.7 \pm 23\text{ml}$ with extremes ranging from -2ml to -149ml (fig: 1) . We distinguished three groups: the first whose decline is not significant at $2\text{-}29\text{ml}$, the second between $30\text{-}39\text{ml}$ and the third greater than or equal to 40ml .

Table 1 : Epidemiological characteristics of the cohort

	Frequency
Average age (years)	61±9
Man Woman	132/03
Smoking status	
Tuxedo	66(48.9%)
Former smoker	66(48.9%)
Non-smoker	03(2.2%)
Average duration of smoking (years)	40
Average withdrawal duration (years)	8 ± 4
Average cumulative quantity of tobacco (P/A)	50±23
Exposure to wood smoke	48(35.5%)
GOLD stadiums	
Stage I	7(5.1%)
Stage II	(63.7%)
Stage III	(27.4%)
StageIV	(3.7%)
Average frequency of exacerbations/year	2.4±1

Values are expressed as mean ± confidence interval.

Figure 1 : Histogram of annual decline in FEV1 in a cohort of 135 patients



To better appreciate the annual decline in FEV1 according to age in our COPD subjects, the patients were divided into two groups, the first group under 60 years old and the second group ≥ 60 years old. The choice of age ≥ 60 years was not done randomly, it reflects the average age of the population studied. Data analysis (Table 2) indicates that COPD under 60 years of age have an average annual FEV1 loss of 64.52ml , while the average FEV1 decline in COPD ≥ 60 years of age is 31.60ml . The difference between the

two groups is very significant (T: 3.85, P: 0.000).

Table 2 : decline in FEV1 in COPD subjects according to age

Age of COPD	Mean FEV decline (ml)	T	P	P<0.05	95% IC
COPD <60 years (74)	46.52 ± 28	3.85	0.000	**	[7.2, 22.5]
COPD ≥ 60 years (61)	31.60 ± 11				

B PCO: chronic obstructive pulmonary disease, FEV1: maximum expiratory volume per second

, CI: Confidence interval . Shown are the correlation coefficients (= T); * p < 0.05; ** p < 0.05; NS: not significant (p > 0.05).

Analysis of data according to smoking status shows that the average decline in FEV among smokers is

51.10ml higher than that of ex-smokers which is 29.74ml. The difference between these two COPD smoking statuses is very significant (T: 5.88, P: 0.000) (table 3)

Table 3 : decline in FEV1 in COPD subjects according to smoking status

	Smoking status	FEV decline/year	T	P	P<0.05	95% CI
Mean	Smoker(66)	51.10 ±24	5.88	0.000	**	[14.1, 28.5]
FEV1 decline	Former smoker (66)	29.74 ± 14				

CI: confidence interval, FEV: forced expiratory volume per second, COPD: chronic obstructive pulmonary disease Correlation coefficients (= T) are shown; * p < 0.05; ** p < 0.05; NS: not significant (p > 0.05).

To check whether the tobacco consumption expressed in packs per year of COPD subjects will have an influence on the annual decline in FEV1, we divided the COPD patients into two groups according to the average tobacco consumption: the first group of patients having consumed less than 50P / A, the second with high tobacco consumption ≥ 50

P/A. Table 4 shows that the average decline in FEV among heavy smokers ≥ (50P/A) is 40.33ml, slightly higher than that of the first group with consumption below 50P/A (39.72ml). However, there is no significant difference between the two groups of COPD patients (P>0.05).

Table 4 : Annual decline in FEV: quantity of tobacco, duration of withdrawal, duration of smoking, BMI

	Quantity of tobacco (P/A)	Mean FEV1 decline	T	P	P<0.05	95% CI
COPD	<50P/A (75)	39.72±20	-0.15	0.8	NS	[-8,7.4]
	≥ 50 P/A (57)	40.33 ± 26				
	Duration of smoking	Mean FEV1 decline	T	P	P<0.05	95% CI
COPD	<40 years (36)	43.70±17		0.2		
	≥40 years (96)	38.53 ± 24	1.1		NS	[-3, 13]
	Weaning duration (years)	Average decline FEB1	T	P	P<0.05	95% CI
COPD	<8 years	26.88±12				
	≥8 years old	32.28 ± 18	-1.36	0.4	NS	[-13.5,2.6]

	BMI (kg/m2)	Mean FEV1 decline	T	P	P<0.05	95% CI
COPD	≤21kg/m2 (75)	39.13 ± 24	-0.35	0.7	NS	[-9.5, 6.6]
	>21kg/m2 (60)	40.6 ± 22				

COPD: chronic obstructive pulmonary disease, FEV1: maximum expiratory volume per second

,BMI : body mass index. Shown are the correlation coefficients (= T) ; ** p < 0.05; NS: not significant (p > 0.05).

Similarly, we compared the average decline in FEV among COPD patients whose duration of smoking was less than 40 years and their counterparts who had consumed tobacco for more than 40 years. The threshold of 40 years is the average duration of tobacco consumption. in our series. The analysis of the data carried out by the T test indicates that the average declines of these two categories of COPD patients are closed (43.70ml vs 38.53ml). The difference is not significant (T: 1.1, P>0.05). (table 4) . We evaluated the drop in FEV1 in COPD ex-smokers according to the duration of withdrawal, thus we divided them into two groups; the first stopped smoking for less than 8 years and the second group stopped

smoking for more than 8 years. The threshold of 8 years is the average duration of smoking cessation among the ex-smokers in our series. Data analysis shows that the average decline in FEV1 in the first COPD group is 26.88ml, similar to that of the 2nd group which is 32.28ml. There is no significant difference between these two groups (T-1.63, P>0.05). We compared the annual decline in FEV in undernourished COPD and in others with a BMI>21 kg/m2. Table 4 of the mean comparisons of FEV1 decline shows that the mean FEV1 decline in malnourished subjects is 39.13ml, slightly lower than that of COPD subjects with a BMI greater than 21 kg/m2 (40.6ml). COPD malnourished and those with a BMI

Table 5: Variations in FEV1 decline between T1 and T3 in COPD subjects exposed to biomass

	Mean FEV1 T1vs T3	T	P	P<0.05	95% CI
Exposure to biomass (03)	1.343± 0.250	2.21	0.15	NS	[-0.02, 0.07]
	1.316± 0.254				

FEV: maximum expiratory volume per second. Correlation coefficients (= T) are shown; ** p < 0.05; NS: not significant (p > 0.05).

Normal is not significant (T-0.35, P>0.05)

For COPD exposed to biomass, no variations in FEV1 were observed during the evolution between T1 and T3 (P>0.05) (table 5) .

Table 6 : The decline in average FEV1 according to the GOLD severity stages

GOLD stadiums	Mean FEV1 decline	T	P	P<0.05	95% CI
Stage I (7)	25.57±21	2.21	0.05	NS	[-39.1, 0.9]
Stage II(86)	44.67 ± 27				
Stage II(86)	44.67 ± 27	3.4	0.001	**	[4.4, 16]
Stage III(37)	34.02 ± 5				
Stage III(37)	34.02 ± 5	-4.29	0.000	**	[-16.5,-5.9]
Stage VI(5)	22.8 ± 4				

IC : confidence index, FEV: maximum expiratory volume per second.
Shown are the correlation coefficients (= T); ** p < 0.05; NS: not significant (p > 0.05)

We note that there is a significant difference in the average decline between stage II/III COPD (44.67ml Vs 34.02ml) (T: 3.4, P<0.05) but the average decline in FEV of stage I COPD is approach to that of stage II, thus we note no significant difference between these first two stages (p>0.05), as well as between stage III and IV COPD (34.02ml VS 22.8ml)(T: -4.29,P <0.05). (painting 6) Figure 2 shows an overlap between the error bar of stage I and II and no overlap between stages III and IV

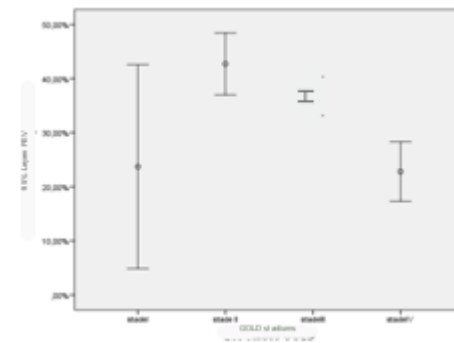


Figure 2 : Error bars between the values of the mean FEV1 decline according to the GOLD stages

Exacerbations are complications that accelerate the progression of the disease. To clarify the impact of these acute episodes on pulmonary function: we evaluated the annual decline in FEV1 in COPD with the two categories: frequent exacerbators

Table 7 : the average decline in FEV1 in COPD subjects according to the frequency of exacerbations

Frequencies of exacerbations	Mean FEV1 decline	T	P	P<0.05	95% CI
<3EX/YEAR	34.22 ±24	-2.61	0.008	**	[-17.8,-2]
≥ 3EX/YEAR	44.41 ± 20				

CI: confidence index, FEV: maximum expiratory volume per second. EX: exacerbation
Shown are the correlation coefficients (= T); ** p < 0.05; NS: not significant (p > 0.05).

THE frequent exacerbators ≥ 3EX/year and those with fewer exacerbations < 3EX/year. Analysis of the data by the T test shows that the decline in FEV in frequent exacerbators is 44.41 ml, higher than that of B PCOhaving fewer exacerbations 34.22ml. The difference between these two categories

is very significant (T: - 2.61, P < 0.05) (Table 7).

Figure 3 shows that there is no overlap between the confidence interval of the mean decline in FEV

COPD subjects with frequent exacerbations (≥ 3EX/year) and COPD subjects with fewer exacerbations

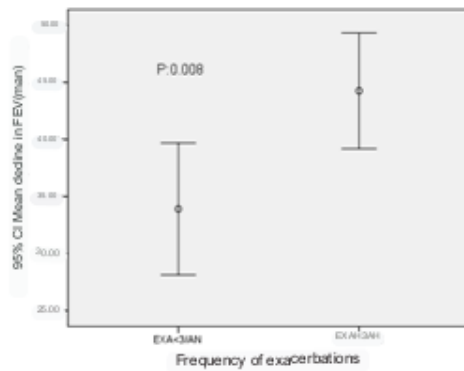


Figure 3 : Error bars of mean FEV1 decline values and frequency of exacerbations

Discussion

The evolution of respiratory function in our COPD patients was assessed by spirometry. Each patient benefited from a spirometric measurement, following an exacerbation.

In total, we performed 405 spirometries during this period. FEV1 is the gold standard parameter in monitoring the natural course of COPD [7] but also in large clinical trials of pharmacotherapy for this disease. We used threshold values previously reported in the literature [8,9], namely, a fall in FEV1 of 40 ml per year is defined as a rapid decline, and an average value of less than 40 ml per year as a physiological decline in FEV1. FEB1.

For a long time, scientists have been interested in the changes in respiratory function occurring in smokers and particularly in COPD. The pioneering study in the evaluation of the annual decline in FEV1 is the study by Fletcher and Peto [1]. The present study showed that the average annual decline in FEV1 was 39 ml± 23 ml with variations ranging from -2 to -146 ml. This decline in respiratory function is consistent with the results of four recent studies [9, 10,11,12] whose annual decline was between 32-33 ml.

In the UPLIFT study [12] (Understanding Potential Long-term Impact on Function with Tiotropium) international, multicenter, 4-year, placebo-controlled, double-blind, randomized study specifically designed to study the effect of Tiotropium on the decline

of respiratory function in COPD subjects, the authors demonstrated that the annual decline FEV1 was 39 ml in COPD subjects who were on tiotropium throughout the study period.

A.Ramirez-vanegaz et al [13] in a prospective study compared the decline in FEV1 in COPD smokers and COPD exposed to biomass over a 15-year follow-up period. The results showed a greater decline in the post-smoking COPD group of 42 ml/year. Previous studies [14,15,16] performed in clinical trials showed a larger annual decline of approximately 44 ml. We did not note significant annual variations in FEV1 in COPD subjects exposed to biomass ($P>0.05$). groups of COPD subjects were identified: those with a non-significant decline 24.4% (≤ 29 ml), others declining slowly (37%) (30-39 ml) and the last group whose decline is accelerated from -40 to -146 ml. This last group is mainly composed of active smokers. A significant loss of lung volume (≥ 40 ml) is observed in 38.5% of our COPD. This is a rate similar to that found by Vestbo et al [8]. This significant decline can be explained by the high number of active smokers in our cohort (48%). C. Casanova's team [9] analyzed the long-term evolution of FEV1 in a cohort of 1198 COPD patients followed from January 1997 to December 2009. The authors reported a statistically significant decline of

less than 86 ml/year in 18% of cases and not significant. (-28 ml/year) in 82%.

Annual variations in FEV1 in COPD differ from one GOLD stage to another and within the same stage. They are heterogeneous, they depend on several influential factors; smoking status, [10] , age, BMI, frequency of exacerbations and genetic factors specific to each patient.

The results of our study showed that the annual decline in FEV1 in COPD patients is inversely linked to the severity of the disease: severe stages decline less than moderate and mild stages. Our results are consistent with the results of the UPLIFT study [11] , the TORCH study [16] and the study of Vestbo et al [8] . Furthermore, there is a statistically significant difference between the annual decrease in FEV1 and the severity stages; between stage II and III (44 ml vs 34 ml, P: 0.001), stage III and IV (34 ml vs 22 ml, P: 0.000). On the other hand, we did not note any difference between stage I and II (P>0.05) which can be explained by the low percentage of mild forms in our series. This drop is similar to that found by Vestbo et al [8], TORCH [16] and Nishimura et al [10] and P. Sanchez- Salcedo et al [17] who concluded that the highest FEV in (%) and in (l) is linked to a rapid decrease during the progression of the disease. This confirmation completely contradicts certain studies [1] which reported the acceleration of the decline in FEV1 in COPD patients with severe obstruction.

A recent study [18] including 400 COPD patients showed rates of decline in FEV higher than those found in our study and for all GOLD stages. These significant decreases can be explained by the importance of the population studied compared to ours.

The literature reports that the decline in FEV1 accelerates with age in healthy subjects. According to Ware et al [19] , the annual decline in a 25 year old subject is 12.9 ml, much lower than that of a 75 year old which is 59 ml. ml . It can be speculated that the decline in FEV in subjects with COPD accelerates more with age. On the other hand, our study demonstrated that the

annual decline in FEV in subjects under 60 years is greater than that of over 60 years with a significant difference (P0.05). Our results are similar to those of C. Casanova et al [9] who reported that those who declined rapidly were significantly younger than those who declined slowly. Conversely, in the observational ECLIPSE study conducted by Vestbo et al [8], revealed that the decline in lung function in COPD was not correlated with age.

Furthermore, other more recent studies [9,17] have demonstrated that the decrease in FEV1 was similar in both young COPD and elderly subjects.

Not only is smoking a risk factor for COPD, but once the disease is established, smoking is also associated with faster progression of the disease.

The present study confirmed the deleterious effect of smoking on the decline in pulmonary function: in fact the greatest drop in FEV1 is observed in active smokers 51 ml vs 29 ml than in ex-smokers with a significant difference (P: 0.000).An increase of 22 ml/year additional among active smokers.

This is consistent with the literature which reports a decrease in lung function in COPD smokers twice as fast as in COPD non-smokers [20].

Concerning the cumulative quantity of tobacco, the duration of smoking and the duration of cessation, no significant correlation was observed between these parameters and the average annual decline in FEV1 in COPD patients.

Curiously, the decline in FEV in COPD subjects weaned for more than 8 years was no different from that of patients who had been weaned recently . One of the physiopathological hypotheses is the persistence of inflammatory phenomena secondary to smoking . The other is secondary to smoking in the former. Another hypothesis mentioned would probably be incomplete smoking cessation in the latter.

Our results agree with those of the study [344] which concludes that there is no

relationship between the drop in FEV1 and tobacco consumption.

The Japanese study did not demonstrate a significant relationship between the quantity of tobacco and the different groups of FEV1 decline.

In the EUROSCOPE study, L. Watson et al [21] showed that the number of packs of cigarettes per year and the age of smoking initiation are not associated with annual variations in FEV, in a COPD population of moderate severity. However, in severe COPD, the opposite is true, demonstrated by X. Wang et al. [22], the link exists between the decline in FEV and the cumulative quantity of tobacco

The present study revealed a significant correlation between the average annual decline in FEV and the frequency of exacerbations; a difference of 10 ml between frequent exacerbaters and infrequent exacerbaters. The effect of exacerbations on the evolution of respiratory function is similar to that of previous studies [23,24]. A weaker effect was found in the ECLIPSE study [8] evaluating the impact of exacerbations on respiratory function; the authors concluded that these exacerbations were associated with a drop in FEV of 2 ± 0.5 ml per year. Conversely, other studies have not identified this association between the frequency of exacerbations and the drop in FEV1. It is likely that the lack of correlation is due to a slower progression of the population studied which is essentially composed of mild to moderate stages with less exacerbations. [25]

Conclusion

The annual decline in physiological FEV1 is less than 40 ml. The results obtained from our series show a decline ≥ 40 ml in only 38% of cases. A significant reduction was observed in stage II patients (moderate COPD). This finding suggests the interest of therapeutic intervention at an early stage of COPD severity where we can hope to act on potentially reversible mechanisms which are at the heart of the disease. origin of the rapid decline in FEB. The average annual loss of

FEV is closely correlated with active smoking. . This discovery highlights the importance of smoking cessation as a tool in secondary and tertiary prevention at all stages of the disease. Exacerbations accelerate the decline in lung function. It is necessary to reduce the frequency and severity of these episodes. Given that the majority of exacerbations are due to tracheobronchial infections that are more viral than bacterial, anti-flu and anti-pneumococcal vaccination therapy is essential at all stages.

Bibliography

[1]- 36-Fletcher.C, Peto.R : The natural history of chronic airflow obstruction. BMJ 1977; 1:1645-8

[2]-Dunnill.MS, . (1962). Postnatal growth of the lung. British Medical Journal, 17(4), 32

[3]-Carillo.S . (2004). Histology of the respiratory system. Montpellier Nîmes Faculty of Medicine . -

[4]- Ketata W, Rekik WK, Ayadi H, Kammoun S.Vieillessement de l'appareil respiratoire : modifications anatomiques et conséquences physiologiques.Rev Pneumol Clin2012 Octobre, Vol 68, 5, 282-289

[5]-SchnemannH . —Is there an association between impaired pulmonary function and mortality in never smokers? Thorax ,2004,59,81

[6]-Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA: Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002; 57:847-52

[7]-Lange P, and al.Lung function trajectories Leading in COPD N Engl J Med 2015; 373:111-122

[8]-Vestbo.J,Edwards.LD,Scanlon.PD et al.Changes in forced expiratory volume in 1

second over time in COPD. *N Engl J Med* 2011;365(13):1184-1192.

[9]- Casanova.C, DE Torres. JP, Aguirre-Jaime.A et al. The progression of COPD in heterogeneous the experience of the BODE cohort. *Am J Respir Crit Care Med* 2011;184(5):1015-1021

[10]- Nishimura.M, Makita.H, Nagai.K et al. Annual change in pulmonary function and clinical phenotype in COPD. *Am J Respir Crit Care Med* 2012(185(1);44-52.

[11]- Tanabe.N, Shigeo.M, Tanake.S et al. Emphysema distribution and annual changes in pulmonary function in male patients with COPD. *Respir. Reseach* 2013;31.

[12]- Decramer.M, Celli.B, Kesten.S, Lystig.T , Mehra.S, Tashkin.DP . Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomized controlled trial. *Lancet.* 2009; 374(9696):1171-1178.

[13]- Ramirez-Venegas.A , Sansores.RH , Perez Padilla.RH et al. Survival of patients with COPD due to biomass smoke and tobacco. *Am J Respir Crit Care Med* 2006;173:393-7.

[14]- Tashkin.DP, Celli.B, Burkhart.D, Keslem.D et al. A 4 -year trial of tiotropium in COPD. *N Engl J Med* 2008;359;1543-1554.

[15]- Calverely.PM, Anderson.JA, Celli.B , Ferguson.GR et al. Salmeterol and fluticasone propionate and survival in COPD. *N.Engl J. Med* 2007;356,775-789..

[16]- Celli.BR, Thomas.NE, Anderson.JA et al. Effect of pharmacotherapy on rate. Results from the TORCH. study. *Am J Respir Crit Care Med* 2008;178:332-338

[17]- Sanchez Salcedo.P, Diva.M , Casanova.C et al. Disease progression in young patients with COPD: rethinking the Fletcher and Peto model. *Eur Respir J* 2014;44(2):324-331.

[18]- Oussedik.F et al. The impact of exacerbations on respiratory function. *Rev Mal Respir Jan* 2016(33).183-184

[19]- Ware.JH, Dockery.DW , TA.Louis, Xu. Xiping, BG. Ferris, FE. Speizer : Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. *Am J Epidemiol* 1990; 132 :685-700.

[20]- Atsou.K. Epidemiology of COPD. *J. Fran Viet Pneum* 2012, 03(8) ;12 -26

[21]- Watson.L, Vonk.JM, Lofdhal.CG et al. Predictors of lung function and its decline in mild to moderate COPD in association with gender. *EUROSCOPE Study Respir Med* 2006(100),746-753.

[22]- Wang.X, Mensiga.T, Scoulen.J et al. Determinants of maximally attained level of pulmonary function. *Am J Crit Care Med* 2004;169:941-948

[23]- Jones.PW, Chen.WH , et al. Characterizing and quantifying the symptomatic characteristics of COPD exacerbations. *Chest* 2011;139:1388-94

[24]- Celli.BR, Cote.CG, Marin.JM et al. The body-mass index, airflow obstruction and dyspnea and exercise capacity index in COPD. *N Engl J Med* 2004;350:1005-12

[25]- De Torres.JP, Casanova.C , Hernandez.C et al. Gender associated differences in determinants of quality of life in patients with COPD. A case series study. *Health qual Life Outcomes* 2006;4;72

