

Early Diagnosis of Airway Inflammation in Smokers: Still a Challenge

A. Pacheco Galván

Servicio de Neumología. Hospital Ramón y Cajal. Universidad de Alcalá. Madrid. Spain.

Chronic obstructive pulmonary disease (COPD) is a heterogeneous entity whose main sign is barely reversible chronic airflow limitation (CAL) caused by the interaction of smoking, other environmental pollutants, infections and, less certainly, eosinophilic bronchial inflammation. Recent studies, however, have suggested that these factors should be investigated at the onset of disease in order to improve the efficacy of interventions on clinical course. Such an approach is justified because it is likely that we have overemphasized the study and treatment of advanced stages of COPD. The problem of a large and growing number of patients with COPD has been linked to two factors: *a*) that the onset of disease is insidious and the morbidity of the condition is clearly underestimated by the patient, such that the specialist is consulted late, and *b*) that physicians—particularly those in primary care—are insufficiently aware of the epidemiology of the problem. When proactive programs to detect COPD are set in motion, the results never cease to amaze us. A recent study, for example, found that up to 22% of unsuspected COPD cases were diagnosed through a primary care screening program.¹ Moreover, the future offers little hope, given that COPD, now the sixth cause of death worldwide, is expected to become the second by 2020.² Such predictions require us to reconsider whether or not we are making sufficient effort to investigate the stage of COPD that comes before the development of CAL.

COPD manifests itself many years before the onset of CAL, during a “nondiagnostic” period of spirometry, and although smoking is nearly always in the background, it is also sure that certain very effective accomplices cooperate in the development of CAL. A change in our approach to COPD, similar to the change in attitude toward asthma, now conceives it to be a disease of airway and parenchymal inflammation that damages bronchial and pulmonary structures, causes anomalous remodeling and leads to progressive loss of

lung function long before it is detected spirometrically. The reason for criticizing the exclusively functional view we have taken until now is that the disease is already well established when spirometry detects CAL according to accepted criteria. This is to say, by the time airway–parenchymal inflammation has left its mark, the inflammatory process may already be irreparable even if smoking stops.³ From this perspective, we derive the need to review inflammatory events during the spirometrically “silent” phase, which is to say, we feel the need to know more about how ventilatory function parameters correlate with patient symptoms and particularly with underlying inflammatory airways disease (IAD) when patients are not yet ill (forced expiratory volume in one second [FEV₁] > 80% and the ratio FEV₁/forced vital capacity [FVC] > 70%). What usually happens during the period before spirometric change is that the patient is said to have chronic smoker’s bronchitis, a diagnosis that perhaps lacks specificity. The patient, in turn, blames smoking as the overall cause of symptoms and does not consider continuing to work with his or her physician, or possibly the physician might prescribe antibiotics or a mucolytic agent. Paradoxically, placing too much emphasis on smoking gives rise to failure to prevent rapid deterioration of lung function, which develops only in some smokers.

If there is a need for a description of underlying IAD in the smoker, a parallel example is asthma, where there are 3 stages in the progression of disease: subclinical IAD, symptomatic IAD, and finally lung function involvement.^{4,5} A single instance of spirometric findings within the normal range in a smoker gives, therefore, insufficient information. It would be more useful to know the rate of FEV₁ decline in that patient, and we should therefore give close attention to epidemiological studies that analyze the reasons for such loss in smokers in order to apply the findings in clinical practice.

We know that only one of every 5 or 6 smokers is susceptible to the development of COPD, meaning that over the years CAL will make its appearance as a result of excessive decline in FEV₁. The annual decline is approximately 90 mL for a smoker and 20 mL for a nonsmoker. Nevertheless, many years ago Burrows et

Correspondence: Dr. A. Pacheco Galván.
Servicio de Neumología. Hospital Ramón y Cajal.
Ctra. Colmenar, km 9. 28034 Madrid. Spain.
E-mail: apacheco@separ.es

Manuscript received December 9, 2002.
Accepted for publication February 2, 2003.

al⁶ used regression modelling to establish that smoking predicts only 15% of the variability in FEV₁ deterioration. Other additional risk factors must therefore be explored. Besides poor lung function due to childhood bronchial infections and to the rare presence of α_1 -antitrypsin deficit, FEV₁ deterioration in smokers may be linked to asthma⁷ — or more specifically to bronchial hyperreactivity and airway inflammation. Three epidemiological studies published in recent years allow us to be certain that the asthmatic will develop irreversible CAL when smoking is an additional risk factor. Apostol et al⁸ analyzed FEV₁ decline in 4000 individuals, concluding that a pathological reduction in FEV₁ was reached in 17.8% of smoker asthmatics but only in 8.5% of nonsmoker asthmatics. A synergistic effect of smoking on asthma also emerged in the Copenhagen City Heart Study,⁹ which followed 17 000 subjects for 18 years. The mean FEV₁ for 60-year-old smokers without asthma was 3.05 L—higher than the mean of 1.99 L for asthmatics of equal age and height who did not smoke. Finally, Tracey et al¹⁰ reported that atopy and bronchial hyperreactivity were significant predictors of FEV₁ decline in smokers over 65 years old. From these studies we can infer that there is a striking synergistic effect between the inflammation associated with asthma and the inflammation caused by smoking, and we must not fail to take it into consideration when examining an individual patient. These studies are consistent with the Dutch hypothesis concerning chronic obstruction of airways, specifically that there is a common origin for asthma and COPD related initially to allergic sensitization and bronchial hyperreactivity and then to a set of variables, including smoking, that eventually lead to distinct CAL phenotypes.

For many years we have known that smoking first causes permanent bronchiolar IAD without tissue destruction or fibrosis, and we therefore assume that IAD is potentially reversible. But is the IAD of smokers who develop CAL different from that of smokers who do not? Smokers who develop COPD have greater inflammation and fibrosis in addition to smooth muscle hypertrophy, and inflammation can be progressive. Neutrophils are present in the bronchial lumen of patients with COPD and a greater number of CD8 lymphocytes are present in the bronchial wall of smokers who develop COPD than of smokers who do not.¹¹ Nevertheless, other tissue studies have shown that CAL is associated with the presence of active submucosal eosinophils in the large bronchi of smokers but not of nonsmokers with CAL.¹² The number of eosinophils is also known to increase during exacerbations of chronic bronchitis and the increase has recently been related to the presence of eosinophil chemoattractants (RANTES), although we do not know whether the increase persists in the postacute phase.¹³ In fact, the known efficacy of corticosteroids

against the re-exacerbation of COPD may be due to the predominance of airway eosinophilia in the pattern of bronchial inflammation.¹¹ More and more studies are calling into question the rigid distinctions between COPD and asthma from the vantage of IAD, and entities considered “bridges” between COPD and asthma are being described with extraordinary frequency: eosinophilia in COPD, COPD with mastocytosis of the bronchial mucosa, asthma with neutrophil predominance, bronchitis with eosinophilia, and more. Some authors advocate that CAL be considered a syndrome or the end result of a wide range of conditions, encompassing such entities as extrinsic juvenile asthma and smoker’s emphysema, that lead to permanent airway obstruction.

A study of the onset of chronic bronchitis published over 10 years ago warned of greater FEV₁ decline in the presence of eosinophilia and encouraged early treatment with steroids based on their potential ability to slow down the rate of deterioration.¹⁴ The most important progress in analyzing IAD has come with the availability of induced sputum, a reliable, reproducible sampling technique for analyzing IAD *in situ* rather than indirectly in circulating blood. By using sputum induction researchers have been able to describe such processes as eosinophilic bronchitis, an eosinophilic inflammation of the airway in which sputum eosinophil counts exceed 2% before spirometric abnormalities or bronchial hyperreactivity can be detected. Very little is known about the true prevalence of early inflammatory airway eosinophilia, but research in this area may be crucial—particularly in smokers given that their inflammation might be reversible with antiinflammatory treatment. Rather than insisting on the simplistic position that smokers have COPD because they smoke, research is trying to determine relevant additional characteristics of specific smokers by analyzing early IAD more carefully while we wait a few years for genetic analysis to tell us definitively whether or not certain smokers are susceptible to accelerated loss of FEV₁.

The old concept of chronic bronchitis as cough and/or expectoration lasting longer than 3 months for 2 consecutive years does little to help us distinguish chronic bronchitis from the initial stages of asthma. Nevertheless, that definition is still widely subscribed, leading to disagreement when its application discourages further enquiry, as both physician and patient blame smoking for all symptoms. Studies of symptoms that distinguish chronic bronchitis from asthma have confirmed variations in the credibility of established diagnoses. León Fábregas et al,¹⁵ for example, demonstrated the utility of the International Union against Tuberculosis and Lung Disease respiratory symptom questionnaire, which led to correct diagnosis of 91% of chronic bronchitis patients and asthmatics. In Holland, Thiadens et al¹⁶ analyzed 80 subjects with chronic bronchitis symptoms evaluated by questionnaires, spirometry and methacholine challenge

testing, finding that 36.9% were in fact asthmatics. Turner-Warwick and Openshaw¹⁷ asserted that a history of chronic expectoration does not rule out a diagnosis of asthma given that 43% of their asthmatic patients also met the diagnostic criteria for chronic bronchitis. The reason for such disagreement may be inconsistency in diagnosing asthma, especially when onset is late, and also the confounding of symptoms in asthmatics who smoke. An expert panel convened by the US National Asthma Education and Prevention Program¹⁸ issued guidelines stating that asthma should also be suspected in the presence of the following signs and symptoms: cough, expectoration, wheezing, chest tightness, or dyspnea. The Normative Aging Study of 1995 established that individuals with chronic respiratory complaints such as asthma, wheezing, dyspnea, chronic cough, and sputum production had greater bronchial hyperreactivity and higher circulating eosinophil counts than a control group without such complaints, once the data had been adjusted for age and smoking.¹⁹ It is therefore quite possible that the adult asthmatic with eosinophilic bronchial inflammation might suffer all symptoms of chronic bronchitis and continue smoking, defying the general opinion that asthmatics smoke less (although this may in fact occur in extrinsic juvenile asthma). Very few studies have enrolled smokers in groups of asthmatics for fear of confusing asthma with COPD, and as a result the mystery still surrounds the coexistence of smoking-related IAD alongside IAD mediated by eosinophilic inflammation. When studies have looked at CAL without specifying whether it arises from chronic bronchitis or asthma, however, they have demonstrated that prolonged sputum production and occasional wheezing have proven to be signs of inflammatory response of mucosa in smokers and such response may become bronchial hyperreactivity or eosinophilia in blood or sputum, and that both signs point to eosinophilic inflammation of the bronchial mucosa.^{4,19-21} It may be that the trees (cigarette smoke) obscure our view of the forest (the full range of inflammatory response).

Eosinophilic bronchitis, which is being reported more often since the advent of induced sputum in clinical practice, is present in over 20% of patients with chronic cough, with cough variant asthma (chronic bronchitis but with bronchial hyperreactivity), and with respiratory symptoms but no functional changes, and even in those with gastroesophageal reflux.²² Diagnosing eosinophilic bronchitis is important because it can progress to irreversible CAL and because it can be effectively treated with inhaled corticosteroids.²³ This clinical entity, which is clearly also associated with asthma, has been demonstrated in preasthmatic states (subclinical IAD) and, according to a recent study, is clearly pathogenic given that treatment with beclomethasone lasting 3 months was unable to prevent progression to

asthma in 13% after one year.⁵ Early IAD has been studied less intensely in COPD than in asthma. Linden et al²⁴ demonstrated more neutrophil and eosinophil derived markers in bronchial lavage fluids of chronic bronchitis patients who were smokers without CAL than in lavage fluid from chronic bronchitis patients with CAL. Furthermore, patients with chronic bronchitis who have already developed COPD are known to have two types of IAD that are becoming more and more distinguishable: neutrophilic and eosinophilic COPD. Airway neutrophilia is more evident in severe COPD.¹¹ Chanez et al,²⁵ however, studying smokers with CAL but no signs of asthma and negative bronchodilator tests, reported that up to 50% of their patients had higher eosinophil counts and cationic protein levels in bronchoalveolar lavage fluid and that they therefore responded in the steroid trial. Pizzichini et al²⁶ also reported that induced sputum tests showed signs of chronic eosinophilic inflammation in over 40% of patients with COPD.

Bronchial hyperreactivity in turn seems to take on the role of main indicator of IAD in asthma and very probably in chronic bronchitis, given that it must be considered the sign that accompanies respiratory symptoms. Triggers of bronchial hyperreactivity have been classified as provocative factors and allergens. Depending on the degree of underlying hyperreactivity, provocative factors may cause different degrees of acute reversible obstruction, mainly by bronchospasm (eg, smoke inhalation, pharmacological agents or cold air). Allergens, on the other hand, cause hyperreactivity by way of an inflammatory process (viral infection, allergen inhalation, low molecular weight sensitizers, and ozone). It is unknown whether tobacco smoke can cause bronchial hyperreactivity through the presence of an allergen in smoke to which only certain individuals would be susceptible. If such is the case, they would in fact be "atypical atopic" smokers, if that expression can be used. Consistent with this interpretation, a curious study from Japan reported the possibility that tobacco smoke can induce acute eosinophilic IAD (eosinophilic pneumonia) in smokers, demonstrated by a tobacco smoke provocation test and by a positive test of lymphocytic stimulation by cigarette extracts.²⁷

As early as 1976, Barter and Campbell²⁸ demonstrated that smokers who had a positive methacholine challenge test suffered greater FEV₁ decline over the years than did those whose tests were negative. Many later studies that have also traced the parallel evolution of bronchial hyperreactivity and spirometry have similarly found a significant correlation not only of bronchial hyperreactivity with FEV₁ decline but also with respiratory symptoms of all types (cough, dyspnea, expectoration, chest tightness, wheezing, etc).^{20,21}

After examining the evidence discussed here, we can agree that smoking is the main risk factor for

developing scarcely reversible CAL. Nevertheless, we must ask whether it is enough for us to act only to encourage the patient to quit smoking to keep airway inflammation from progressing beyond its early stages. That has been assumed to be the case since the well-known, and recently reaffirmed, epidemiological study of Anthonisen et al²⁹ related smoking and CAL. However, the unanswered question would be whether all smokers have the same IAD. I will conclude with two assertions: *a*) it may be useful to perform a broad study using induced sputum and bronchial hyperreactivity testing of smokers with chronic respiratory symptoms and spirometry within the normal range, because it may be possible to achieve early identification of high-risk patients who are responsive to antiinflammatory treatment, further justifying, if necessary, the effective and reasoned advice to quit smoking, and *b*) now may be the moment to clear our minds of dogmas that assign a diagnosis of chronic bronchitis/COPD to a smoker with chronic symptoms, because it may be that by thinking only about the smoke we may be missing the fire. By accepting the term “chronic airflow limitation syndrome” we may open up a wider field of vision, an intellectual position that is nearly always advisable when reflecting on complex issues.

REFERENCES

- Miravittles M, Fernández I, Guerrero T, Murio C. Desarrollo y resultados de un programa de cribado de la EPOC en atención primaria. *El Proyecto PADOE*. *Arch Bronconeumol* 2000;36:500-5.
- Murray CJ, López AD. Alternative projection of mortality by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.
- Shapiro SD. End-stage chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:339-40.
- Hahtela T. The importance of inflammation in early asthma. *Respiratory Medicine* 1987;89:461-2.
- Ryttilä P, Metso T, Heikkinen K, Saarelainen P, Helenius IJ, Hahtela T. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. *Eur Respir J* 2000;16: 824-30.
- Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. *Am Rev Respir Dis* 1977;115:195-205.
- O'Byrne PM, Postma DS. The many faces of airway inflammation. *Am J Respir Crit Care Med* 1994;159:S41-S66.
- Apostol GC, Jacobs DR, Tsai AW, Crow RS, Williams D, Townsend MC, et al. Early life factors contribute to the decrease in lung function between ages 18 and 40. *Am J Respir Crit Care Med* 2002;166:166-72.
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilation function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
- Tracey M, Villar A, Dow L, Coggon D, Lampe FC, Holgate ST. The influence of increased bronchial responsiveness, atopy and serum IgE on decline in FEV₁. A longitudinal study in the elderly. *Am J Respir Crit Care Med* 1995;151:656-62.
- Saetta M. Airway inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;160:S17-S20.
- Lams BEA, Sousa AR, Rees PJ, Lee TH. Subepithelial immunopathology of the airways in smokers with and without chronic obstructive pulmonary disease. *Eur Respir J* 2000;15:512-6.
- Zhu J, Quiu YS, Majumdar S, Gambale E, Matin D, Turato G, et al. Exacerbations of bronchitis: bronchial eosinophilia and gene expression for IL-4, IL-5, and eosinophil chemoattractants. *Am J Respir Crit Care Med* 2001;164:109-16.
- Lebowitz MD, Postma DS, Burrows B. Adverse effects of eosinophils and smoking on the natural history of newly diagnosed chronic bronchitis. *Chest* 1995;108:55-61.
- León Fábregas M, De Diego Damiá A, Perpiñá Tordera M. Utilidad del cuestionario de síntomas respiratorios IAUFLD para el diagnóstico diferencial del asma bronquial y la bronquitis crónica. *Arch Bronconeumol* 2000;36:441-9.
- Thiaden HA, Postma DS, De Bock GH, Huysman DA, Van Houwelingen HC, Springer MP. Asthma in adult patients presenting with symptoms of acute bronchitis in general practice. *Scand J Prim Health Care* 2000;18:188-92.
- Turner-Warwick M, Openshaw P. Sputum in asthma. *Postgrad Med J* 1987;63(Suppl 1):79-82.
- US Department of Health and Human Services, Public Health Service, National Heart Lung and Blood Institute. Expert Panel Report II: guidelines for the diagnosis and management of asthma. Bethesda (Maryland): NIH Publication no. 97.4051, 1997.
- Annema JT, Sparrow D, O'Connor GT, Rijcken B, Koeter GH, Postma DS, et al. Chronic respiratory symptoms and airway responsiveness to methacholine are associated with eosinophilia in older men: The Normative Aging Study. *Eur Respir J* 1995;8:62-9.
- Hospers JJ, Postma DS, Rijcken B, Weiss ST, Schouten JP. Histamine airway hyperresponsiveness and mortality from chronic obstructive pulmonary disease: a cohort study. *Lancet* 2000;356: 1313-7.
- Nagai A, Thurlbeck WM, Cono K. Responsiveness and variability of airflow obstruction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:635-9.
- Gibson PG, Fugimura M, Niimi A. Eosinophilic bronchitis: clinical manifestations and implications for treatment. *Thorax* 2000; 57:178-82.
- Brightling CE, Woltman G, Wardlaw AJ, Pavord ID. The development of irreversible airflow obstruction in a patient with eosinophilic bronchitis without asthma. *Eur Respir J* 1999;14:1228-30.
- Linden M, Rasmussen JB, Piitulainen E, Tunek A, Larson M, Tegner H, et al. Airway inflammation in smokers with nonobstructive and obstructive chronic bronchitis. *Am Rev Respir Dis* 1993;148: 1226-32.
- Chanez P, Vignola AM, O'Shaughnessy T, Enander I, Li D, Jeffery PK, et al. Corticosteroid reversibility in COPD is related to features of asthma. *Am J Respir Crit Care Med* 1997;155:1529-34.
- Pizzichini E, Pizzichini MMM, Gibson P, Parameswaran K, Gleich GJ, Berman L, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1998;158:1511-7.
- Matsui S, Yamashita N, Maruyama M, Araya J, Oda H, Fujita T, et al. Acute eosinophilic pneumonia induced by cigarette smoking: positive lymphocyte stimulation test of a cigarette extract. *Nihon-Kokyu-Gakkai-Zasshi* 2000;38:807-11.
- Barter CE, Campbell AH. Relationship of constitutional factors and cigarette smoking to decrease in one-second expiratory volume. *Am Rev Respir Dis* 1976;113:305-14.
- Anthonisen NR, Connett JE, Murria RP. Smoking and lung function of lung health study participants after 11 years. *Am J Respir Crit Care Med* 2002;166:675-9.