## Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts

*To the Editor*:

Reduction of the future risk of exacerbations represents one of the major aims in the management of chronic obstructive pulmonary disease (COPD) (1). Although inhaled corticosteroids (ICSs) are commonly prescribed to prevent these disadvantageous events, nonresponse is common and ICS therapy is associated with substantial side effects, including increased risk of pneumonia (2) and fractures. Thus, there is a great interest in defining the COPD population most likely to benefit from ICS treatment (3). Peripheral blood eosinophil counts are increasingly recognized as a biomarker for a beneficial response to ICSs in COPD, although most of the current knowledge is derived from *post hoc* analyses of clinical trials and retrospective explorations (4). Little is known about the long-term stability of blood eosinophils in COPD and the impact of sex, age, smoking, and baseline eosinophil counts. Also, it remains unknown whether the trajectory of blood eosinophils differs between patients with COPD and control subjects without COPD. Therefore, the aims of this study were to determine the stability of blood eosinophil counts over time in patients with COPD and control subjects without COPD derived from the general population and to examine the impact of sex, age, smoking status, and eosinophil counts at baseline on eosinophil stability.

Data obtained from the Clinical Practice Research Datalink were analyzed. The study population consisted of all individuals aged 40 years and older with a diagnosis of COPD recorded by a read code during the period of data collection (January 1, 2005, to January 31, 2015). Each patient with COPD was matched with up to two control subjects without COPD by sex, year of birth, and medical practice. Patients were monitored from the date of the first blood eosinophil count up to the last valid eosinophil count during the period of data collection. Only patients with at least two blood eosinophil counts on different dates were included. Subjects with a history of asthma or a COPD exacerbation within 30 days of the start of follow-up were excluded. All subjects using maintenance systemic corticosteroid therapy 30 days before the start of follow-up, irrespective of the medical indication, were excluded in the sensitivity analysis.

The primary outcome of interest was stability of blood eosinophils, defined as blood eosinophil count, which persistently remained less than $0.34 \times 10^9$ cells/L or at least $0.34 \times 10^9$ cells/L throughout follow-up (5). Blood eosinophil counts that did not persistently remain less than $0.34 \times 10^9$ cells/L or at least $0.34 \times 10^9$ cells/L during follow-up were considered unstable. The use of absolute blood eosinophil counts has been found to be more reliable compared with the use of cutoffs expressed as a percentage of total leukocyte count (6).

Kaplan–Meier survival curves were plotted to describe the stability of eosinophil count for patients with COPD and matched control subjects (using the LIFETEST procedure, SAS 9.4; SAS Institute, Cary, NC). All patients were categorized according to eosinophil count at baseline ($<0.34 \times 10^9$ or $\geq 0.34 \times 10^9$ cells/L), age (40–59, 60–79, and $\geq$80 yr), sex, and smoking status (current smoking, "yes" or "no").

From the inception cohort of 677,147 subjects, 226,352 had a read code of COPD and were matched with 450,795 control subjects without COPD. A total of 39,824 patients with COPD and 90,772 control subjects without COPD met the various inclusion criteria for this study population. Baseline characteristics are

**Table 1.** Baseline Characteristics of Patients with COPD and Control Subjects without COPD

| Characteristic | Patients with COPD (*n = 39,824*) | Non-COPD Control Subjects (*n = 90,772*) |
|---|---|---|
| Follow-up time, yr, mean (SD) | 3.0 (2.3) | 2.9 (2.1) |
| Number of females, n (%) | 18,284 (45.9) | 44,468 (48.9) |
| Age, yr, mean (SD) | 69.4 (10.6) | 69.9 (10.6) |
| Age category, n (%) | | |
| 40–59 yr | 7,159 (18.0) | 15,001 (16.5) |
| 60–79 yr | 25,358 (63.7) | 57,899 (63.8) |
| ≥80 yr | 7,307 (18.3) | 17,872 (19.7) |
| Index blood eosinophil count | | |
| Absolute, $\times 10^9$ cells/L, mean (SD) | 0.23 (0.26) | 0.21 (0.35) |
| Percentage, mean (SD) | 3.0 (3.2) | 2.9 (3.0) |
| Index blood eosinophil count category, n (%) | | |
| Low (<2.0%) | 14,492 (36.4) | 33,486 (36.9) |
| Moderate (2.0–3.9%) | 15,231 (38.3) | 35,755 (39.4) |
| High (4.0–5.9%) | 6,496 (16.3) | 14,644 (16.1) |
| Very high (≥6.0%) | 3,605 (9.2) | 6,887 (7.6) |
| Smoking status, n (%) | | |
| Never | 4,412 (11.1) | 46,581 (51.3) |
| Current | 16,107 (40.5) | 13,298 (14.7) |
| Former | 19,286 (48.4) | 30,849 (33.9) |
| Missing | 19 (0.05) | 44 (0.05) |
| Drug use 6 mo before, n (%) | | |
| SABAs | 22,202 (55.8) | 2,317 (2.6) |
| LABAs | 3,728 (9.4) | 181 (0.2) |
| SAMAs | 3,473 (8.7) | 275 (0.2) |
| LAMAs | 6,879 (17.3) | 193 (0.2) |
| ICSs | 11,667 (28.2) | 1,270 (1.4) |
| Xanthine derivatives | 314 (0.8) | 27 (0.0) |
| History of comorbidities, n (%) | | |
| Cardiovascular diseases | 9,397 (23.6) | 18,334 (28.5) |
| Stroke | 2,993 (7.5) | 5,720 (6.3) |
| Rheumatoid arthritis | 1,402 (3.5) | 2,434 (2.7) |
| Anxiety | 6,005 (15.1) | 11,065 (12.2) |
| Osteoporosis | 2,609 (6.6) | 4,730 (5.2) |
| Any cancer (excluding nonmelanoma skin cancer) | 6,227 (15.6) | 14,426 (15.9) |
| Chronic liver disease | 122 (0.3) | 174 (0.2) |
| Pulmonary fibrosis | 332 (0.8) | 160 (0.2) |

*Definition of abbreviations*: COPD = chronic obstructive pulmonary disease; ICSs = inhaled corticosteroids; LABAs = long-acting $\beta_2$-agonists; LAMAs = long-acting muscarinic antagonists; SABAs = short-acting $\beta_2$-agonists; SAMAs = short-acting muscarinic antagonists.

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presented in Table 1. The mean ± SD absolute eosinophil counts were $(0.23 \pm 0.26) \times 10^9$ cells/L for patients with COPD and $(0.21 \pm 0.35) \times 10^9$ cells/L for control subjects without COPD ($P < 0.001$). The prevalence of peripheral blood eosinophilia ($\geq 0.34 \times 10^9$ cells/L) was 34.9% in patients with COPD and 25.8% in control subjects without COPD ($P < 0.001$). The long-term stability of the blood eosinophil count was lower in patients with COPD versus those without COPD ($P < 0.001$) (Table 2). The stability of the blood eosinophil count was higher in patients with COPD with baseline counts less than $0.34 \times 10^9$ cells/L compared with patients with baseline counts of at least $0.34 \times 10^9$ cells/L. In addition, the stability of blood eosinophils in COPD was highest in individuals aged 40–59 years and decreased with increasing age in both study groups. In both patients with COPD and control subjects without COPD, females had significantly higher stability in blood eosinophil counts compared with males ($P < 0.001$). There was no difference in stability between current smokers and nonsmokers among patients with COPD. In control subjects without COPD, stability was higher in nonsmokers compared with smokers.

**Table 2.** Proportion of Patients with COPD and Control Subjects without COPD with Stable Eosinophil Counts Stratified by Sex, Age, Eosinophil Counts, and Smoking Status at Various Time Points

| | Proportion with Stable Eosinophil Counts at Time Point (%) | | | | | | |
|---|---|---|---|---|---|---|---|
| | 6 mo | 9 mo | 1 yr | 2 yr | 4 yr | 6 yr | 8 yr |
| Patients with COPD | 85 | 82 | 75 | 62 | 49 | 42 | 35 |
| Absolute blood eosinophil count | | | | | | | |
| $<0.34 \times 10^9$, cells/L | 95 | 93 | 90 | 86 | 80 | 77 | 75 |
| $\geq 0.34 \times 10^9$, cells/L | 80 | 70 | 63 | 45 | 30 | 23 | 18 |
| Age | | | | | | | |
| 40–59 yr | 95 | 93 | 85 | 83 | 76 | 71 | 67 |
| 60–79 yr | 93 | 90 | 80 | 79 | 70 | 65 | 60 |
| ≥80 yr | 91 | 89 | 77 | 73 | 66 | 61 | 58 |
| Sex | | | | | | | |
| Female | 94 | 92 | 89 | 81 | 75 | 70 | 68 |
| Male | 92 | 89 | 85 | 75 | 65 | 61 | 57 |
| Smoking status | | | | | | | |
| Yes | 95 | 90 | 88 | 81 | 72 | 69 | 62 |
| No | 95 | 90 | 88 | 79 | 72 | 69 | 62 |
| Non-COPD control subjects | 96 | 93 | 91 | 85 | 77 | 73 | 69 |
| Absolute blood eosinophil count | | | | | | | |
| $<0.34 \times 10^9$, cells/L | 97 | 95 | 94 | 90 | 85 | 79 | 77 |
| $\geq 0.34 \times 10^9$, cells/L | 83 | 75 | 79 | 50 | 33 | 23 | 19 |
| Age | | | | | | | |
| 40–59 yr | 97 | 95 | 92 | 88 | 82 | 78 | 75 |
| 60–79 yr | 96 | 94 | 91 | 85 | 77 | 71 | 69 |
| ≥80 yr | 94 | 91 | 88 | 81 | 73 | 68 | 65 |
| Sex | | | | | | | |
| Female | 97 | 95 | 93 | 89 | 81 | 77 | 73 |
| Male | 95 | 92 | 90 | 83 | 73 | 68 | 64 |
| Smoking status | | | | | | | |
| Yes | 93 | 91 | 89 | 83 | 73 | 68 | 65 |
| No | 95 | 93 | 91 | 88 | 80 | 74 | 71 |

*Definition of abbreviation*: COPD = chronic obstructive pulmonary disease.

This is the first population-based study that showed that the stability of peripheral blood eosinophil counts was significantly lower in patients with COPD compared with control subjects without COPD. In patients with COPD the stability was approximately 85% at 6 months, 62% at 2 years of follow-up, and declined progressively thereafter. This decreased stability might be related to fluctuations in disease stability or adaptations in pharmacologic COPD management during the follow-up, which was obviously not present in control subjects without COPD. However, Kreindler and colleagues (7) showed that inhaled corticosteroids had only limited effect on peripheral blood eosinophil counts and did not affect patient stratification when using cutoffs for eosinophils. The impact of oral courses of corticosteroids remains currently unknown. Second, this study indicated that stability of blood eosinophil counts was higher in patients with COPD with a baseline eosinophil count less than $0.34 \times 10^9$ cells/L. It was previously reported that patients with higher blood eosinophil counts have more exacerbations (5), which may have implications for the stability of eosinophil levels in COPD in this study. The present study revealed a significant impact of age and sex on peripheral blood eosinophil stability, which has implications for the use of eosinophils as a biomarker in regular COPD management and pharmacologic studies, including the frequency of reassessment. Although more data are warranted, age-related changes in eosinophil function were previously reported (8). The current analyses showed that smoking status had no impact on the stability of blood eosinophils in COPD, although it was previously shown that the percentage of current smokers is lower among patients with relative eosinophilia (9). Finally, the results indicate that the prevalence of peripheral blood eosinophilia is increased in patients with COPD compared with control subjects without COPD, suggesting that eosinophilia is at least partially disease related. These data extend our understanding of blood eosinophils as a potential biomarker in COPD; in addition, this is the largest study to date investigating the stability of blood eosinophilia over time. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Transpulmonary Pressure Meaning: Babel or Conceptual Evolution?

*To the Editor*:

Loring and colleagues (1) propose to reintroduce terms such as airway opening pressure (Pao), alveolar pressure (Palv), pleural pressure (Ppl) (site-specific), and lung recoil elastic pressure (Pel[L]) and to define transpulmonary pressure ($P_L$) as the difference between Pao and Ppl, according to the terminology developed by nonclinician physiologists.

In distinction from classic physiology, respiratory intensive care is oriented toward the mechanically ventilated patient, obligating early intensivists to invent a new terminology. Indeed, although Pao just refers to the pressure at the airways, the terms peak pressure (dynamic plus static), plateau pressure (Pplat), and positive end-expiratory pressure (PEEP; static pressure at zero flow) define key moments of the respiratory cycle, allowing an easy computation of airway resistance and driving pressure. Obviously, beyond intrapulmonary airway obstruction/closure, as indicated by Loring and colleagues (1), other phenomena make Pplat not necessarily identical to the pressure in all alveolar units:

1. Units flooded, consolidated, or collapsed are not distended by gas pressure. In this condition, even the "recoil pressure" is a physiological abstraction instead of a reality.
2. The end-inspiratory airway pressure at zero flow decreases with time, a basis for estimating "tissue resistance" (2).
3. If enough time is allowed for static measurements, even the difference between $O_2$ uptake and $CO_2$ output may slightly influence the Pplat (3).