

Exhaled Breath Temperature Is Not Helpful for Identifying Cellular Bronchitis in Severe Asthma

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To the Editor:

Sputum cytometry is a reliable method for assessing the luminal cellular inflammatory component associated with asthma and other airway diseases [1]. Increased mucosal vascularity associated with inflamed airways can raise airway temperatures, and, therefore, exhaled breath temperature (EBT) has been suggested as an easy method for assessing the presence of airway inflammation [2]. However, results are conflicting. Breath temperature is reported to increase faster during single breath exhalation in asthma patients than in healthy individuals [3], and a plateau temperature in a small group of asthma patients during tidal exhalation using a commercially available device (X-halo, Delmedica) was observed to be higher than in the controls, while anti-inflammatory treatment significantly improved their spirometry values [4]. In contrast, Lessmann et al [5] found no such differences or any association with other markers of inflammation (eg, fraction of exhaled nitric oxide [FeNO] or with differential cell percentage in sputum). We wished to extend this study by examining plateau EBT and its relationship with sputum cellularity in patients with severe asthma, including those who had additional comorbid conditions, such as chronic airflow limitation or eosinophilic granulomatosis and polyangiitis (EGPA) without a vasculitic component.

We recruited 70 individuals (61 asthma patients, 9 healthy controls) to this cross-sectional observational study (Table). Of

these, 53 had severe asthma alone, 4 had asthma and associated chronic airflow limitation, and 4 had EGPA (Table). Asthma patients had eosinophilic bronchitis (EB), defined as sputum eosinophilia (>2%), neutrophilic bronchitis (NB), defined as sputum neutrophilia (>65% and raised total cell count of >10 × 10⁶/g), mixed bronchitis, defined as sputum eosinophilia and neutrophilia, and pauci-granulocytic bronchitis, defined as a normal sputum cell count [1]. Nine healthy never smokers served as controls. Asthma control (ACQ-5), clinical stability, spirometry, and demographics were assessed. EBT was measured [4] using an X-halo breath thermometer. All participants fasted for at least 1 hour prior to the start of the test, and no strenuous or moderate physical activity was permitted. Environmental temperature was measured using an electronic thermometer, and body temperature was measured orally with an electronic thermometer. Sputum was induced and quantitative cytometry performed [1]. FeNO was measured using the Niox Vero device (Circassia). Quantitative variables were expressed as mean (SD), after determining the normality of the distribution using the Shapiro-Wilk test. Qualitative variables were expressed as absolute and relative frequencies. Subgroups were compared using an ANOVA test (comparison of the different diagnoses and sputum cytometry-based endotypes), the *t* test (comparison of the reference or control subgroup or population [controls] with each of the other subpopulations), and the χ^2 test or Fisher exact test. The correlation between EBT and FeNO or FEV₁ was analyzed using the Pearson correlation coefficient (ρ). All statistical analyses were performed using SAS, Version 9.4 of the SAS System for Windows. An α level of .05 was considered significant in all statistical procedures. Our Institutional Review Board approved the study, and participants provided their written informed consent.

There were no statistical differences between the EBT of the asthma patients (mean, 34.3 [0.7] °C) and that of the control group (mean, 34.4 [0.4] °C) ($P=.89$), after adjustment for ambient and core temperatures. Similarly, there were no statistical differences between the EBT associated with various sputum cytometry-based endotypes and the healthy group as follows: EB (mean, 34.2 [0.7] °C) ($P=.76$), NB (mean, 34.6 [0.2] °C) ($P=.37$), mixed (mean, 34.8 [0.4] °C) ($P=.07$), PG (mean, 34.3 [0.9] °C) ($P=.75$), and healthy (mean 34.4°C,[0.4]) ($P=.43$). No correlation was established between EBT and the cell differential percentage, FeNO, or FEV₁ (%) (Supplementary Figure 1). No difference was found between the EBT of asthma patients who were stable ($n=39$) (mean, 34.3 [0.6]) and that of those whose condition worsened ($n=20$) (mean, 34.4 [0.7]) ($P=.43$). Finally, no statistically significant differences were found between the mean EBT of patients with severe asthma alone (34.3 [0.7]) and that of patients with associated comorbid conditions (34.3 [0.9]) ($P=.4$).

Table. Demographics of the Study Population.

Disease		Asthma	Asthma+comorbidities (COPD+EGPA)	Controls
		n=53	n=8	n=9
Male, No. (%)		27 (50.9)	3 (37.5)	4 (44.5)
Age		54.4 (13.1)	63.5 (15.1)	29.4 (2.1)
Atopy, No. (%)		34 (68)	4 (57.1)	3 (37.5)
Sputum cytometry-based endotypes, No. (%)	EB	24 (45.3)	3 (37.5)	0 (0)
	NB	8 (15.1)	1 (12.5)	0 (0)
	Mixed (EB+NB)	4 (7.6)	0 (0)	0 (0)
	PG	10 (18.9)	3 (37.5)	0 (0)
	NPS	7 (13.2)	1 (12.5)	1 (11.1)
	Healthy	0 (0)	0 (0)	8 (88.9)
Patients with exacerbations, No. (%)		16 (31.4)	4 (50)	0 (0)
Mean (SD) ACQ5		2.6 (1.6)	1.7 (1.4)	0 (0)
Mean (SD) FeNO, ppb		44 (36.9)	31.9 (22.5)	16 (8)
Mean (SD) FEV ₁ , L		1.98 (0.7)	1.56 (0.4)	3.76 (0.8)
Mean (SD) FEV ₁ , %		66 (0.2)	61 (0.2)	100 (0.1)
Mean (SD) initial room temperature, °C		24.5 (1.2)	25.7 (2.2)	24.2 (1.6)
Mean (SD) EBT, °C		34.3 (0.7)	34.3 (0.9)	34.4 (0.4)
Mean (SD) initial body temperature, °C		36.6 (0.4)	35.9 (1.5)	36.5 (0.4)
ICS, No. (%)		46 (86.8)	8 (100)	0 (0)
Mean (SD) ICS dose, µg		1,286.8 (860.9)	725 (620.5)	0 (0)

Abbreviations: ACQ5, Asthma Control Questionnaire; COPD, chronic obstructive pulmonary disease; EB, eosinophilic bronchitis; EBT, exhaled breath temperature; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in the first second; ICS, inhaled corticosteroids; NB, neutrophilic bronchitis; NPS, nonprocessable sputum; PG, pauci-granulocytic.

Bronchial temperature is determined by the ratio of the thermal energy of the blood flowing along the vascular network of the alveoli to the alveolar gas content. It was recently hypothesized that EBT reflects causes that would modify blood flow within the airway walls, as blood is a carrier of thermal energy and, subsequently, of bronchial inflammation. However, contrary to previous observations by Popov et al [4] and Garcia et al [6], who had observed higher EBT in asthma patients than in nonasthma patients, and consistent with the observations of Lessmann et al [5], we did not find a higher EBT in patients with severe asthma (including those with comorbid airflow limitation, severe eosinophilia, and sinus disease and receiving high doses of corticosteroids) than in nonasthma controls. Similarly, it was not associated with a direct measurement of luminal inflammation (ie, sputum cell counts) or indirect measurements (FeNO). Although the equipment used had been validated and reference values provided for many of the technical factors that could potentially influence EBT, other factors may not have been controlled for [7]. This is the first study to examine EBT in patients with severe asthma and different sputum cytometry-based endotypes who are most likely to benefit from monitoring biomarkers such as

EBT. In summary, although our relatively small study of 70 persons might have been underpowered to identify subtle quantitative differences between subgroups, we do not believe that EBT measurement would help to guide anti-inflammatory treatment in patients with severe asthma.

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Conflicts of Interest

Dr. Moya is an investigator for AstraZeneca and Sanofi Genzyme. During the past 3 years, Dr. Nair reports the following: grants and personal fees from AstraZeneca, Teva, Sanofi, and Genentech; grants from Cyclomedica, Equillium, Methaphram, and Foresee; personal fees from Arrowhead Pharma, GSK, CSL Behring, and Roche.

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