Exhaled breath temperature is not helpful to identify cellular bronchitis in severe asthma

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0862

doi: 10.18176/jiaci.0862

Key words: Exhaled breath temperature. Severe asthma. Eosinophilic bronchitis

Palabras clave: Temperatura del aliento exhalado. Asma severa. Bronquitis eosinofílica.

To the Editor,

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

We recruited 70 (61 asthmatics, 9 normal subjects) subjects to this cross-sectional observational study (Table 1). 53 had severe asthma alone, while 4 had asthma and associated chronic airflow limitation, and 4 had EGPA (Table 1). Asthmatic patients included eosinophilic bronchitis (EB) defined as sputum eosinophilia (>2%), neutrophilic bronchitis (NB) as sputum neutrophilia (>65% and raised total cell count of >10 x 10^6/g), mixed as sputum eosinophilia and neutrophilia, and pauci-granulocytic (PG) as sputum normal cell count [1]. Nine healthy, never smokers served as control subjects. Asthma control (ACQ-5), clinical stability, spirometry, and demographics were assessed. EBT was measured [4] using a breath thermometer X-halo. Prior to the start of the test, all the subjects fasted for at least 1 hour and no moderate physical activity was permitted. Also, environmental temperature was measured with an electronic thermometer and the body temperature was measured orally with an electronic thermometer. Sputum was induced and quantitative cytometry perfomed [1]. FeNO was measured using Niox Vero (Circassia, Morrisville, NC). The characteristics of the study population were summarized using mean and standard deviation (SD), after testing for normal distribution using the Shapiro-Wilk test, for quantitative variables. The qualitative variables were represented as absolute and relative frequencies. The comparisons between populations (subgroups) were made using an ANOVA test (comparison of the different Diagnosis and Sputum cytometry-based endotypes), Student's test (Comparison of the reference or control subgroup or population [control subjects] with each of the other subpopulations) and the chi-square test or Fisher's exact test. The correlation between EBT and FeNO or FEV1 were analysed using Pearson's correlation coefficient (ρ or rho). All statistical analyses were performed using SAS© software, Version 9.4 of the SAS System for Windows. A level of $\alpha = 0.05$ was considered significant in all statistical procedures. Our Institutional Review Board approved the study and participants provided written informed consent.

There were no statistical differences between the EBT of the asthmatic patients (mean 34.3ºC, SD 0.7) compared to the control group (mean 34.4ºC, SD 0.4) (p=0.89), when controlled for ambient and core temperatures. There were also no statistical differences between the EBT

doi: 10.18176/jiaci.0862

associated with various sputum cytometry-based endotypes compared to the healthy group: EB (mean 34.2ºC, SD 0.7) (p=0.76), NB (mean 34.6ºC, SD 0.2) (p=0.37), mixed (mean 34.8ºC, SD 0.4) (p=0.07) PG (mean 34.3ºC, SD 0.9) (p=0.75) and healthy (mean 34.4ºC, SD) (p=0.43). EBT was not correlated between the cell differential %, FeNO, or with FEV1 (%) (Supplementary Figure 1). No difference was found in the EBT of patients with asthma who were stable (n=39) (mean 34.3, SD 0.6) compared to those who exacerbated (n=20) (mean 34.4, SD 0.7) (p=0.43). Finally, no statistically significant differences were found in mean EBT (34.3, SD 0.7) of patients with severe asthma alone compared to those with associated co-morbid conditions (34.3, SD 0.9) (p=0.4).

Bronchial temperature is determined by the thermal energy of the blood flowing along the vascular network of the alveoli to the alveolar gas content. It has been hypothesized recently that the EBT may be reflective of 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 asthmatics compared to non-asthmatics, and consistent with the observations of Lessmann *et al.* [5], we did not find a higher EBT in severe asthmatics (including those with co-morbid airflow limitation, severe eosinophilia and sinus disease, and on high doses of glucocorticosteroids) compared to non-asthmatic controls, nor did it relate to a direct measurement of luminal inflammation (ie sputum cell counts) or indirect (FeNO). Although the equipment used had been validated and reference values provided for many of the technical factors that could potentially influence EBT, there could be other factors that may not have been controlled [7]. This is the first study to examine EBT in patients with severe asthma and different sputum cytometry-based endotypes who are the most likely to benefit by monitoring biomarkers such as EBT. In summary, although our relatively small study of 70 subjects might have been underpowered to identify subtle quantitative differences between sub-groups, we do not believe that EBT measurement would be helpful to guide anti-inflammatory treatment in patients with severe asthma.

Key Message

Exhaled breath temperature (EBT) has been hypothesized as a method to assess the presence of airway inflammation; however, the results of the current available studies are contradictory. Sputum cytometry is a reliable method to assess the cellular inflammatory component associated with asthma instead. We further analysed the exhaled breath temperature based on the sputum cellularity in patients with severe asthma. Our results revealed that EBT is not a useful measurement to guide the treatment of patients with severe asthma. These findings may lead to focus future research on new methods to assess airway inflammation based on sputum cytometry. #EBT #sputum #asthma

Acknowledgements

We acknowledge Fernando Aleman and Bhavini RajKumar for their substantional contribution to this study.

Funding

No funding was received for this study.

doi: 10.18176/jiaci.0862

Conflicts of interest

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

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doi: 10.18176/jiaci.0862

Table. Demographics of the study population.

Disease		Asthma	Asthma +co-morbidities (COPD+EGPA)	Control Subjects
		n=53	n=8	n=9
Male (n, %)		27 (50.9)	3 (37.5)	4 (44.5)
Age (mean, SD)		54.4 (13.1)	63.5 (15.1)	29.4 (2.1)
Atopy (n, %)		34 (68)	4 (57.1)	3 (37.5)
Sputum cytometry-based endotypes (n, %)	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)
Exacerbated (n, %)		16 (31.4)	4 (50)	0 (0)
ACQ 5 (mean, SD)		2.6 (1.6)	1.7 (1.4)	0 (0)
FeNO (ppb) (mean, SD)		44 (36.9)	31.9 (22.5)	16 (8)
FEV_1 (L) (mean, SD)		1.98 (0.7)	1.56 (0.4)	3.76 (0.8)
FEV_1 (%) (mean, SD)		66 (0.2)	61 (0.2)	100 (0.1)
Initial room temperature (ºC) (mean, SD)		24.5 (1.2)	25.7 (2.2)	24.2 (1.6)
EBT (ºC) (mean, SD)		34.3 (0.7)	34.3 (0.9)	34.4 (0.4)
Initial body temperature (ºC) (mean, SD)		36.6 (0.4)	35.9 (1.5)	36.5 (0.4)
ICS (n, %)		46 (86.8)	8 (100)	0 (0)
ICS dose (mcg) (mean, SD)		1,286.8 (860.9)	725 (620.5)	0 (0)

Abbreviations: COPD=chronic obstructive pulmonary disease; EGPA= eosinophilic granulomatosis with polyangiitis; SD=standard deviation; EB= Eosinophilic bronchitis; NB=Neutrophilic bronchitis; PG= pauci-granulocytic; NPS=non procesable sputum; ACQ5=asthma control questionnaire; FeNO= fractional exhaled nitric oxide; FEV1= Forced Expiratory Volume in the first second; EBT=exhaled breath temperature; ICS=inhaled corticosteroids.

doi: 10.18176/jiaci.0862