

# The Added Value of Exhaled Breath Temperature in Respiratory Medicine

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**The added value of exhaled breath temperature in respiratory medicine**Todor A. Popov<sup>1</sup>, Tanya Z. Kralimarkova<sup>1</sup>, Marina Labor<sup>2,3</sup>, Davor Plavec<sup>3,4</sup><sup>1</sup>Clinic of Allergy and Asthma, Medical University Sofia, Bulgaria<sup>2</sup>Pulmonology Department, University Hospital Center Osijek, Croatia<sup>3</sup>Faculty of Medicine, J.J. Strossmayer University, Osijek, Croatia<sup>4</sup>Research Department, Children's Hospital Srebrnjak, Zagreb, Croatia**Abstract**

Recognition of the huge economic burden chronic respiratory diseases pose for society motivated fundamental and clinical research leading to insight into the role of airway inflammation in various disease entities and their phenotypes. However, no easy, cheap and patient-friendly methods to assess it have found a place in routine clinical practice. Measurement of exhaled breath temperature (EBT) has been suggested as a non-invasive method to detect inflammatory processes in the airways as a result of increased blood flow within the airway walls. As EBT values are within a narrow range, the thermometers designed for the purpose of assessing it need to be precise and very sensitive. EBT increases linearly over the pediatric age range and seems to be influenced by gender, but not by height and body weight. In non-smoking individuals with no history of respiratory disease EBT has a natural circadian peak about noon and increases with food intake and physical exercise. When interpreting EBT in subjects with alleged airway pathology, the possibilities of tissue destruction (chronic obstructive pulmonary disease, cystic fibrosis) or excessive bronchial obstruction and air trapping (severe asthma) need to be considered, as these conditions drive (force) EBT down. A prominent advantage of the method is to assess EBT when patients are in a steady state of their disease and to use this "personal best" to monitor them and guide their treatment. Individual devices outfitted with microprocessors and memory have been created, which can be used for personalized monitoring and disease management by telemedicine.

**Index Terms:** body temperature, thermometry, exhaled breath temperature, airway inflammation, airway remodeling, daily monitoring, personalized medicine, telemedicine.

## Introduction

### Body temperature: the revival of a hot topic.

Some 200 years ago, when the less numerous human population was plagued by infectious diseases, special focus of the art of medicine involved different patterns of increased body temperature and fever, as evidenced by the monograph of Alexander Philips Wilson, which had multiple editions around the turn of the 18<sup>th</sup> century [1] (Fig. 1).

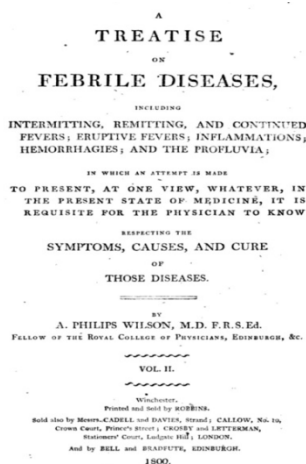


Figure 1. A.P. Wilson's "A treatise on Febrile Diseases", 1800

Since that time the control of communicable diseases has dramatically improved, but body temperature measurement has remained an integral part of routine patient examination in clinical practice. The value of 37°C is postulated to be the cut-off point between health and pathology. However, even this most conservative physiological parameter should be perceived as having individual variability, which has to be taken into account when making a judgment about measurements in the febrile range [2].

Humans are warm-blooded species (in scientific terminology "endothermic homeotherms"). Mammalian organisms need to maintain the temperature of vital organs (core body temperature) within a narrow range in order to allow essential enzymatic reactions to occur. The body heat produced as a result of metabolic processes becomes part of a thermal balance, which is regulated through radiation, conduction, convection and/or evaporation [3].

*Exhaled breath temperature in humans*

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2  
3 The blood circulation and the border surfaces with the ambient environment play a crucial  
4  
5 role in this heat exchange. Extreme exogenous and endogenous noxious influences can drive  
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7 the core body temperature beyond the narrow range of 33.2–38.2°C [4] and can have fatal  
8  
9 consequences, while modern day medicine artificially induces hyperthermia in cancer  
10  
11 treatment [5] or hypothermia to allow prolonged surgical interventions of vital organs [6].  
12  
13

14  
15 For practical purposes thermometry at traditional body sites is performed giving estimates of  
16  
17 the actual core temperature with a reasonable degree of approximation [4]. Thus, rectal temperature is  
18  
19 considered most representative of the core body temperature, but its measurement is uncomfortable for  
20  
21 patients and carries the risk of bacterial contamination. Oral temperature is generally 0.5°C lower than  
22  
23 the rectal temperature and is more prone to influences from the ambient environment, while the  
24  
25 temperature of the tympanic membrane taken by infrared tympanic thermometers was found to be  
26  
27 imprecise compared to rectal values [7].  
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30  
31 All other conditions of measurement being equal, the differences between the  
32  
33 temperature values at specific body sites are due to the influence of the “core-to-surface”  
34  
35 interface. While this may be considered a confounding factor from the viewpoint of  
36  
37 evaluation of the “true” core temperature, differences due to the core-to-surface gradient may  
38  
39 present an opportunity to obtain useful information about pathology associated with the  
40  
41 interface itself. This is particularly relevant for complex anatomical structures, such as the  
42  
43 lungs, involving vascularized tissues and a plethora of airways of different sizes with  
44  
45 hierarchical architectonics.  
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**The benefits of a ‘breath thermometer’.**

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52  
53 Perception of the airways as an interface between body core temperature and the  
54  
55 ambient environment became the rationale for attempts to measure exhaled breath  
56  
57 temperature (EBT). The deep structures of the lung typically have temperature representative  
58  
59 of the body core. Its level is determined by the blood flowing along the rich vascular network  
60

*Exhaled breath temperature in humans*

1  
2  
3 of the alveoli. During breathing, gases and thermal energy are being exchanged between the  
4  
5 inner milieu of the organism and the ambient environment. The temperature of the inhaled air  
6  
7 is tempered during its flow in and out of the branching airways, which have a separate system  
8  
9 of blood supply from the left side of the heart. As blood is the main carrier of thermal energy,  
10  
11 processes that would modify its flow within the airway walls might reflect on the temperature  
12  
13 of the outgoing air, i.e. EBT. High precision gauging devices may pick up this signal and  
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15 indicate clinical inferences.  
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**Technical aspects of EBT measurement.**

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23  
24 The first experiments assessing EBT were made in conjunction with eNO  
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26 measurement and were conducted in adults by Paredi et al. [8] and in children by Piacentini et  
27  
28 al. [9]. Both teams used fast reacting thermal sensors placed in front of the mouth of the tested  
29  
30 subjects, which recorded the rise of EBT during single breath maneuvers and used the mean  
31  
32 of three exhalation attempts. This required constant temperature of the indoor environment,  
33  
34 minimal air movement and subject training. Whilst the Paredi team considered the rate of  
35  
36 increase of EBT as indicative of asthma, the researchers in Verona carried out a series of  
37  
38 experiments demonstrating that the plateau of the exhaled temperature curve was the variable,  
39  
40 distinguishing asthmatics from healthy controls [10].  
41  
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44

45 An alternative approach for EBT measurement was introduced by Popov et al., who  
46  
47 made use of a specifically designed portable device [11]. It dwelt upon the notion of  
48  
49 accumulation of the expired thermal energy of the tested subject into an insulated vessel  
50  
51 containing a heat sink with high thermal capacity, thus making the measurement less  
52  
53 dependent on ambient factors. The subjects exhaled continuously into the thermal chamber of  
54  
55 the device until the temperature of the heat sink reached a plateau, indicating that a thermal  
56  
57 equilibrium was reached inside the closed system. Because of the easy use and acceptability  
58  
59 by the patients, the instrument allowed repeated measurements over time, with the potential  
60

1  
2  
3 of use as an individual device for measurements at home or in the working environment. Its  
4  
5 usability was further improved by upgrading the overall design, introducing electronic  
6  
7 processor and memory allowing automatic detection of the end of measurement, follow up  
8  
9 and analysis of the temperature curve on the monitor of a computer [12]. Despite these  
10  
11 technical improvements, the acquisition of measurement skills with the device, by both  
12  
13 patients and medical personnel, is essential for obtaining meaningful results. A detailed  
14  
15 description of the engineering aspects of the device and method for EBT measurement has  
16  
17 been the subject of a specialized review [13]. Further improvements of its applicability  
18  
19 involved shortening of the time for measurement and rendering it less dependent on the  
20  
21 conscientious cooperation of the subjects (this latter line of improvement would allow using  
22  
23 the device in early infancy).  
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### **Impact of ambient air temperature on EBT measurement results**

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32  
33 Even with this closed-circuit multi-breath technique, the issue of the confounding  
34  
35 influence of the characteristics of the ambient air on the end results of EBT measurement  
36  
37 remains. As can be expected, the temperature of the ambient air inhaled during the  
38  
39 measurement affects the accuracy<sup>1\*</sup>, but not the precision<sup>\*\*</sup> of the measurements. The initial  
40  
41 analysis of 132 measurements made with EBT as dependent variable and room temperature  
42  
43 (values on separate days in the range 18–25°C), atmospheric pressure (range 954–982 mbar)  
44  
45 and humidity (ranges 22–72%) as independent variables, did not detect any of the ambient  
46  
47 conditions as significant determinants, hence we recommend that the measurements are made  
48  
49 in a controlled/indoor environment with air temperatures within this range (11).  
50  
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55 In a recent real life study Carpagnano et al. measured EBT of 867 volunteers in 3  
56  
57 different outdoor and indoor (hospital and shopping mall) environments with ambient air  
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\* Accuracy = the degree of closeness of measurements of a quantity to that quantity's true value.

\*\* Precision = the degree to which repeated measurements under unchanged conditions show the same results.

*Exhaled breath temperature in humans*

1  
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3 temperature ranging from 0 to 38 °C [14]. Out of this random cohort, 298 subjects had never  
4  
5 smoked and were free of respiratory and other diseases. The regression model with their EBT  
6  
7 values as a dependent variable and the ambient air temperature as an independent one outlined  
8  
9 an association, in which the increase of external temperature by 1°C corresponded on average  
10  
11 to EBT increase of 0.19°C. For this reason it is important to measure the external temperature  
12  
13 and if necessary to apply a correction factor to the results obtained. Independent technical  
14  
15 experiments conducted by the manufacturer of X-halo arrived at the same value of this  
16  
17 conversion coefficient. More data are needed to verify whether this relationship is strictly  
18  
19 straight linear, or whether an intermediate plateau could exist at room temperature as  
20  
21 suggested in earlier studies.  
22  
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24  
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26  
27 Logie et al. demonstrated that the temperature of the inspired air affects both the slope  
28  
29 and the plateau of EBT and is a significant predictor of EBT in children [15]. This was  
30  
31 corroborated in the elderly (60-80 years of age) in a study by Bijmens et al. [16].  
32  
33

34  
35 As for atmospheric pressure and humidity, there are no new data to suggest that they  
36  
37 significantly affect EBT measurement if within a reasonably acceptable range.  
38  
39

**EBT and temperature taken at traditional measurement sites**

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41  
42  
43 The initial proof-of-concept studies started a long and continuous process of  
44  
45 assessment of the precision and repeatability of EBT measurements. It was demonstrated that  
46  
47 the day-to-day measurements in healthy subjects were repeatable with an intraclass  
48  
49 correlation coefficient of 0.99 [11]. One of the crucial questions, which needed to be  
50  
51 answered, was whether EBT is just another surrogate measure of core body temperature, or  
52  
53 whether it also captures the signal emitted by the airways. The pooled analysis of numerous  
54  
55 EBT and body temperature measurements of healthy subjects and asthmatics did not disclose  
56  
57  
58  
59  
60

any meaningful correlation between EBT and any of them, while there was a highly significant correlation between otic and axillary temperatures (Table 1).

		Exhaled Breath Temperature
	Axillary Temperature	R=0.01 (P>0.1)
Otic Temperature	R=0.71 (P<0.01)	R=0.06 (P>0.1)

Table 1. The lack of correlation between EBT and body temperatures measured at traditional sites suggests that it is a different physiological indicator.

Partially different results were found by Flouris and Cheung in an experiment with healthy volunteers showing that there was a significant correlation (R=0.58) between rectal temperature and EBT, but changes in EBT were on a larger scale (3 times the change in rectal temperature), thus regulating the core temperature as a reaction to thermal stress [17].

Thus, while core body temperature determines the operative thermal state of humans as a species, EBT represents organ specific physiological modulation of its values, but also reflects pathological changes of the respiratory system.

### **Physiological factors affecting EBT measurement**

Similar to all other new methods with potential clinical applications, EBT measurement requires careful assessment of possible confounding factors to be taken into consideration. EBT is affected by the ambient environment and by different activities in both health and disease states. In an initial report multiple regression analysis did not indicate a significant association of EBT with gender, height, weight, heart rate, blood pressure [11]. Age was a special focus of attention, as the method holds high promise for use in the pediatric population: a positive correlation (R=0.75, P<0.001) was established in healthy children in the age range between 3 and 17 years [18], supported also by the results of Barreto et al. [19] and



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2  
3 Vermeulen et al. [20]. In the study of Logie et al., multiple regression analysis indicated slow  
4 vital capacity (strongly correlated to age) as a predictor of EBT in a study of 60 children aged  
5  
6  
7  
8 between 9 and 11 years of age [15]. Age did not seem to be a major determining factor in the  
9  
10 pooled analysis of our adult control subjects free of respiratory diseases, but there were  
11  
12 indications that in elderly people EBT may tend to be lower [16], probably also in relation to  
13  
14  
15 accompanying geriatric morbidities.  
16

17  
18 Gender is another important determinant of EBT. The pooled analysis we did on all  
19  
20 our adult healthy control subjects outlined a trend towards somewhat higher EBT in 83 male  
21  
22 subjects compared with the EBT of 107 women, but it was not statistically significant. In the  
23  
24 larger study of Carpagnano et al. (143 men and 155 women) a significant gender difference  
25  
26 emerged with EBT of the male subjects being about 1°C higher [14]. The same was found in  
27  
28 elderly subjects over 60 years of age [16]. This gender difference may be still preserved in  
29  
30 asthma according to a cross sectional study involving 69 subjects on maintenance treatment,  
31  
32 where men had significantly higher EBT [21 Crespo].  
33  
34  
35

36  
37 Healthy subjects have different circadian course of EBT compared with their axillary  
38  
39 temperature: the acrophase (peak temperature) was registered at 19h for EBT and at 13h for  
40  
41 axillary temperature [22]. The bathyphase (trough temperature) was the same for both  
42  
43 circadian rhythms at 1h. Repeated measures analysis found both circadian fluctuations to be  
44  
45 statistically significant. Whether this is also true for patients with inflammatory airway  
46  
47 disease, remains to be determined.  
48  
49

50  
51 Food intake, especially highly caloric fast utilized carbohydrate products, increase  
52  
53 EBT within the next hour [23]. Doubling the amount of energy food proportionally increased  
54  
55 EBT.  
56

57  
58 Tufvesson et al. found that EBT correlated with an increase in the numbers of club  
59  
60 cell (Clara) protein (CC16) in plasma and urine after exercise challenge in asthmatics and

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2  
3 healthy controls [24]. As CC16 levels in plasma reflect an overall epithelial involvement and  
4  
5 as no difference between asthmatics and healthy controls appeared, this finding was  
6  
7 concluded to be a physiological rather than a pathophysiological response.  
8  
9

10  
11 Air pollution from traffic was found to significantly influence EBT in elderly subjects,  
12  
13 proportionally to the density of the traffic [16]. One other environmental factor affecting the  
14  
15 respiratory system is tobacco smoke. Smoking the first cigarette for the day was found to  
16  
17 trigger inflammatory events within the next hour, as evidenced by increase of EBT [25,26].  
18  
19 Apart from the immediate effect of smoking a cigarette, the issue of the association between  
20  
21 EBT and cigarette smoking seems to have long term consequences. There was a significant  
22  
23 inverse correlation between EBT and the number of pack-years in 80 current smokers [25].  
24  
25 Multiple regression analysis with 'EBT' as dependent variable and 'age', 'gender', 'height',  
26  
27 'weight' and 'pack-years' as independent variables, identified only 'pack-years' as  
28  
29 significantly contributing to the overall equation. Similarly, a study replicated these results  
30  
31 confirming that EBT is sensitive to the acute effect of cigarette smoke, but also found  
32  
33 significantly higher EBT in current smokers compared to non-smokers and demonstrated that  
34  
35 after cessation of smoking EBT progressively decreased over time since the last cigarette was  
36  
37 smoked [27]. The results of a prospective, observational, non-interventional cohort study of  
38  
39 146 patients, smokers and ex-smokers with a smoking history of >20 pack years without  
40  
41 chronic obstructive pulmonary disease (COPD) at the start of the study, indicated the  
42  
43 possibility that the acute effect of smoking one cigarette at baseline can identify the subjects  
44  
45 who will develop COPD in the course of the two year follow up [28].  
46  
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54 In-season high pollen counts increase EBT in sensitized subjects with allergic  
55  
56 rhinoconjunctivitis with or without asthma [29]. Any natural components of the ambient air  
57  
58 or gases, aerosolized fluids or particulate matter that can be inhaled accidentally or  
59  
60 intentionally can potentially influence EBT and need to be specifically explored.

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Inhalatory therapeutic and diagnostic agents have the potential of impacting EBT due to their effect on bronchial vasculature and airway geometry, which has to be taken into consideration if this method is used for diagnostic and monitoring purposes. In asthmatics and healthy controls inhalation of 400 mcg of salbutamol did not consistently change EBT, about half of the studied asthmatics increased or decreased their EBT beyond the margin of repeatability of this measurement, which was calculated to be  $\pm 0.25^{\circ}\text{C}$ ; whether they represent phenotypes with specific clinical implications remains to be investigated [30]. On the other hand Svensson et al. [31] found that EBT increased after eucapnic voluntary hyperventilation and methacholine challenge test in both asthmatics and healthy subjects representing in their opinion a physiologic vascular effect present after these challenges in the whole respiratory system.

Body height and body mass index (BMI) do not seem to be significant determinants in both adults and children. An exception is the study of the elderly by Bijmens et al. [16] that pointed out BMI as the EBT predictor, interpreted by the authors as being associated with systemic inflammation. However, the associations between age, gender, weight, height, other physiological indices and EBT need to be revisited with the increasing number of subjects.

**Reference values for EBT in healthy subjects**

The usability of random single point EBT measurements as an objective marker for diagnostic purposes in respiratory medicine requires establishment of normal reference values. Bearing in mind the multiplicity of the already discussed potential confounders of technical, environmental and physiological nature, this task necessitates sieving through a significant random sample of individuals free of respiratory disease from the general population. Carpagnano et al. tackled this issue by measuring EBT in 867 volunteers, of whom 298 healthy never smokers were selected to compute a normal EBT range [14]. The team used a 'decision-tree' statistical technique called CHAID (CHi-squared Automatic Interaction

Detection) and came up with a reference value of EBT in healthy Caucasian non-smoking subjects of  $30.459 \pm 2.955^\circ\text{C}$ .

### **Determinants of EBT in respiratory diseases**

The airways and deep structures of the lung modulate the gas content and the temperature of the air we inhale so as to ensure optimal gas exchange and to prevent damage to the tissues involved in the process. The mechanisms by which the temperature of the lung tissues is regulated involve modulation of the caliber of the airways and the blood flow through the vast vascular network of the bronchial tree. Pathological processes which affect this intricate regulation would reflect on the overall heat exchange during breathing, turning EBT either up or down (Fig. 3).

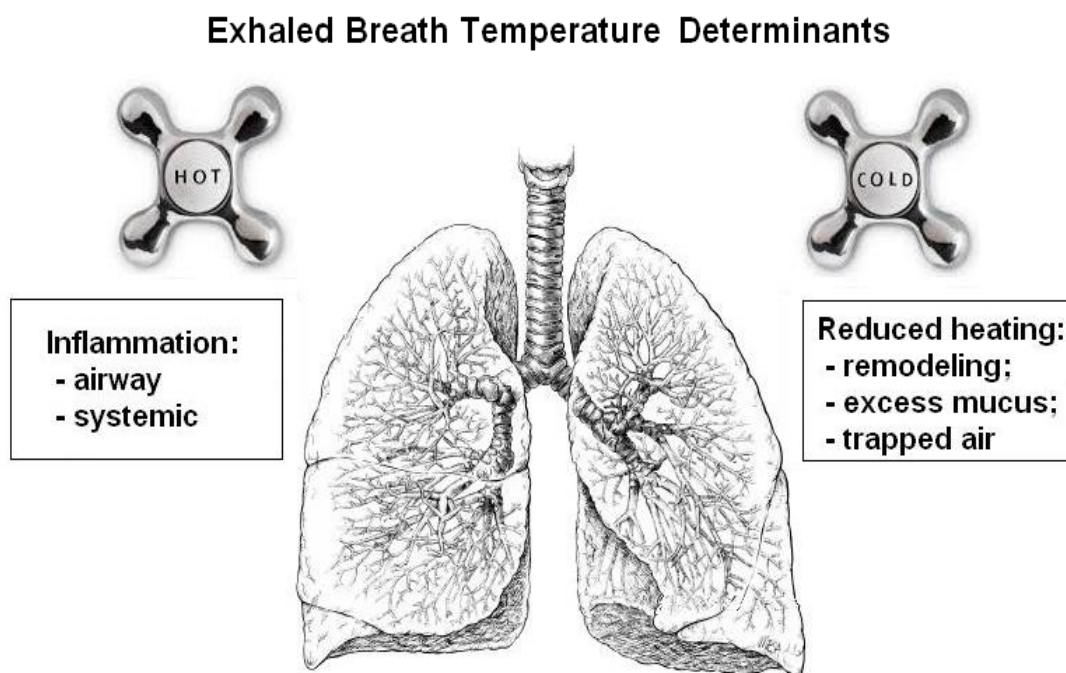


Figure 3. EBT determining vectors acting in opposite directions.

### **‘Turning EBT up’: the inflammatory vector**

Vasodilatation is an inherent feature of inflammation, which is a prominent characteristic of asthma and obstructive lung diseases in general [32]. The increased vascularity of the airways in asthma [33] is partly due to the elevated number of vessels

*Exhaled breath temperature in humans*

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2  
3 associated with angiogenesis and vasodilation caused by the release of mediators, such as  
4  
5 histamine, bradykinin [34], and nitric oxide (NO) [35]. Acetylcholine is the most important  
6  
7 mediator to trigger active vasodilation to body heating, although co-transmitters appear to be  
8  
9 principally involved in the overall response. Vasoactive intestinal peptide, substance P,  
10  
11 histamine, prostaglandins, and transient receptor potential (TRP) V1 receptor activation seem  
12  
13 to be included. There appears to be a role for nitric oxide in active vasodilation, as the  
14  
15 response is attenuated by nitric oxide synthase inhibition [36].  
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20 The relationship between the level of EBT and the bronchial blood flow, presumably  
21  
22 due to increased vascularity, has been clearly demonstrated in a clinical experiment [37]. The  
23  
24 level of exhaled nitric oxide (eNO) was assessed, but some differences between EBT and  
25  
26 eNO were observed: compared to the healthy controls, EBT was increased in all asthmatic  
27  
28 subjects, while eNO was only increased in those patients on inhaled corticosteroids,  
29  
30 suggesting that these two methods are picking different subtypes of asthmatic inflammation.  
31  
32  
33

**‘Turning EBT down’: the reduced airways heating surface**

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35  
36 Histological studies of the airways in COPD patients found decreased bronchial  
37  
38 vascularity, the major determinant of EBT: reduction of the number of capillaries surrounding  
39  
40 the alveoli, structural changes in the small pulmonary arteries comprising the hypertrophy of  
41  
42 the inner membrane of secondary arteries and the smooth muscle cells [38]. These changes  
43  
44 result from repeated bouts of inflammation and lead to airway remodeling. The proposed  
45  
46 sequence of events involves signals from the damaged airway epithelium which elicit  
47  
48 immunological responses mobilizing underlying mesenchymal cells to start tissue repair. As  
49  
50 different types of inflammation (driven by specific sensitization to allergens, environmental  
51  
52 hazards or infection) persist or frequently recur in chronic respiratory diseases, the repair  
53  
54 process turns pathological in the course of time [39]. The repair process itself is not strictly  
55  
56 defined and may exhibit specific features along the continuum from the upper airways to the  
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3 respiratory bronchioles in the periphery of the bronchial tree. This may also be influenced by  
4  
5 the airway geometry and by structural differences in the extracellular matrix (ECM) scaffold  
6  
7 along the cascade of branching airways. This hypothesis was confirmed by Churg et al., who  
8  
9 suggested that genes involved in tissue repair were up-regulated in small airways but were  
10  
11 differentially expressed or down-regulated in the lung parenchyma after exposure to cigarette  
12  
13 smoke [40]. Furthermore, some studies have identified phenotypically unique subpopulations  
14  
15 of fibroblasts, key players in tissue repair, in central airways and in the parenchyma [41, 42].  
16  
17 The end result, the imperfect repair, is tissue remodeling with loss of elastic recoil,  
18  
19 degradation of alveolar walls (i.e. emphysema) and substantial heterogeneity of lung function  
20  
21 and gas volumes with gas trapping, further potentiated by hypoxia [43]. All these pathological  
22  
23 mechanisms impair the thermal exchange between the airway wall and the flow of air and  
24  
25 decrease more or less EBT. Contributors to this decrease are the thickened basement  
26  
27 membrane, the reduced vascular bed and eventually the hyperproduction of mucus [44, 45].  
28  
29 The relatively low EBT when the disease is under control may surge again when a new  
30  
31 inflammatory episode occurs.  
32  
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37

### **EBT in respiratory diseases**

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41 The usefulness of single time-point measurement for diagnostic purposes is limited by  
42  
43 the mere nature of the processes shaping EBT: “pure” airway inflammation on the one hand  
44  
45 and reduction of the thermal convection airway surface (remodeling, tissue destruction, excess  
46  
47 mucus, shutting out of lung segments by obstruction/plugging) on the other, are two extremes  
48  
49 with a broad gray area between them in different lung disease entities [47] (Figure 3):  
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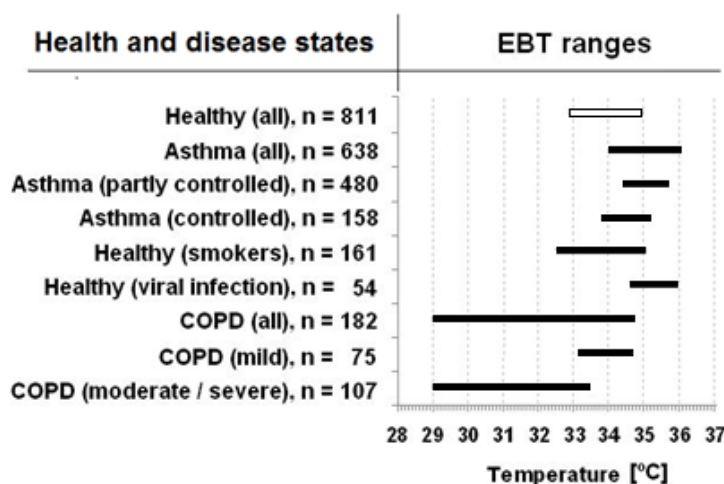


Figure 2. EBT ranges in healthy subjects and in patients with different respiratory diseases.

**Asthma**

Most studies on EBT so far have been done in asthmatic patients and have sought association with different anthropometric, clinical, lung function, laboratory and quality of life indices (Table 2).

Association of EBT with:		References
Age:		
- children	Yes	18, 50
- adults (19-60 years)	No	11,14
- elderly (>60 years)	Yes	16
Symptoms	Yes	8, 9, 11, 47, 48, 49, 54, 55, 56, 57, 58, 59
Spirometry/ FEV1	No	8, 9, 10, 47, 48, 49, 54, 55, 56, 57, 58, 59
FeNO	Yes	8, 9, 37, 48
Sputum eosinophils	Yes	9, 48, 56
Blood:		
- eosinophils	Yes	55, 57
- CRP	Yes	55, 57
- periostin	Yes	55

Figure 2. Association of EBT with basic patient characteristics in patients with asthma.

All studies have found increased EBT in asthmatic patients compared to control subjects without respiratory diseases in both adults and children, thus substantiating the utility of this approach to non-invasively assess airway inflammation.

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3 Garcia et al. documented significantly higher EBT in 50 patients with uncontrolled  
4 asthma compared with 50 patients with controlled asthma, EBT in both of these groups being  
5 significantly higher than in 50 healthy controls [47].  
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9  
10 Piacentini et al. [48] and Leornardi et al. [49] found significantly higher EBT in  
11 asthmatic children and matched healthy controls. A significant positive relationship was also  
12 observed by the Piacentini team between EBT and both exhaled nitric oxide and the  
13 percentage of eosinophils in samples from induced sputum [48].  
14  
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20 However, single point EBT measurements did not differ significantly in 134 asthmatic  
21 children in terms of asthma control and treatment decisions by their physicians [50, Hamill].  
22 A possible reason for this negative finding could be the confounding role that age plays in  
23 childhood [18, 51].  
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29  
30 Piacentini et al. were the first to come up with the hypothesis about a relationship  
31 between EBT and airway remodeling in children/adolescence. In one study they found a  
32 significant correlation between EBT and metalloproteinase-9 in asthmatic children [52], and  
33 in another trial they documented a significant negative correlation between EBT and  
34 diffusion lung capacity of carbon monoxide (DL<sub>CO</sub>) [53].  
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42 Introducing repeated measurements over time provides added value to the EBT  
43 method. Comparing EBT in patients with EBT measurement reveals asthma improvement in  
44 the course of the anti-inflammatory treatment. This has been documented for pharmaceutical  
45 products [11,54,55], for specific allergen immunotherapy [56] and for an acoustic medical  
46 device mobilizing secretions from the lower airways of asthmatics [57]. Similarly to serial  
47 peak expiratory flow (PEF) measurement, it follows a day-to-day pattern in line with the  
48 control of asthma [58].  
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58 In a recent study EBT has shown promise as a marker and predictor of asthma  
59 exacerbation in children and adolescents [59]. However, studies on natural exacerbations  
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3 require serial measurements and are rather difficult to design and implement due to the  
4  
5 unpredictability of these events. Alternatively, studies withholding asthma medications to  
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7 precipitate mild exacerbations of asthma face ethical issues. The availability of affordable  
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9 patient-friendly devices for daily EBT monitoring would reveal whether exacerbations could  
10  
11 be reliably predicted so as to provide a window of opportunity for early preventive measures.  
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15 Exercise, particularly in children, can elicit bronchoconstriction and is used in clinical  
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17 practice to prove the existence of airway hyperresponsiveness. Peroni et al. demonstrated that  
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19 EBT rises significantly after a standardized exercise test [60]. Two studies have addressed the  
20  
21 effect of exercise on EBT in asthmatic swimmers [61,62]. After a training session EBT  
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23 increased both in the athletes with and without asthma. However, in the study of Svenson et  
24  
25 al. EBT remained higher in the asthmatics whose FEV<sub>1</sub> dropped by >10% compared to the  
26  
27 remaining asthmatics [61].  
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**COPD**

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33 The notion that EBT may also be affected by airway remodeling was supported by  
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35 data in patients with chronic degenerative respiratory disease. Paredi et al. were the first to  
36  
37 report slower rise of exhaled breath temperature in COPD [63]. A study of adolescents who  
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39 survived bronchopulmonary dysplasia found their EBT to be significantly lower than in age  
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41 matched asthmatics, suggesting that different pathogenetic mechanisms characterize this  
42  
43 chronic obstructive disease state [64]. Kløkstad et al. found significantly lower EBT in COPD  
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45 patients compared with smokers and healthy controls, which made them suggest that even  
46  
47 though airway inflammation was present in this disease, the structural damage of  
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49 airway/alveolar tissue with consequently impaired blood flow might have resulted in an  
50  
51 overall lower breath temperature [65]. This notion was further illustrated by the same team by  
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53 demonstrating that when COPD patients exacerbated, this still led to an increase of EBT [66].  
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60 The same pattern was found by Labor et al. [28] but the difference between groups ('healthy'

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3 smokers, symptomatic smokers and COPD GOLD stage-I did not reach statistical  
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5 significance. The prolonged duration of the measurement procedure with the multiple breath  
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7 EBT measurement device provides indirect evidence of the lower potential of the airways to  
8  
9 “heat up” the outgoing air [67].  
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12 Lázár Z et al. found distinct differences in EBT of patients with stable COPD, of  
13  
14 patients with COPD at onset and also after recovery from an acute exacerbation, of control  
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16 smoking/ex-smoking control subjects [69]. Patients with stable COPD had lower EBT values  
17  
18 than smokers/ex-smokers. EBT was higher at the onset of acute exacerbations of COPD  
19  
20 compared to the patients in a stable condition, and decreased after recovery. The increased  
21  
22 EBT during exacerbations positively correlated with the sputum leukocyte counts.  
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27 Labor et al. were first to investigate EBT as a susceptibility marker to cigarette smoke  
28  
29 in order to predict COPD development in smokers at risk [28]. Results of this study showed  
30  
31 the potential of a change in EBT from baseline, after smoking a cigarette ( $\Delta$ EBT), to be  
32  
33 significantly predictive for development of manifest COPD and for the disease progression  
34  
35 after 2 years. The same team is extending their EBT studies in an attempt to establish the  
36  
37 COPD diagnosis in the pre-symptomatic stage, before significant end organ damage [70].  
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### 41 **Cystic fibrosis**

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43 Cystic fibrosis (CF) is characterized by chronic airway infection and inflammation  
44  
45 pushing EBT up, and structural changes of the airways and lung tissues, pushing it down.  
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47 Subsequently, Garcia et al. did not find significant differences between the EBT of adult CF  
48  
49 patients and healthy controls [71]. Similarly, Bade et al. did not find differences in the  
50  
51 absolute EBT values of patients and controls, but established a slower rise of EBT in CF  
52  
53 patients [72].  
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57 A multinational team studied 57 CF patients and measured their EBT by a single-  
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59 breath method. They also assessed the temperature of sputum and directly of the airway  
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3 lumen and wall using fiberoptic bronchoscopy [73]. The investigators found a significant  
4  
5 inverse correlation between EBT and FEV<sub>1</sub>, with EBT values of the more obstructed subjects  
6  
7 higher than those of the controls.  
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**Lung cancer**

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12 Cancerous growth in the lungs is characterized by inflammation and increased  
13  
14 vascularity. Carpagnano et al. measured EBT in 82 consecutive patients with suspected non-  
15  
16 small-cell lung cancer (NSCLC) in order to explore the applicability of the method for  
17  
18 diagnostic and monitoring purposes [74]. In 40 patients cancer diagnosis was confirmed by  
19  
20 the standard work-up, while the remaining 42 were labeled as false-positive and were used as  
21  
22 controls. EBT turned out to be significantly higher in the NSCLC patients compared to the  
23  
24 healthy subjects. EBT was correlated with the number of pack-years and associated with the  
25  
26 stage of lung cancer. The authors determined the cut-off value for EBT that could screen  
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28 patients with lung cancer with high sensitivity and specificity.  
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34 In a subsequent study the same team enrolled 44 consecutive patients with  
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36 radiological suspicion of lung cancer and ten healthy non-smoker volunteers, in all of whom  
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38 EBT was measured [75]. The researchers also measured leukotriene B<sub>4</sub>, a marker of airways  
39  
40 inflammation, and vascular endothelial growth factor (VEGF), a marker of neoangiogenesis,  
41  
42 in exhaled breath condensate. They confirmed the previous finding of a higher EBT in lung  
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44 cancer patients compared to the controls. A multiple linear regression model showed that the  
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46 exhaled VEGF was the only predictor of elevated of EBT, which they interpreted as evidence  
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48 that angiogenesis was driving the increase in EBT in lung cancer. The study suggested the  
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50 potential for use of EBT in monitoring lung cancer progression.  
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**Infections**

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56 Both viral and bacterial infections have a direct bearing on exacerbations of chronic  
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58 lung diseases. Infections can be confined to the respiratory system, but can also be associated  
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3 with systemic symptoms including general febrile episodes, so it is important to be aware of  
4 the relationship between fever and EBT. Six generally healthy subjects measured their EBT  
5 and ear temperature (ET) daily for periods of between 5 months and 2 years, using personal  
6 hand-held devices uploading the results on a specialized web site [76]. They were instructed  
7 to start recording both ET and EBT at 8-hour intervals if they felt signs of a general  
8 indisposition and if their ET exceeded 37°C. Six episodes of fever were documented during  
9 the study: 2 cases of rhinovirus infections in which EBT rose by 1.2-1.9°C above baseline,  
10 preceding by 24-72 hours a moderate increase of ET of up to 38°C; 2 cases of influenza in  
11 which EBT rose by >2.0°C about 6 hours before increase of ET up to 40°C; 2 cases of  
12 bacterial infections, urinary and GI, during which EBT rose by ≈1.0°C simultaneously with  
13 the rise of ET (up to 39°C). These results prompted the conclusion that EBT rises during viral  
14 infections, affecting the respiratory system earlier than ET, providing a window of  
15 opportunity for early treatment. This may have implications for patients at risk of  
16 exacerbations of underlying obstructive airway diseases. The method may also discriminate  
17 between different disease agents, which warrant specific research designs.

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20 The issue of asthma exacerbations in the pediatric range was explored by Xepapadaki  
21 et al. [77]. They documented significant EBT increase at the onset of virus triggered asthma  
22 exacerbations. The possibility of using personal devices for EBT measurement opens the door  
23 for prospective studies to assess the value of serial home measurements. EBT measurements  
24 may predict in advance the onset of viral infections, providing the opportunity to prevent or  
25 abate subsequent exacerbations.

**Applicability of EBT measurement**

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28 The idea that motivated initial research into the measurement of EBT was rather  
29 simple and straightforward: as airway inflammation has gained unanimous recognition as the  
30 hallmark of asthma, and as increased temperature is a prominent feature of inflammation,  
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3 detecting the thermal signal from the inflamed airways would be a simple measure of the  
4 state of asthma control. Insight into the nature of the processes shaping EBT gained  
5 complexity as data started to accumulate over time [46]. An important element configuring  
6 the EBT model is airway remodeling. This is in contrast to FeNO, the closest approximation  
7 of what EBT measurement can be used for, which is associated exclusively with eosinophilic  
8 airway inflammation and hyperresponsiveness. In fact, in cases of advanced chronic lung  
9 disease, where FeNO has little value, EBT can get quite low, thus adding an important  
10 dimension to the applicability of the method. As a matter of fact, these two non-invasive  
11 methods can be used conjointly to detect the eosinophilic airway inflammation signal by  
12 assessing increased FeNO in subjects with decreased EBT due to airway remodeling.  
13 Baseline EBT is compounded by the processes of inflammation and remodeling, which act in  
14 opposite directions and sometimes the resulting vector could be lying within the “normal”  
15 range. From this point of view the broad clinical spectrum of chronic airway diseases should  
16 be regarded as individual combinations of inflammation and remodeling. Documenting EBT  
17 at a time point of adequate disease control may serve as a reference point to warn of  
18 imminent inflammatory exacerbation, and of advancement of remodeling/destruction in the  
19 long run. A prerequisite to this end would be monitoring with user friendly individual devices  
20 for EBT measurement.

**Future perspectives**

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49 EBT, which was initially an unexplored area on the map of human physiology and  
50 disease, is gradually being completed. It has the potential to satisfy the need of current clinical  
51 practice in the field of lung diseases for a simple, cheap and non-invasive tool to assess and  
52 monitor the state of the airways. Ongoing systematic research will determine its place in the  
53 clinical setting and as a tool in home monitoring in line with the modern trends of  
54 personalized and telemedicine. The usefulness of this approach should be enhanced by either  
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3 combining it with other objective measurements, or by breaking it down to components that  
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5 could possibly differentiate between phenotypes of airway diseases. This second option  
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7 prompted the idea of assessing separately the contribution of the central and peripheral  
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9 airways to compliment the standard integral EBT measurement [78]. This will help avoid  
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11 false-negative findings of 'normal' EBT in subjects with equal part of both inflammatory and  
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13 degenerative disorders. It will also help evaluate the kinetics of different diagnostic and  
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15 therapeutic approaches, adding a new dimension in differentiating health from airway  
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17 pathology.  
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