

The Added Value of Exhaled Breath Temperature in Respiratory Medicine

Popov, Todor A.; Kralimarkova, Tanya Z.; Labor, Marina; Plavec, Davor

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The added value of exhaled breath temperature in respiratory medicineTodor A. Popov¹, Tanya Z. Kralimarkova¹, Marina Labor^{2,3}, Davor Plavec^{3,4}¹Clinic of Allergy and Asthma, Medical University Sofia, Bulgaria²Pulmonology Department, University Hospital Center Osijek, Croatia³Faculty of Medicine, J.J. Strossmayer University, Osijek, Croatia⁴Research 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 18th century [1] (Fig. 1).

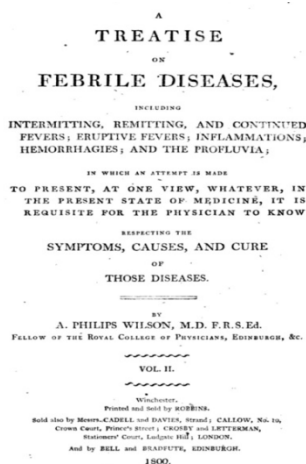


Figure 1. A.P. Wilson's "A treatise on Febrile Diseases", 1800

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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3 The blood circulation and the border surfaces with the ambient environment play a crucial
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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
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9 consequences, while modern day medicine artificially induces hyperthermia in cancer
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11 treatment [5] or hypothermia to allow prolonged surgical interventions of vital organs [6].
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15 For practical purposes thermometry at traditional body sites is performed giving estimates of
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17 the actual core temperature with a reasonable degree of approximation [4]. Thus, rectal temperature is
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19 considered most representative of the core body temperature, but its measurement is uncomfortable for
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21 patients and carries the risk of bacterial contamination. Oral temperature is generally 0.5°C lower than
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23 the rectal temperature and is more prone to influences from the ambient environment, while the
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25 temperature of the tympanic membrane taken by infrared tympanic thermometers was found to be
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27 imprecise compared to rectal values [7].
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31 All other conditions of measurement being equal, the differences between the
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33 temperature values at specific body sites are due to the influence of the “core-to-surface”
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35 interface. While this may be considered a confounding factor from the viewpoint of
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37 evaluation of the “true” core temperature, differences due to the core-to-surface gradient may
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39 present an opportunity to obtain useful information about pathology associated with the
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41 interface itself. This is particularly relevant for complex anatomical structures, such as the
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43 lungs, involving vascularized tissues and a plethora of airways of different sizes with
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45 hierarchical architectonics.
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The benefits of a ‘breath thermometer’.

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

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3 of the alveoli. During breathing, gases and thermal energy are being exchanged between the
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5 inner milieu of the organism and the ambient environment. The temperature of the inhaled air
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7 is tempered during its flow in and out of the branching airways, which have a separate system
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9 of blood supply from the left side of the heart. As blood is the main carrier of thermal energy,
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11 processes that would modify its flow within the airway walls might reflect on the temperature
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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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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
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28 al. [9]. Both teams used fast reacting thermal sensors placed in front of the mouth of the tested
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30 subjects, which recorded the rise of EBT during single breath maneuvers and used the mean
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32 of three exhalation attempts. This required constant temperature of the indoor environment,
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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
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38 experiments demonstrating that the plateau of the exhaled temperature curve was the variable,
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40 distinguishing asthmatics from healthy controls [10].
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45 An alternative approach for EBT measurement was introduced by Popov et al., who
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47 made use of a specifically designed portable device [11]. It dwelt upon the notion of
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49 accumulation of the expired thermal energy of the tested subject into an insulated vessel
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51 containing a heat sink with high thermal capacity, thus making the measurement less
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53 dependent on ambient factors. The subjects exhaled continuously into the thermal chamber of
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55 the device until the temperature of the heat sink reached a plateau, indicating that a thermal
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57 equilibrium was reached inside the closed system. Because of the easy use and acceptability
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59 by the patients, the instrument allowed repeated measurements over time, with the potential
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3 of use as an individual device for measurements at home or in the working environment. Its
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5 usability was further improved by upgrading the overall design, introducing electronic
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7 processor and memory allowing automatic detection of the end of measurement, follow up
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9 and analysis of the temperature curve on the monitor of a computer [12]. Despite these
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11 technical improvements, the acquisition of measurement skills with the device, by both
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13 patients and medical personnel, is essential for obtaining meaningful results. A detailed
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15 description of the engineering aspects of the device and method for EBT measurement has
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17 been the subject of a specialized review [13]. Further improvements of its applicability
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19 involved shortening of the time for measurement and rendering it less dependent on the
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21 conscientious cooperation of the subjects (this latter line of improvement would allow using
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23 the device in early infancy).
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30 **Impact of ambient air temperature on EBT measurement results**

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33 Even with this closed-circuit multi-breath technique, the issue of the confounding
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35 influence of the characteristics of the ambient air on the end results of EBT measurement
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37 remains. As can be expected, the temperature of the ambient air inhaled during the
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39 measurement affects the accuracy^{1*}, but not the precision^{**} of the measurements. The initial
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41 analysis of 132 measurements made with EBT as dependent variable and room temperature
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43 (values on separate days in the range 18–25°C), atmospheric pressure (range 954–982 mbar)
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45 and humidity (ranges 22–72%) as independent variables, did not detect any of the ambient
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47 conditions as significant determinants, hence we recommend that the measurements are made
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49 in a controlled/indoor environment with air temperatures within this range (11).
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55 In a recent real life study Carpagnano et al. measured EBT of 867 volunteers in 3
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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

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3 temperature ranging from 0 to 38 °C [14]. Out of this random cohort, 298 subjects had never
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5 smoked and were free of respiratory and other diseases. The regression model with their EBT
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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
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15 experiments conducted by the manufacturer of X-halo arrived at the same value of this
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17 conversion coefficient. More data are needed to verify whether this relationship is strictly
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19 straight linear, or whether an intermediate plateau could exist at room temperature as
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21 suggested in earlier studies.
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27 Logie et al. demonstrated that the temperature of the inspired air affects both the slope
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29 and the plateau of EBT and is a significant predictor of EBT in children [15]. This was
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31 corroborated in the elderly (60-80 years of age) in a study by Bijmens et al. [16].
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35 As for atmospheric pressure and humidity, there are no new data to suggest that they
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37 significantly affect EBT measurement if within a reasonably acceptable range.
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EBT and temperature taken at traditional measurement sites

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

Exhaled breath temperature in humans

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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
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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
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12 indications that in elderly people EBT may tend to be lower [16], probably also in relation to
13
14 accompanying geriatric morbidities.
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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
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30 asthma according to a cross sectional study involving 69 subjects on maintenance treatment,
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32 where men had significantly higher EBT [21 Crespo].
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37 Healthy subjects have different circadian course of EBT compared with their axillary
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39 temperature: the acrophase (peak temperature) was registered at 19h for EBT and at 13h for
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41 axillary temperature [22]. The bathyphase (trough temperature) was the same for both
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43 circadian rhythms at 1h. Repeated measures analysis found both circadian fluctuations to be
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45 statistically significant. Whether this is also true for patients with inflammatory airway
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47 disease, remains to be determined.
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51 Food intake, especially highly caloric fast utilized carbohydrate products, increase
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53 EBT within the next hour [23]. Doubling the amount of energy food proportionally increased
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55 EBT.
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58 Tufvesson et al. found that EBT correlated with an increase in the numbers of club
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60 cell (Clara) protein (CC16) in plasma and urine after exercise challenge in asthmatics and

Exhaled breath temperature in humans

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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.
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11 Air pollution from traffic was found to significantly influence EBT in elderly subjects,
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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
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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',
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27 'weight' and 'pack-years' as independent variables, identified only 'pack-years' as
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29 significantly contributing to the overall equation. Similarly, a study replicated these results
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31 confirming that EBT is sensitive to the acute effect of cigarette smoke, but also found
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33 significantly higher EBT in current smokers compared to non-smokers and demonstrated that
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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
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43 possibility that the acute effect of smoking one cigarette at baseline can identify the subjects
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45 who will develop COPD in the course of the two year follow up [28].
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54 In-season high pollen counts increase EBT in sensitized subjects with allergic
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56 rhinoconjunctivitis with or without asthma [29]. Any natural components of the ambient air
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58 or gases, aerosolized fluids or particulate matter that can be inhaled accidentally or
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60 intentionally can potentially influence EBT and need to be specifically explored.

Exhaled breath temperature in humans

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3 Inhalatory therapeutic and diagnostic agents have the potential of impacting EBT due
4 to their effect on bronchial vasculature and airway geometry, which has to be taken into
5 consideration if this method is used for diagnostic and monitoring purposes. In asthmatics
6 and healthy controls inhalation of 400 mcg of salbutamol did not consistently change EBT,
7 about half of the studied asthmatics increased or decreased their EBT beyond the margin of
8 repeatability of this measurement, which was calculated to be $\pm 0.25^{\circ}\text{C}$; whether they
9 represent phenotypes with specific clinical implications remains to be investigated [30]. On
10 the other hand Svensson et al. [31] found that EBT increased after eucapnic voluntary
11 hyperventilation and methacholine challenge test in both asthmatics and healthy subjects
12 representing in their opinion a physiologic vascular effect present after these challenges in the
13 whole respiratory system.
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29 Body height and body mass index (BMI) do not seem to be significant determinants in
30 both adults and children. An exception is the study of the elderly by Bijmens et al. [16] that
31 pointed out BMI as the EBT predictor, interpreted by the authors as being associated with
32 systemic inflammation. However, the associations between age, gender, weight, height, other
33 physiological indices and EBT need to be revisited with the increasing number of subjects.
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Reference values for EBT in healthy subjects

42 The usability of random single point EBT measurements as an objective marker for
43 diagnostic purposes in respiratory medicine requires establishment of normal reference values.
44 Bearing in mind the multiplicity of the already discussed potential confounders of technical,
45 environmental and physiological nature, this task necessitates sieving through a significant
46 random sample of individuals free of respiratory disease from the general population.
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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).

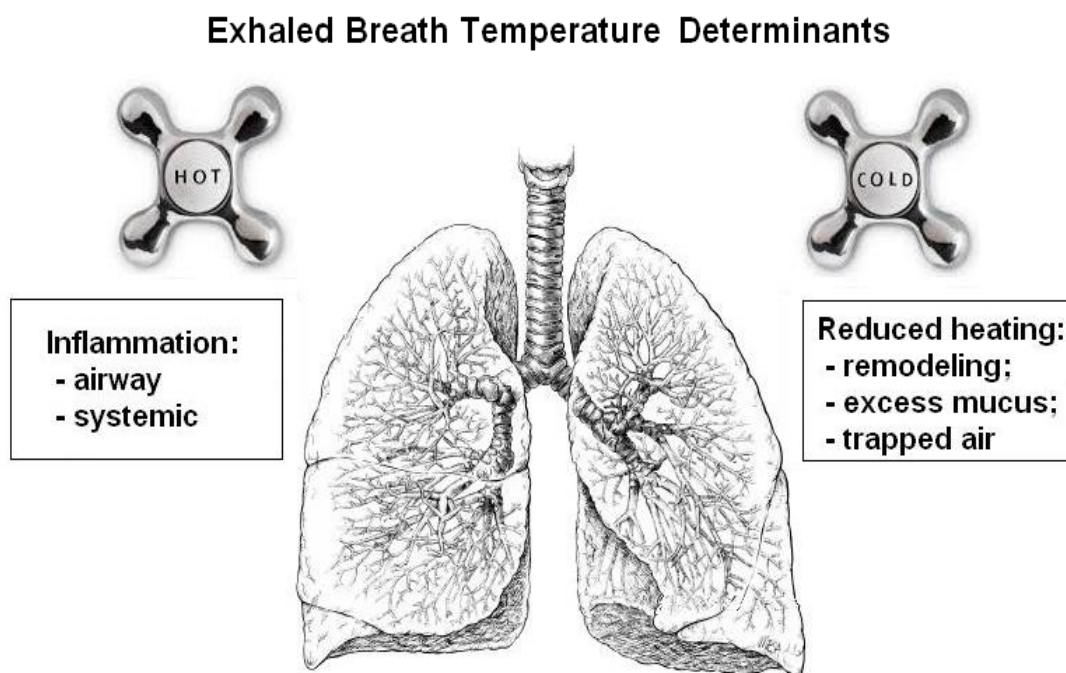


Figure 3. EBT determining vectors acting in opposite directions.

‘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

1
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
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‘Turning EBT down’: the reduced airways heating surface

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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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Exhaled breath temperature in humans

1
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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.
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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
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49 with a broad gray area between them in different lung disease entities [47] (Figure 3):
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Exhaled breath temperature in humans

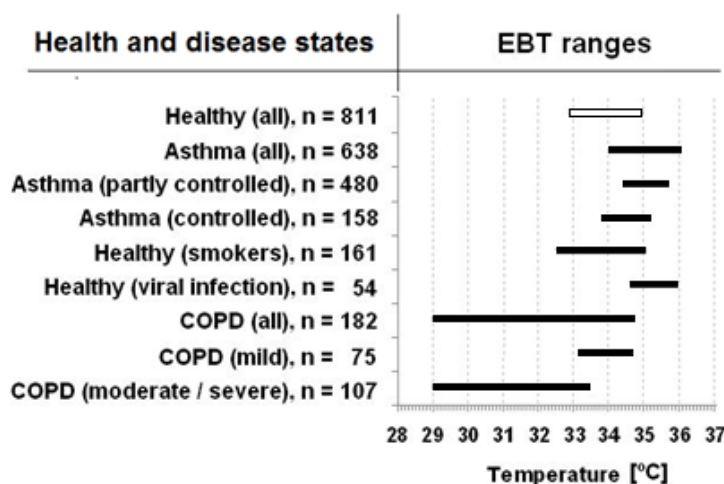


Figure 2. EBT ranges in healthy subjects and in patients with different respiratory diseases.

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.

Exhaled breath temperature in humans

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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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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].
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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_{CO}) [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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Exhaled breath temperature in humans

1
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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
6
7 precipitate mild exacerbations of asthma face ethical issues. The availability of affordable
8
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.
12
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14
15 Exercise, particularly in children, can elicit bronchoconstriction and is used in clinical
16
17 practice to prove the existence of airway hyperresponsiveness. Peroni et al. demonstrated that
18
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
22
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 FEV₁ 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
34
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
38
39 survived bronchopulmonary dysplasia found their EBT to be significantly lower than in age
40
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
44
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
48
49 airway/alveolar tissue with consequently impaired blood flow might have resulted in an
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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
4
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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11

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
15
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 (Δ 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.
46
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
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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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Exhaled breath temperature in humans

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3 lumen and wall using fiberoptic bronchoscopy [73]. The investigators found a significant
4
5 inverse correlation between EBT and FEV₁, with EBT values of the more obstructed subjects
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7 higher than those of the controls.
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Lung cancer

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11
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
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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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35 In a subsequent study the same team enrolled 44 consecutive patients with
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37 radiological suspicion of lung cancer and ten healthy non-smoker volunteers, in all of whom
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39 EBT was measured [75]. The researchers also measured leukotriene B₄, a marker of airways
40
41 inflammation, and vascular endothelial growth factor (VEGF), a marker of neoangiogenesis,
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43 in exhaled breath condensate. They confirmed the previous finding of a higher EBT in lung
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45 cancer patients compared to the controls. A multiple linear regression model showed that the
46
47 exhaled VEGF was the only predictor of elevated of EBT, which they interpreted as evidence
48
49 that angiogenesis was driving the increase in EBT in lung cancer. The study suggested the
50
51 potential for use of EBT in monitoring lung cancer progression.
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Infections

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57 Both viral and bacterial infections have a direct bearing on exacerbations of chronic
58
59 lung diseases. Infections can be confined to the respiratory system, but can also be associated
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Exhaled breath temperature in humans

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3 with systemic symptoms including general febrile episodes, so it is important to be aware of
4
5 the relationship between fever and EBT. Six generally healthy subjects measured their EBT
6
7 and ear temperature (ET) daily for periods of between 5 months and 2 years, using personal
8
9 hand-held devices uploading the results on a specialized web site [76]. They were instructed
10
11 to start recording both ET and EBT at 8-hour intervals if they felt signs of a general
12
13 indisposition and if their ET exceeded 37°C. Six episodes of fever were documented during
14
15 the study: 2 cases of rhinovirus infections in which EBT rose by 1.2-1.9°C above baseline,
16
17 preceding by 24-72 hours a moderate increase of ET of up to 38°C; 2 cases of influenza in
18
19 which EBT rose by >2.0°C about 6 hours before increase of ET up to 40°C; 2 cases of
20
21 bacterial infections, urinary and GI, during which EBT rose by ≈1.0°C simultaneously with
22
23 the rise of ET (up to 39°C). These results prompted the conclusion that EBT rises during viral
24
25 infections, affecting the respiratory system earlier than ET, providing a window of
26
27 opportunity for early treatment. This may have implications for patients at risk of
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29 exacerbations of underlying obstructive airway diseases. The method may also discriminate
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31 between different disease agents, which warrant specific research designs.
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39 The issue of asthma exacerbations in the pediatric range was explored by Xepapadaki
40
41 et al. [77]. They documented significant EBT increase at the onset of virus triggered asthma
42
43 exacerbations. The possibility of using personal devices for EBT measurement opens the door
44
45 for prospective studies to assess the value of serial home measurements. EBT measurements
46
47 may predict in advance the onset of viral infections, providing the opportunity to prevent or
48
49 abate subsequent exacerbations.
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51

Applicability of EBT measurement

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55 The idea that motivated initial research into the measurement of EBT was rather
56
57 simple and straightforward: as airway inflammation has gained unanimous recognition as the
58
59 hallmark of asthma, and as increased temperature is a prominent feature of inflammation,
60

Exhaled breath temperature in humans

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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.
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Future perspectives

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47 EBT, which was initially an unexplored area on the map of human physiology and
48 disease, is gradually being completed. It has the potential to satisfy the need of current clinical
49 practice in the field of lung diseases for a simple, cheap and non-invasive tool to assess and
50 monitor the state of the airways. Ongoing systematic research will determine its place in the
51 clinical setting and as a tool in home monitoring in line with the modern trends of
52 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
4
5 could possibly differentiate between phenotypes of airway diseases. This second option
6
7 prompted the idea of assessing separately the contribution of the central and peripheral
8
9 airways to compliment the standard integral EBT measurement [78]. This will help avoid
10
11 false-negative findings of 'normal' EBT in subjects with equal part of both inflammatory and
12
13 degenerative disorders. It will also help evaluate the kinetics of different diagnostic and
14
15 therapeutic approaches, adding a new dimension in differentiating health from airway
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17 pathology.
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