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DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

The added value of exhaled breath temperature in respiratory medicine

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Abstract

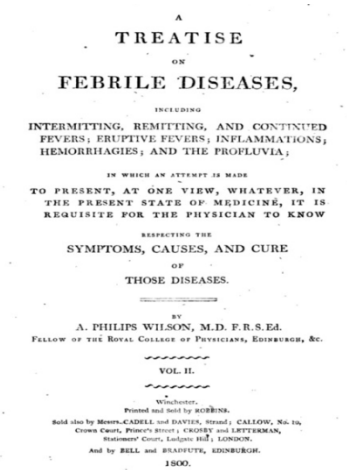
Recognition of the huge economic burden chronic respiratory diseases pose for society motivated fundamental and clinical research leading to insight into the role of airway inflammation in various disease entities and their phenotypes. However, no easy, cheap and patient-friendly methods to assess it 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).



A
TREATISE
ON
FEBRILE DISEASES,
INCLUDING
INTERMITTING, REMITTING, AND CONTINUED FEVERS; ERUPTIVE FEVERS; INFLAMMATIONS; HEMORRHAGIES; AND THE PROFLUVIA;
IN WHICH AN ATTEMPT IS MADE
TO PRESENT, AT ONE VIEW, WHATEVER, IN THE PRESENT STATE OF MEDICINE, IT IS REQUISITE FOR THE PHYSICIAN TO KNOW
RESPECTING THE
SYMPTOMS, CAUSES, AND CURE
OF
THOSE DISEASES.
BY
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FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, EDINBURGH, &c.
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1800.

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].

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

For practical purposes thermometry at traditional body sites is performed giving estimates of the actual core temperature with a reasonable degree of approximation [4]. Thus, rectal temperature is considered most representative of the core body temperature, but its measurement is uncomfortable for patients and carries the risk of bacterial contamination. Oral temperature is generally 0.5ºC lower than the rectal temperature and is more prone to influences from the ambient environment, while the temperature of the tympanic membrane taken by infrared tympanic thermometers was found to be imprecise compared to rectal values [7].

All other conditions of measurement being equal, the differences between the temperature values at specific body sites are due to the influence of the “core-to-surface” interface. While this may be considered a confounding factor from the viewpoint of evaluation of the “true” core temperature, differences due to the core-to-surface gradient may present an opportunity to obtain useful information about pathology associated with the interface itself. This is particularly relevant for complex anatomical structures, such as the lungs, involving vascularized tissues and a plethora of airways of different sizes with hierarchical architectonics.

The benefits of a ‘breath thermometer’.

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

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

Technical aspects of EBT measurement.

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

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

of use as an individual device for measurements at home or in the working environment. Its usability was further improved by upgrading the overall design, introducing electronic processor and memory allowing automatic detection of the end of measurement, follow up and analysis of the temperature curve on the monitor of a computer [12]. Despite these technical improvements, the acquisition of measurement skills with the device, by both patients and medical personnel, is essential for obtaining meaningful results. A detailed description of the engineering aspects of the device and method for EBT measurement has been the subject of a specialized review [13]. Further improvements of its applicability involved shortening of the time for measurement and rendering it less dependent on the conscientious cooperation of the subjects (this latter line of improvement would allow using the device in early infancy).

Impact of ambient air temperature on EBT measurement results

Even with this closed-circuit multi-breath technique, the issue of the confounding influence of the characteristics of the ambient air on the end results of EBT measurement remains. As can be expected, the temperature of the ambient air inhaled during the measurement affects the accuracy[1*], but not the precision[**] of the measurements. The initial analysis of 132 measurements made with EBT as dependent variable and room temperature (values on separate days in the range 18–25ºC), atmospheric pressure (range 954–982 mbar) and humidity (ranges 22–72%) as independent variables, did not detect any of the ambient conditions as significant determinants, hence we recommend that the measurements are made in a controlled/indoor environment with air temperatures within this range (11).

In a recent real life study Carpagnano et al. measured EBT of 867 volunteers in 3 different outdoor and indoor (hospital and shopping mall) environments with ambient air

[*] 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.

temperature ranging from 0 to 38 ºC [14]. Out of this random cohort, 298 subjects had never smoked and were free of respiratory and other diseases. The regression model with their EBT values as a dependent variable and the ambient air temperature as an independent one outlined an association, in which the increase of external temperature by 1°C corresponded on average to EBT increase of 0.19°C. For this reason it is important to measure the external temperature and if necessary to apply a correction factor to the results obtained. Independent technical experiments conducted by the manufacturer of X-halo arrived at the same value of this conversion coefficient. More data are needed to verify whether this relationship is strictly straight linear, or whether an intermediate plateau could exist at room temperature as suggested in earlier studies.

Logie et al. demonstrated that the temperature of the inspired air affects both the slope and the plateau of EBT and is a significant predictor of EBT in children [15]. This was corroborated in the elderly (60-80 years of age) in a study by Bijnens et al. [16].

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

EBT and temperature taken at traditional measurement sites

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

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

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

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

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

Food intake, especially highly caloric fast utilized carbohydrate products, increase EBT within the next hour [23]. Doubling the amount of energy food proportionally increased EBT.

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

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

Air pollution from traffic was found to significantly influence EBT in elderly subjects, proportionally to the density of the traffic [16]. One other environmental factor affecting the respiratory system is tobacco smoke. Smoking the first cigarette for the day was found to trigger inflammatory events within the next hour, as evidenced by increase of EBT [25,26]. Apart from the immediate effect of smoking a cigarette, the issue of the association between EBT and cigarette smoking seems to have long term consequences. There was a significant inverse correlation between EBT and the number of pack-years in 80 current smokers [25]. Multiple regression analysis with 'EBT' as dependent variable and 'age', 'gender', 'height', 'weight' and 'pack-years' as independent variables, identified only 'pack-years' as significantly contributing to the overall equation. Similarly, a study replicated these results confirming that EBT is sensitive to the acute effect of cigarette smoke, but also found significantly higher EBT in current smokers compared to non-smokers and demonstrated that after cessation of smoking EBT progressively decreased over time since the last cigarette was smoked [27]. The results of a prospective, observational, non-interventional cohort study of 146 patients, smokers and ex-smokers with a smoking history of >20 pack years without chronic obstructive pulmonary disease (COPD) at the start of the study, indicated the possibility that the acute effect of smoking one cigarette at baseline can identify the subjects who will develop COPD in the course of the two year follow up [28].

In-season high pollen counts increase EBT in sensitized subjects with allergic rhinoconjunctivitis with or without asthma [29]. Any natural components of the ambient air or gases, aerosolized fluids or particulate matter that can be inhaled accidentally or intentionally can potentially influence EBT and need to be specifically explored.

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 ±0.25°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 Bijnens 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±2.955°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).

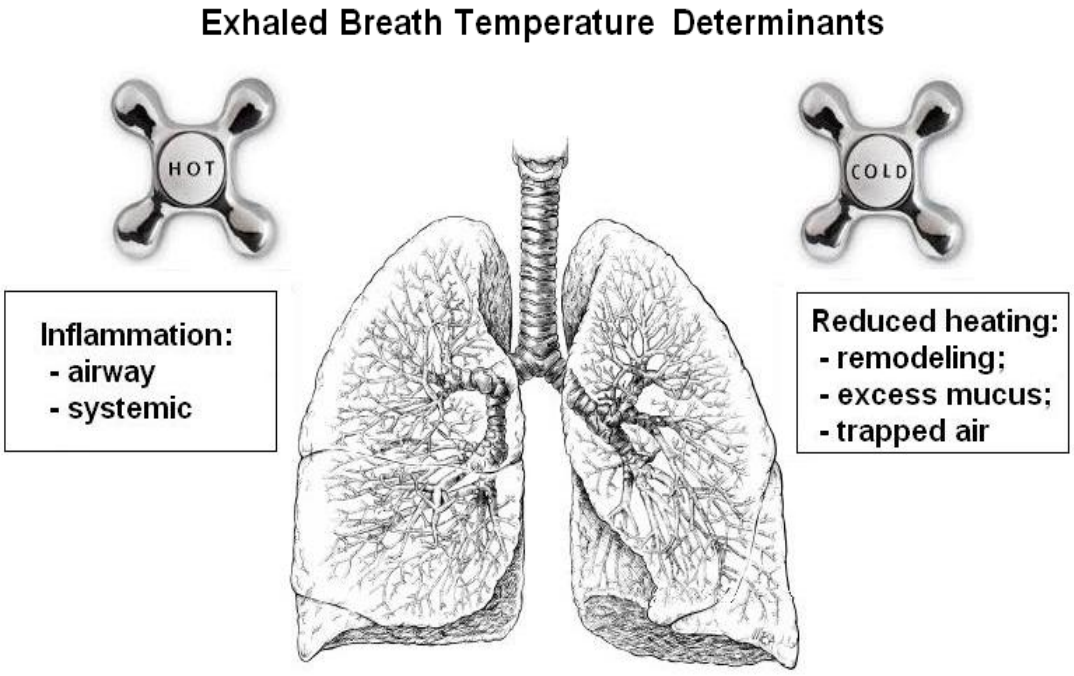

Figure 3. EBT determining vectors acting in opposite directions.

'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

associated with angioneogenesis and vasodilation caused by the release of mediators, such as histamine, bradykinin [34], and nitric oxide (NO) [35]. Acetylcholine is the most important mediator to trigger active vasodilation to body heating, although co-transmitters appear to be principally involved in the overall response. Vasoactive intestinal peptide, substance P, histamine, prostaglandins, and transient receptor potential (TRP) V1 receptor activation seem to be included. There appears to be a role for nitric oxide in active vasodilation, as the response is attenuated by nitric oxide synthase inhibition [36].

The relationship between the level of EBT and the bronchial blood flow, presumably due to increased vascularity, has been clearly demonstrated in a clinical experiment [37]. The level of exhaled nitric oxide (eNO) was assessed, but some differences between EBT and eNO were observed: compared to the healthy controls, EBT was increased in all asthmatic subjects, while eNO was only increased in those patients on inhaled corticosteroids, suggesting that these two methods are picking different subtypes of asthmatic inflammation.

‘Turning EBT down’: the reduced airways heating surface

Histological studies of the airways in COPD patients found decreased bronchial vascularity, the major determinant of EBT: reduction of the number of capillaries surrounding the alveoli, structural changes in the small pulmonary arteries comprising the hypertrophy of the inner membrane of secondary arteries and the smooth muscle cells [38]. These changes result from repeated bouts of inflammation and lead to airway remodeling. The proposed sequence of events involves signals from the damaged airway epithelium which elicit immunological responses mobilizing underlying mesenchymal cells to start tissue repair. As different types of inflammation (driven by specific sensitization to allergens, environmental hazards or infection) persist or frequently recur in chronic respiratory diseases, the repair process turns pathological in the course of time [39]. The repair process itself is not strictly defined and may exhibit specific features along the continuum from the upper airways to the

respiratory bronchioles in the periphery of the bronchial tree. This may also be influenced by the airway geometry and by structural differences in the extracellular matrix (ECM) scaffold along the cascade of branching airways. This hypothesis was confirmed by Churg et al., who suggested that genes involved in tissue repair were up-regulated in small airways but were differentially expressed or down-regulated in the lung parenchyma after exposure to cigarette smoke [40]. Furthermore, some studies have identified phenotypically unique subpopulations of fibroblasts, key players in tissue repair, in central airways and in the parenchyma [41, 42]. The end result, the imperfect repair, is tissue remodeling with loss of elastic recoil, degradation of alveolar walls (i.e. emphysema) and substantial heterogeneity of lung function and gas volumes with gas trapping, further potentiated by hypoxia [43]. All these pathological mechanisms impair the thermal exchange between the airway wall and the flow of air and decrease more or less EBT. Contributors to this decrease are the thickened basement membrane, the reduced vascular bed and eventually the hyperproduction of mucus [44, 45]. The relatively low EBT when the disease is under control may surge again when a new inflammatory episode occurs.

EBT in respiratory diseases

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

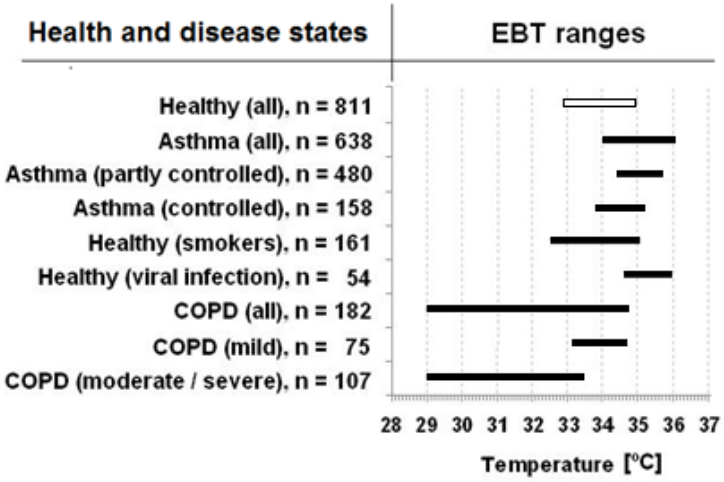

Figure 2. EBT ranges in healthy subjects and in patients with different respiratory diseases.

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.

Garcia et al. documented significantly higher EBT in 50 patients with uncontrolled asthma compared with 50 patients with controlled asthma, EBT in both of these groups being significantly higher than in 50 healthy controls [47].

Piacentini et al. [48] and Leornardi et al. [49] found significantly higher EBT in asthmatic children and matched healthy controls. A significant positive relationship was also observed by the Piacentini team between EBT and both exhaled nitric oxide and the percentage of eosinophils in samples from induced sputum [48].

However, single point EBT measurements did not differ significantly in 134 asthmatic children in terms of asthma control and treatment decisions by their physicians [50, Hamill]. A possible reason for this negative finding could be the confounding role that age plays in childhood [18, 51].

Piacentini et al. were the first to come up with the hypothesis about a relationship between EBT and airway remodeling in children/adolescence. In one study they found a significant correlation between EBT and metalloproteinase-9 in asthmatic children [52], and in another trial they documented a significant negative correlation between EBT and diffusion lung capacity of carbon monoxide (DL_{CO}) [53].

Introducing repeated measurements over time provides added value to the EBT method. Comparing EBT in patients with EBT measurement reveals asthma improvement in the course of the anti-inflammatory treatment. This has been documented for pharmaceutical products [11,54,55], for specific allergen immunotherapy [56] and for an acoustic medical device mobilizing secretions from the lower airways of asthmatics [57]. Similarly to serial peak expiratory flow (PEF) measurement, it follows a day-to-day pattern in line with the control of asthma [58].

In a recent study EBT has shown promise as a marker and predictor of asthma exacerbation in children and adolescents [59]. However, studies on natural exacerbations

require serial measurements and are rather difficult to design and implement due to the unpredictability of these events. Alternatively, studies withholding asthma medications to precipitate mild exacerbations of asthma face ethical issues. The availability of affordable patient-friendly devices for daily EBT monitoring would reveal whether exacerbations could be reliably predicted so as to provide a window of opportunity for early preventive measures.

Exercise, particularly in children, can elicit bronchoconstriction and is used in clinical practice to prove the existence of airway hyperresponsiveness. Peroni et al. demonstrated that EBT rises significantly after a standardized exercise test [60]. Two studies have addressed the effect of exercise on EBT in asthmatic swimmers [61,62]. After a training session EBT increased both in the athletes with and without asthma. However, in the study of Svenson et al. EBT remained higher in the asthmatics whose FEV_1 dropped by >10% compared to the remaining asthmatics [61].

COPD

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

smokers, symptomatic smokers and COPD GOLD stage-I did not reach statistical significance. The prolonged duration of the measurement procedure with the multiple breath EBT measurement device provides indirect evidence of the lower potential of the airways to "heat up" the outgoing air [67].

Lázár Z et al. found distinct differences in EBT of patients with stable COPD, of patients with COPD at onset and also after recovery from an acute exacerbation, of control smoking/ex-smoking control subjects [69]. Patients with stable COPD had lower EBT values than smokers/ex-smokers. EBT was higher at the onset of acute exacerbations of COPD compared to the patients in a stable condition, and decreased after recovery. The increased EBT during exacerbations positively correlated with the sputum leukocyte counts.

Labor et al. were first to investigate EBT as a susceptibility marker to cigarette smoke in order to predict COPD development in smokers at risk [28]. Results of this study showed the potential of a change in EBT from baseline, after smoking a cigarette (ΔEBT), to be significantly predictive for development of manifest COPD and for the disease progression after 2 years. The same team is extending their EBT studies in an attempt to establish the COPD diagnosis in the pre-symptomatic stage, before significant end organ damage [70].

Cystic fibrosis

Cystic fibrosis (CF) is characterized by chronic airway infection and inflammation pushing EBT up, and structural changes of the airways and lung tissues, pushing it down. Subsequently, Garcia et al. did not find significant differences between the EBT of adult CF patients and healthy controls [71]. Similarly, Bade et al. did not find differences in the absolute EBT values of patients and controls, but established a slower rise of EBT in CF patients [72].

A multinational team studied 57 CF patients and measured their EBT by a single-breath method. They also assessed the temperature of sputum and directly of the airway

lumen and wall using fiberoptic bronchoscopy [73]. The investigators found a significant inverse correlation between EBT and FEV_1, with EBT values of the more obstructed subjects higher than those of the controls.

Lung cancer|

Cancerous growth in the lungs is characterized by inflammation and increased vascularity. Carpagnano et al. measured EBT in 82 consecutive patients with suspected non-small-cell lung cancer (NSCLC) in order to explore the applicability of the method for diagnostic and monitoring purposes [74]. In 40 patients cancer diagnosis was confirmed by the standard work-up, while the remaining 42 were labeled as false-positive and were used as controls. EBT turned out to be significantly higher in the NSCLC patients compared to the healthy subjects. EBT was correlated with the number of pack-years and associated with the stage of lung cancer. The authors determined the cut-off value for EBT that could screen patients with lung cancer with high sensitivity and specificity.

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

Infections

Both viral and bacterial infections have a direct bearing on exacerbations of chronic lung diseases. Infections can be confined to the respiratory system, but can also be associated

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

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

Applicability of EBT measurement

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

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

Future perspectives

EBT, which was initially an unexplored area on the map of human physiology and disease, is gradually being completed. It has the potential to satisfy the need of current clinical practice in the field of lung diseases for a simple, cheap and non-invasive tool to assess and monitor the state of the airways. Ongoing systematic research will determine its place in the clinical setting and as a tool in home monitoring in line with the modern trends of personalized and telemedicine. The usefulness of this approach should be enhanced by either

combining it with other objective measurements, or by breaking it down to components that could possibly differentiate between phenotypes of airway diseases. This second option prompted the idea of assessing separately the contribution of the central and peripheral airways to compliment the standard integral EBT measurement [78]. This will help avoid false-negative findings of 'normal' EBT in subjects with equal part of both inflammatory and degenerative disorders. It will also help evaluate the kinetics of different diagnostic and therapeutic approaches, adding a new dimension in differentiating health from airway pathology.

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