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Measurement of exhaled breath temperature in science and clinical practice

Educational aims

- To review the link between inflammation and increased vascularity and blood flow of the airways, and exhaled breath temperature.
- To position exhaled breath temperature (EBT) as a physiological characteristic differing from core temperature measured at other body sites.
- To review the existing experience about measuring EBT in different disease states of the respiratory system.
- To emphasise the influence of airway remodeling/destruction in modulating EBT.

Summary

Evaluation of the exhaled breath temperature (EBT) has been suggested as a new method to detect and monitor pathological processes in the respiratory system. The putative mechanism of this approach is based upon changes in the blood flow in the conducting airways that are characteristic of different disease states, which influence the temperature of the exhaled gases. The first attempts to prove this concept were made in conjunction with measurement of exhaled nitric oxide fraction (F_{eNO}) about a decade ago. They made use of an open-circuit, single-breath method in a closed indoor environment, and demonstrated associations between EBT on the one hand, and bronchial blood flow, F_{eNO} and sputum cellular content on the other.

These findings have been further extended to practical applicability with the introduction of multiple-breath, portable hand-held devices. Measurement of EBT using these is less dependent on the ambient environment and easier to perform. Studies have been conducted to explore the relationship between EBT and different physiological characteristics, and to assess possible confounding influences in the process of measurement. The value of the method has been explored in the diagnosis and monitoring of asthma, chronic obstructive pulmonary disease and other respiratory diseases. While initially, emphasis focused on airway inflammation as the

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primary process to be captured by this method, it was subsequently realised that destructive and other remodelling processes reducing the integral contact surface of the conducting airways and/or damaging their vasculature would also affect the end result by shifting EBT downwards. As obstructive airway disease is, in most cases, a combination of airway inflammation and remodelling/destruction, EBT should be viewed as an individual characteristic indicating fluctuating changes in the balance of these processes. Hence, an important potential application of the method is in monitoring airway diseases.

EBT measurement has emerged as an attractive noninvasive new approach in respiratory and, possibly, other diseases. Systematic research will determine its place in clinical practice.

Measuring body temperature with a variety of cheap and affordable devices, *i.e.* thermometers, has long established itself as a standard method in daily healthcare. The rationale behind this approach is that the human organism needs to maintain the temperature of its vital organs (core body temperature) within a narrow range to allow essential enzymatic reactions to occur. Changes outside this range are indicative of pathological states and processes [1].

Temperature measurement has long been used to assess fever and its course as a diagnostic and prognostic tool in infectious diseases. Nowadays, thermometry is applied in a broader spectrum of disease states, in which inflammatory processes play a part, or when controlled hypothermia is required [2]. For practical purposes, thermometry at traditional body sites is performed, giving estimates of the actual core temperature with a reasonable degree of approximation [3]. These are referred to as rectal, axillary, oral and tympanic/otic temperatures and are strongly correlated. All other conditions of measurement being equal, the differences between the temperature values at those body sites are due to the influence of the core-to-surface interface. While this may be considered a confounding factor from the point of view 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 the essence of the attempts to measure exhaled breath temperature (EBT). The deep structures of the lung typically have temperatures representative of the body core. It is determined by the blood flowing along the rich vascular network of the alveoli, imparting its thermal

energy to the alveolar gas content. During the breathing cycle, not only gases but also energy are 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 deriving from the left ventricle of the heart through the bronchial arteries. As blood is the main carrier of thermal energy, processes that would modify its flow within the airway walls might be reflected in the temperature of the outgoing air, *i.e.* EBT. High-precision gauging devices may pick up this signal and provide a basis for clinical inferences.

Evolution of the method for EBT measurement

EBT is one of the many characteristics of exhaled breath, the analysis of which is regarded as a promising noninvasive approach to respiratory and other diseases [4]. One of the components of exhaled breath that has become the focus of intensive research and has proven useful in assessing inflammation in asthma is the exhaled nitric oxide fraction (*FeNO*). The first experiments compared EBT to *FeNO* and were conducted about a decade ago in adults by PAREDI *et al.* [5] in London, UK and in children by PIACENTINI *et al.* [6] in Verona, Italy. Both teams used fast-reacting thermal sensors placed in front of the mouths of the tested subjects and analysed the rise of EBT during single-breath manoeuvres on a computer screen. This required a tightly closed laboratory environment with a constant temperature, minimal air movement and subject training to allow the recording of comparable

exhaled temperature curves. While the London team considered the rate of increase of EBT as indicative of asthma [5, 7], the researchers in Verona performed a series of experiments demonstrating that the plateau of the exhaled temperature curve is the variable distinguishing asthmatics from healthy controls [8, 9].

An alternative approach for EBT measurement was introduced by Popov *et al.* [10], who made use of a specifically designed portable device. This is based upon the principle of accumulation of the expired thermal energy of the tested subject in an insulated vessel containing a heat sink with high thermal capacity, thus making the measurement less dependent on ambient factors (fig. 1).

The subject exhales continuously into the thermal chamber of the device until the temperature of the heat sink reaches a plateau, indicating that a thermal equilibrium has been reached inside the closed system. Because of the ease of operation and the acceptability on the part of the patients, this instrument allows repeated measurements over time, with the potential for use as an individual device for measurements at home or in the working environment. Its usability has been further improved by upgrading the overall design, introducing an electronic processor and memory allowing automatic detection of the end of measurement, follow-up and analysis of the temperature curve on a computer [11]. Despite these technical improvements, acquiring measurement skills with the devices by both patients and medical personnel is essential for obtaining meaningful results. A detailed

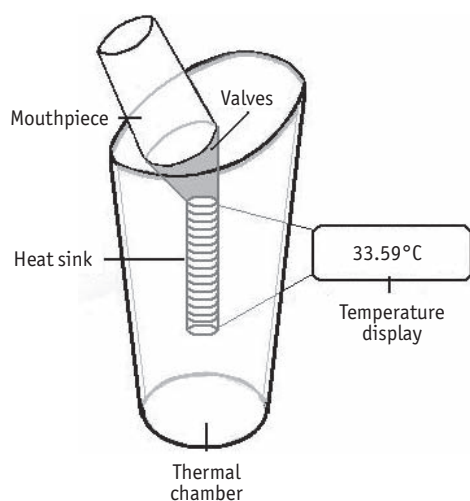


Figure 1
Schematic of the concept of a portable exhaled breath temperature measuring device.

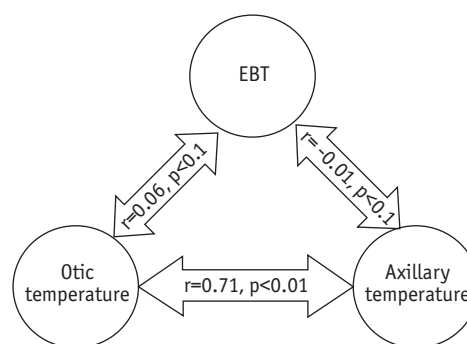


Figure 2
The lack of correlation between exhaled breath temperature (EBT) and body temperatures measured at traditional sites suggests that it is a different physiological indicator [10].

description of the engineering aspects of the device and method for EBT measurement has been the subject of a specialised review [12]. Ways to upgrade its applicability should involve shortening of the time for measurement and rendering it less dependent on the conscientious cooperation of the subjects (the latter improvement would make it usable also in infancy and in individuals unable to grasp verbal instructions).

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 and other anthropometric characteristics

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 [10]. One of the crucial questions that 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 (fig. 2).

Multiple regression analysis did not indicate a strong association of EBT with sex, height, weight, heart rate or blood pressure

Educational questions

1. What makes EBT different from temperatures measured at other body sites?
 - a. The quantity of epithelial lining fluid
 - b. Changes in the temperature in the alveolar compartment
 - c. The blood flow of the bronchial wall
 - d. The rate of breathing
 - e. All of the above
2. What are the confounders affecting EBT?
 - a. Food intake
 - b. Circadian influences
 - c. Smoking
 - d. Technical faults during the measurement process
 - e. All of the above
3. Which of the following anthropometric characteristics correlate with age in children?
 - a. Age
 - b. Sex
 - c. Weight
 - d. Height
 - e. All of the above
4. At what time during the day-night cycle is EBT at its highest in healthy individuals?
 - a. 7 h
 - b. 13 h
 - c. 19 h
 - d. 1 h
 - e. No significant differences around the clock

[10]. Age was a special focus of attention, as the method has potential for use in the paediatric population: a positive correlation ($r=0.75$, $p<0.001$) was established in healthy children aged between 3 and 17 years [13], supported also by the results of BARRETO *et al.* [14]. In a study by LOGIE *et al.* [15], multiple regression analysis pointed to slow vital capacity as a predictor of EBT in a study of 60 children aged between 9 and 11 years. However, they used an open, single-breath method in their assessments, in which room temperature also played a role. Age did not seem to be a major determining factor in adulthood, but there were indications that in elderly people, EBT may tend to be lower, probably also in relation to accompanying geriatric morbidities.

Healthy subjects have a different circadian course of EBT compared with axillary temperature: the acrophase (peak temperature) was registered at 19 h for EBT and at 13 h for axillary temperature [16]. The bathyphase (trough temperature) was the same for both circadian rhythms at 1 h. Repeated measures analysis found both circadian fluctuations to be statistically significant. Whether this is also true in patients with inflammatory airway diseases remains to be determined.

Factors affecting EBT measurement

EBT is affected by different activities in both health and disease states. Food intake is known to increase EBT. A study is in progress to determine the magnitude and nature of the food-dependent changes in EBT. Any natural components of the ambient air or gases, aerosolised fluids or particulate matter that can be inhaled by accident or intentionally can potentially influence EBT and need to be specifically explored. Thus, smoking one cigarette may give rise to increased blood flow in the airways with subsequent inflammatory events, as evidenced by the increase of EBT [17]. Seasonal high pollen counts increase EBT in sensitised subjects with allergic rhinoconjunctivitis with or without asthma [18]. Inhaled therapeutic and diagnostic agents have the potential to influence EBT due to their effect on the bronchial vasculature and the airway geometry, which has to be taken into consideration if this method is to be used for diagnosis and monitoring. In asthmatics and healthy controls, inhalation of 400 µg salbutamol did not consistently change the EBT, neither did it change after a methacholine challenge [19]. Still,

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.

EBT in respiratory diseases

Most studies on EBT to date have been performed in asthmatic patients and have suggested the utility of this approach to assess noninvasively changes in the degree of airway inflammation [5–8, 10]. EBT measurement captures asthma improvement in the course of anti-inflammatory treatment [20, 21]. Similarly to serial peak expiratory flow measurement, it follows a day-to-day pattern in line with the control of asthma [22].

XEPAPADAKI *et al.* [23] carried out a case-control study in 29 asthmatic children with or without a viral infection. They determined that EBT increases at the onset of virus-triggered asthma exacerbations. These results could be viewed as preliminary data suggesting a possible role of EBT measurements in the assessment of airway inflammation in children with virus-induced asthma. A longitudinal, prospective study is in progress to determine whether daily EBT measurements may predict in advance the onset of viral infections, giving a window of opportunity to prevent or abate subsequent exacerbations.

PERONI *et al.* [24] investigated the effect of exercise on EBT in a group of 50 controlled or partly controlled asthmatic children. They documented that it was not the baseline EBT, but rather the change in EBT, which correlated with the per cent decrease in forced expiratory volume in 1 s after exercise. They hypothesised that EBT might represent a composite indicator of the pathological mechanisms in asthma, including airway vascular remodelling, rather than just being a marker of airway inflammation. This hypothesis is in keeping with the conclusion of the study by PAREDI *et al.* [7], who suggested that EBT may also represent a marker of airway vascular changes in asthma, as microvascular proliferation at the site of the bronchial mucosa is one of the key features of airway remodelling in asthma correlating with severity.

The notion that EBT may also be affected by airway remodelling was supported by data in patients with chronic degenerative respiratory disease. PAREDI *et al.* [25] were the first to report

slower rise of exhaled breath temperature in chronic obstructive pulmonary disease (COPD). The idea was further confirmed in studies in both children [26, 27] and adults [28–30]. Indeed, when the overall number of airways and their vasculature is reduced by a restrictive remodelling process, this impacts the level of EBT, which would start to decrease proportionally to the level of destruction. KLØKSTAD *et al.* [28] have found significantly lower EBT in COPD patients as 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. This notion was further developed by the same team with the demonstration that when COPD patients exacerbated, this still led to an increase in EBT [29]. Indirect evidence of the lower potential of the airways to heat up the outgoing air is the prolonged duration of the measurement procedure with the multiple-breath EBT measurement device [31].

Discussion

The idea that gave the initial impetus to research into the measurement of EBT was simple and straightforward: as airway inflammation has gained unanimous recognition as hallmark of asthma and as increased temperature is a prominent feature of inflammation, measuring the thermal signal from the inflamed airways would be a simple measure of the state of asthma control. As data started accumulating over time, the insight into the nature of the processes shaping EBT gained complexity. An important element configuring the EBT model

is airway remodelling. 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 be quite low, thus adding an important dimension to the applicability of the method. Indeed, these two noninvasive methods can be used conjointly to detect eosinophilic airway inflammation signal by assessing increased FeNO in subjects with decreased EBT due to airway remodelling. Baseline EBT is formed by the processes of inflammation and remodelling, which act in opposite directions and, sometimes, the resulting vector could be lying within the normal range, as paradoxically suggested by some studies [27, 29]. From this point of view, the broad clinical spectrum of chronic airway diseases should be regarded as individual combinations of inflammation and remodelling. Documenting EBT at a time-point of adequate disease control may serve as a reference to assess the onset of inflammatory exacerbation in the short term and of advancement of remodelling/destruction in the long term. A prerequisite of this would be monitoring with user-friendly, individual devices for EBT measurement.

Conclusion

The temperature of the exhaled breath used to be an unexplored area on the map of human physiology and disease, which is now gradually being filled in. Ongoing systematic research will determine its place in the clinical setting and as a tool in home monitoring.

5. What pathological mechanisms determine the level of EBT in chronic obstructive pulmonary disease patients?
 - a. Inflammation of the airway walls
 - b. Remodeling of the airways
 - c. Destruction of functional lung tissues
 - d. Impaired bronchial blood flow
 - e. All of the above

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