Evaluation of a simple, potentially individual device for exhaled breath temperature measurement

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Summary
Rationale: Inflammation is a universal pathological reaction and is characterized among other things by increased heat production. The question stays whether the contribution of the inflamed lung tissues to the overall exhaled breath temperature (EBT) can be reliably detected and used in everyday clinical practice.

Methods: We have designed a simple device for assessment of EBT and explored its performance under standard indoor conditions. We made our measurements in the morning hours, documenting the ambient conditions (room temperature, humidity, atmospheric pressure), and physiological characteristics of the tested subjects (heart rate, blood pressure, otic and axillary temperature). We assessed its day-to-day reproducibility in 17 healthy volunteers and its ability to discriminate between the same subjects without respiratory disease and uncontrolled asthmatics (n = 14). We also compared the EBT of the 14 asthmatics before and after anti-inflammatory treatment.

Results: No association was found between EBT and any of the ambient conditions: room temperature, atmospheric pressure and humidity. While otic and axillary temperatures, which were measured in parallel, maintained high correlation between each other (Spearman’s rho = 0.71, p < 0.01), EBT did not show meaningful association with any of them. The EBT (°C) of asthmatics (median 35.45, range 34.12–36.09) was higher than that of controls (34.84, 32.29–35.84), (p = 0.009, Mann–Whitney U test). Anti-inflammatory treatment brought down the EBT of the asthmatics (34.78, 33.23–36.06), (p = 0.001, Wilcoxon Signed Ranks test), while significantly improving their spirometry too.

Conclusions: Measurements of EBT with the device we constructed are not significantly influenced by changes within the accepted range of a standard indoor environment. EBT represents a different characteristic of the human organism than otic and axillary temperatures. EBT is increased in uncontrolled asthmatics and decreases under anti-inflammatory treatment.

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Background

Inflammation is a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute or wall off (sequester) both the injurious agent and the injured tissue. It is characterised in the acute form by the classical signs of pain (dolor), heat (calor), redness (rubor), swelling (tumor) and loss of function (functio laesa). Histologically, it involves a complex series of events, including dilatation of arterioles, capillaries and venules, with increased permeability and blood flow, exudation of fluids, including plasma proteins and leukocyte migration into the inflammatory focus. The mere origin of the word (from Latin: inflammatio, inflammare = to set on fire) implies a fervent, heat-producing process. Infections and/or immunologic mechanisms may trigger the production of heat in different disease states. The systemic response to the invasion of the body by microbial pathogens such as bacteria and viruses as well as by nonmicrobial, deleterious physical and chemical insults is denoted as fever and is associated with a complex sequence of events involving different pyrogenic stimuli and neurogenic pathways leading to increase in the core temperature of the body. This has long being recognized as an important characteristic of different morbid conditions and has rendered temperature measurement and monitoring (thermometry) as an integral part of the standard physical examination of patients.

While fever is a systemic reaction of the whole organism, local inflammatory events fuel clinical symptoms in different organs in acute and chronic infectious and noninfectious diseases. Certain organs, like the joints in rheumatic diseases, are readily accessible for physical examination and increased local temperature can be directly assessed, but others, like the lung and airways, are not accessible for direct assessment. Measurement of the core body temperature in the axilla, mouth, ear or rectum may not add useful information for the degree of inflammation in an organ like the lung. At the same time, airway inflammation is considered the most prominent feature of a chronic respiratory disease with heavy burden to society and the individual sufferers like asthma. The current state of knowledge portrays this disorder as infiltration of the airway wall and mucosa by different inflammatory cells, whose products and activity are associated with the disease specific characteristic of airway hyperresponsiveness, leading to recurrent episodes of airflow obstruction. The inflammatory nature of asthma has been proven by hundreds of studies employing invasive (bronchoscopy with biopsies and bronchoalveolar lavage) and noninvasive (sputum examination, volatile and liquid phase components of exhaled air) methods. Despite this sound theoretical basis, the diagnosis and management of asthma in routine practice are based on assessment of symptoms and lung function measurements: spirometry with response to bronchodilators, airway responsiveness to bronchoconstrictors like metacholine, serial peak expiratory flow (PEF) measurements. The reason for this derives from the deficiencies associated with the methods for airway inflammation assessment: bronchoscopy bears substantial discomfort and some risk for the patients; sputum collection and examination is not possible for all subjects and the protocol is rather time consuming; measurement of exhaled breath components, among which nitric oxide appears to be most prominent, is quite sensitive to ambient conditions and technical confounding factors, requires further standardization and is quite expensive for routine application. None of the listed methods allows feasible day-to-day assessment of the level of airway inflammation in primary healthcare and/or by the patients themselves.

Inflammatory changes are also inherent to other acute and chronic respiratory disorders like airway viral infections (usually referred to as “common cold” and “influenza”) and obstructive pulmonary disease (COPD), with specific patterns of the underlying pathogenetic processes. Many of the inflammatory mediators like TNFα, IL1, IL6, IL10 are implicated in the complex network of signals in asthma, COPD, viral and bacterial lung infections and systemic fever states. The role of the pyrogen TNFα in tuberculosis has also been well demonstrated.

It is very likely that inflammation would alter the thermal balance of the affected tissues in respiratory diseases. The question stays whether these changes can be reliably detected against the background of “white noise” emitted during the complex processes of heat exchange in the course of breathing. Paredi et al. and Piacentini et al. have measured the temperature of the exhaled breath of asthmatics by using fast reacting temperature sensors in conjunction with exhaled breath nitric oxide measurements. Their approach to measure the temperature of exhaled breath is rather sophisticated and difficult to standardize, but still they have found a correlation between the amount of the exhaled nitrogen oxide and some features of the temperature recordings they did. This reinforced our long dating idea to devise a precise, simple and reliable thermometer to measure exhaled breath temperature (EBT), so as to start filling in a largely unexplored area on the map of human physiology and pathophysiology.

The present study reveals the potential of a new device and method to measure EBT.

Methods

Device and procedure

The thermometer for EBT measurement consists of two main components: a 0.5 L silver plated flask in a metal cylinder (thermos) and a thermal block with an in-built temperature sensor (Fig. 1). The thermal block has high thermal capacity and excellent heat conduction properties. When the exhaled breath gets in the camera, it overflows the thermal block and fills the flask. The inflow opening is with a reversion valve which closes it during inhalation. Thus the last portion of exhaled air, which has stayed longest in the lungs, remains in the camera and imparts its temperature to the thermal block. The superfluous air comes out through outflow openings. The temperature in the camera is assessed by measuring the resistance of the thermal sensor by means of a digital ohm-meter. The measurement is performed at 1 min intervals and continues until no further increment is noted. The time for reaching this thermal equilibrium is between 5 and 10 min. The thermal sensor is calibrated in two points of the range 0–36 °C and the measured value is extrapolated.
The technical characteristics of the device are as follows:

- measurement range: 20–40 °C,
- discriminating ability: 0.01 °C,
- time until equilibrium: < 10 min,
- Volume of the camera: 0.5 L, and
- weight: 320 g.

The air temperature in the room in which EBT was measured used to be in the range 18–25 °C, atmospheric pressure was 952–982 mPa, and relative humidity was 22–53%. These indoor air characteristics were recorded at the time of onset of the procedure and along with the characteristics of the examined subject. Subjects were instructed to hold the device with one or two hands, to purse their lips around the mouthpiece, and to proceed as if inflating a balloon: to inhale freely through the nose and to exhale into the device at a rate and depth suiting their normal tidal breathing rhythm. The investigator measured with a stopwatch the time elapsed from the beginning of the measurement and at 1 min intervals recorded the indication of the ohm-meter of the device. The measurement lasted until the same value repeated itself on two consecutive measurements 1 min apart. The end value was entered into an EXCEL calculation sheet with a formula converting Ohms to degrees Celsius to yield the final result. After conclusion of the measurement, the device was taken apart, washed with a disinfectant solution, rinsed with water, and left to dry out at room temperature.

Study design

We performed three different series of experiments to evaluate:

1. dependence of the EBT measurement on ambient indoor conditions, on other physiologic characteristic of the tested subjects, and the reproducibility or the measurements on subsequent days ("Reliability study"),
2. the discriminative capacity of the method to differentiate between asthmatics and nonasthmatics ("Discriminative study"), and
3. to assess potential changes in the EBT after anti-inflammatory treatment in asthmatics ("Treatment study").

Subjects

In accordance with the study design, two different sets of subjects from among the personnel and patients of the Clinic of Allergy and Asthma in Sofia were recruited for the study after giving their informed consent:

1. Reliability study: All EBT measurements made were pooled together and possible associations with the other indoor air characteristics (room temperature, atmospheric pressure, relative humidity) were sought. Relationships between EBT and other individual characteristics (age, gender, height, weight, pulse, systolic and diastolic blood pressure, otic and axillary temperature) were explored separately for healthy controls and asthmatics and for both groups together. EBT was measured at approximately the same time on two consecutive days in 17 nonsmoking subjects free of respiratory disease: 4 men; 6 atotics; age [years]: median 39, range 20–65: height [cm]: 165, 155–188; weight [kg]: 64, 48–91; FEV1 [% predicted] 103, 90–120.

\[
 t = \left[ \frac{3287.923}{\ln(80.057R)} \right] - 273, \quad \text{where } t \text{ is temperature [°C], and } R \text{ is resistance [Ohms]. It is specific for the device and has been worked out in the process of calibrating it.} 
\]
Discriminative study: EBT of the same 17 healthy subjects was compared with EBT of 14 patients with uncontrolled asthma as defined according to "level of control" in the latest edition of GINA 2006. The characteristics of the asthmatics are presented in Table 1.

Treatment study: EBT and spirometry were assessed in the same 14 patients with uncontrolled asthma after 1 week of anti-inflammatory treatment with inhaled corticosteroid (ICS) or systemic steroid (SCS) as prescribed by the treating physician.

Statistics

Descriptive analysis was employed to characterize subjects in the three different studies. Reliability analysis calculating intraclass correlation coefficient was used to assess the repeatability of the measurements in the "Reliability study". We could not demonstrate normal distribution of the EBT results, so we resorted to nonparametric tests. Subsequently, we presented summarized data as median (range) values.

Mann–Whitney U test was used to assess differences in EBT between healthy controls and asthmatics in the "Discriminative study". Multiple regression analysis was performed in the search of an association between EBT and the variables characterizing the studies subjects (age, gender, atopy, smoking status, asthma diagnosis, FEV1) and the indoor environment of the laboratory (room temperature, atmospheric pressure, humidity).

Wilcoxon's Signed Ranks test was used to assess changes in EBT of asthmatics before and after anti-inflammatory therapy in the "Treatment study".

Spearman's nonparametric correlation coefficient rho between EBT and otic/axillary temperature measurements was calculated separately for the healthy controls and asthmatics and for both of these groups as a whole.

Multiple regression analysis was performed using the stepwise method to seek association between EBT (dependent variable) and any of the measures of the ambient conditions in the room, where the measurements were performed: temperature, atmospheric pressure, and humidity (independent variables). This same approach was applied to identify associations with the other physiologic characteristics of the subjects: age, gender, height, weight, pulse, systolic, and diastolic blood pressure.

Two-tailed significance of 0.05 was accepted to be statistically meaningful.

SPSS 13 software package was used for the calculations.

Results

Reliability study.

Multiple regression analysis on all 132 measurements made with EBT as dependent variable and room temperature (values on separate days in the range 18–25 °C), atmospheric pressure (range 954–982) and humidity (ranges 22–72) as independent variables, did not pick any of the ambient conditions as significant determinants.

No significant correlations were established between EBT and the other body indices: age, gender, height, weight, heart rate, systolic, and diastolic blood pressure. Spearman’s correlation coefficient relating EBT and otic temperature was low for the healthy controls (rho = 0.16, p > 0.1), the asthmatics (rho = 0.15, p > 0.1), going further down when both groups were analyzed together (rho = 0.06, p > 0.1). At the same time, otic and axillary temperatures maintained high correlation between each other (rho = 0.71, p < 0.01)

### Table 1 Characteristics of subjects with uncontrolled asthma.

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Atopy</th>
<th>FEV1 (%) before Rx</th>
<th>Treatment (Rx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>M</td>
<td>186</td>
<td>98</td>
<td>Y</td>
<td>76</td>
<td>ICS</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>F</td>
<td>158</td>
<td>54</td>
<td>N</td>
<td>65</td>
<td>SCS</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>F</td>
<td>162</td>
<td>50</td>
<td>N</td>
<td>79</td>
<td>ICS</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>167</td>
<td>62</td>
<td>Y</td>
<td>79</td>
<td>ICS</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>M</td>
<td>173</td>
<td>85</td>
<td>N</td>
<td>71</td>
<td>ICS</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>F</td>
<td>163</td>
<td>70</td>
<td>Y</td>
<td>37</td>
<td>SCS</td>
</tr>
<tr>
<td>7</td>
<td>45</td>
<td>F</td>
<td>171</td>
<td>75</td>
<td>N</td>
<td>41</td>
<td>SCS</td>
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<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>167</td>
<td>58</td>
<td>Y</td>
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<td>30</td>
<td>F</td>
<td>162</td>
<td>50</td>
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<td>89</td>
<td>N</td>
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<td>Y</td>
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<td>N</td>
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</tr>
<tr>
<td>14</td>
<td>28</td>
<td>M</td>
<td>180</td>
<td>77</td>
<td>Y</td>
<td>85</td>
<td>ICS</td>
</tr>
</tbody>
</table>

Median: 39 M = 7 Median: 167 Median: 75 Y = 6 Median: 74 ICS = 5


Abbreviations: Y = yes; N = no; M = males; F = females; FEV1 = forced expiratory volume in 1 s; ICS = inhaled corticosteroids; SCS = systemic corticosteroids.
There was a significant difference between EBT treatment study. There was significant difference between EBT discriminative study. The heat balance of the airways by unknown mechanisms.18 suggested that this drug may exert its action by enhancing sely, a study on the protective effect of cromolyn sodium on separate days. It was also evident that air humidity was also an important factor to consider in the process of warming up the inspired air.

The lung serves as an interface between the internal milieu of the organism and the ambient environment for gas, but also for heat exchange. The latter has proven to be of great importance in human physiology and pathophysiology, and has been studied extensively since the middle of the last century.13-15 In a unique, unrepeatable nowadays experiment, McFadden et al.16 introduced in the airways of healthy volunteers a tubing with seven temperature sensors between the glottis and the subsegmental bronchus of the right upper lobe and demonstrated that the temperature of the underlying airway mucosa is decreased by higher ventilation rate and lower initial temperatures of the inspired air. It was also evident that air humidity was also an important factor to consider in the process of warming up of the inspired air.

Thermal balance of the airways was suspected to play an important role in exercise-induced asthma (EIA), where cold air, hyperventilation, and especially the combination of these two factors provoked bronchoconstriction.17 Conversely, a study on the protective effect of cromolyn sodium suggested that this drug may exert its action by enhancing the heat balance of the airways by unknown mechanisms.18 It is generally believed nowadays, that asthmatic airways are more vascularized and have higher blood perfusion rates than normal airways.19,20 Paredi et al.10 dwelt upon the different rate of rise of the EBT in asthmatics vs. controls, which they called ΔeT. They did not find a statistical difference between the absolute temperature plateaus reached by those two groups, but still their published data hint at a higher EBT of the asthmatics. Later the same team reported that ΔeT correlates with bronchial blood flow (Qaw) and exhaled nitric oxide, which gave the ground to conclude that it may reflect existing inflammation.21 Piacentini et al.11 measured EBT in asthmatic children and found significant correlation between peak expiratory temperature (PET) and plateau expiratory temperature (PLET) values and nitric oxide measurements. Very recently, they used professionally developed laboratory equipment to find significant differences between PLET of asthmatic and healthy children, but not between ΔeT of the two groups.22 The device and method in these studies are substantially different from our approach. While the fast reacting thermocouples placed in front of the mouth of the tested subject require stringent control of the laboratory environment in terms of ambient air temperature and ventilation, and extensive training of the tested subjects, our device represents a thermally isolated chamber, which holds an inbuilt metal core with high thermal conductivity, to which each subsequent breath of the tested subject imperatively brings another quantum of energy until a heat equilibrium (temperature plateau) with the lung/airways is reached. The resolution of this thermometer is 0.01 °C and it allows the subjects to breathe at their convenience, even taking breaks to swallow or to make a verbal remarks. What we measure most likely to corresponds to the PET measured by Piacentini’s team.

The starting temperature of the thermal block of our device corresponds to the temperature of the place where
the device is kept. After each measurement, some condense is visible on the silver-plated interior of the thermal camera. It is due to the cooling down of the exhaled breath of the subject before closed system reaches thermal equilibrium. This may have some minimal effect on the duration of the measurement, but it is not likely to affect the level of the final thermal balance reached. The condense should be washed away with disinfectant fluid and water and the dissembled parts need to be disinfected and dried at room temperature before using the device again.

With the single prototype we used in this study, measurement times ranged between 4 and 10 min. As the time to make a measurement (to reach thermal equilibrium) with our device differs between subjects, we anticipated that it might be related to the rate of temperature increase ($\Delta T$). However, no differences emerged between the time to reach equilibrium between asthmatics and healthy controls. We assume that other subject characteristics like ventilation rate, the individual pattern of the respiratory maneuvers may play predominant role in determining the duration of the EBT measurements with our device.

Subjects did not require lengthy training to use the device and did not find the procedure difficult to cope with. The device holds the potential to be further upgraded: it can be made still smaller, and the time for measurement could be shortened. Its construction does not utilize expensive materials. These features make it a suitable candidate for a cheap (individual?) device for EBT measurement in routine practice for purposes still to be identified.

Similarly to a PEF meter, single (point) readings of this personal “inflammometer” may not be very meaningful per se, but repeated daily measurements might help individual asthma management. We also have anecdotal evidence that the device displays sharp increase of the EBT at onset of viral airway infections when no effect on armpit temperature has been recorded. The poor correlation between EBT and otic/axillary temperature measurements suggests that these represent different physiological characteristics. Extensive experiments would identify the separate applications of this simple device for EBT measurement so that it could take a place at the pharmacy shelves alongside the other members of the medical thermometers family.

Conclusions

The device we constructed can measure the temperature of exhaled air in human subjects in a simple and acceptable noninvasive and user-friendly way. The measurements made with it are not significantly influenced by changes within the accepted range of standard indoor environment characteristics. EBT represents a different feature of the human organism than the otic and axillary temperatures. EBT is increased in uncontrolled asthmatics and decreases under anti-inflammatory treatment. Further experiments are warranted to find out if it can be applied as individual device for asthmatics to assess the degree of control of their airway inflammation. Studies in other lung diseases may provide evidence about the validity and usefulness of the method in other chronic and infectious pulmonary diseases.

Conflict of interest

T. Popov and S. Dunev have submitted an application for patent for the EBT device.
T. Kralimarkova, S. Kraeva, and L.M. DuBuske have no employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding related to the information provided in this article.

References


