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## Dynamics of exhaled breath temperature after smoking a cigarette and its association with lung function changes predictive of COPD risk in smokers: a cross-sectional study

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Exhaled breath temperature (EBT) is a biomarker of inflammation and vascularity of the airways already shown to predict incident COPD. This cross-sectional study was aimed to assess the potential of EBT in identifying “healthy” smokers susceptible to cigarette smoke toxicity of the airways and to the risk of developing COPD by analysing the dynamics of EBT after smoking a cigarette and its associations with their demographics (age, smoking burden) and lung function. The study included 55 current smokers of both sexes, 29–62 years of age, with median smoking exposure of 15 (10–71.8) pack-years. EBT was measured at baseline and 5, 15, 30, 45, and 60 min after smoking a single cigarette. Lung function was measured with spirometry followed by a bronchodilator test. To compare changes in EBT between repeated measurements we used the analysis of variance and the area under the curve (EBT<sub>AUC</sub>) as a dependent variable. Multivariate regression analysis was used to look for associations with patient characteristics and lung function in particular. The average (±SD) baseline EBT was 33.42±1.50 °C. The highest significant increase to 33.84 (1.25) °C was recorded 5 min after the cigarette was smoked (p=0.003), and it took one hour for it to return to the baseline. EBT<sub>AUC</sub> showed significant repeatability (ICC=0.85, p<0.001) and was significantly associated with age, body mass index, number of cigarettes smoked a day, baseline EBT, and baseline FEV<sub>1</sub> (R<sub>2</sub> 0.39, p<0.001 for the model). Our results suggest that EBT after smoking a single cigarette could be used as early risk predictor of changes associated with chronic cigarette smoke exposure.

**KEY WORDS:** EBT; cigarette smoking; COPD risk; small airway dysfunction; cigarette smoke toxicity

New estimates predict that by 2020 chronic obstructive pulmonary disease (COPD) will become the third leading cause of death worldwide (1). Its major aetiopathogenic feature – the damage of the small airways (small airway dysfunction) – is present from the early stages of COPD and becomes more prominent as the disease progresses (2). However, current tests of small airway function have not been widely accepted for routine use in the early stages of the disease because their results vary significantly, there are no validated reference ranges, CT scans follow complex protocols, and/or because they cost a lot. Diagnosing COPD in later stages, however, means that the lungs have already been severely damaged. It is therefore essential to find a

new, possibly non-invasive early-stage diagnostic method to prevent the development of the disease. One of the methods showing potential in that respect is exhaled breath temperature (EBT) measurement. It has recently been introduced as a new, non-invasive marker of inflammation of the respiratory tract in patients with respiratory diseases (asthma, COPD, cystic fibrosis, bronchial carcinoma), as it was consistently and significantly higher than in healthy controls (3, 4). As a biomarker of inflammation and vascularity of the airways it can be used alone or in combination with other inflammatory biomarkers like leukocyte and eosinophil counts, exhaled nitric oxide (FeNO), C-reactive protein, and club cell secretory protein (3, 4).

Airway sensitivity to cigarette smoke is somewhat specific in COPD, as less than 30 % of smokers develop

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COPD during their lifetime. Our recent cohort research (4) showed that an increase in EBT five minutes after smoking a single cigarette could be moderately predictive of incident COPD in smokers over two years of follow-up. What that study missed to investigate was the dynamics of EBT after a single smoked cigarette and how this dynamics relates to chronic cigarette smoke exposure and lung function, small airway dysfunction in particular, as an early marker of future COPD. Therefore, the aim of this study was to assess the potential of the dynamics of EBT after smoking a single cigarette in identifying smokers prone to COPD by associating it with lung function (small airway dysfunction) and demographics (age, sex, smoking burden).

## PARTICIPANTS AND METHODS

### Participants and study design

This cross-sectional study included a group of 55 current smokers: 43 women and 12 men, 29–62 years of age, whose median smoking exposure was 15 pack-years (Table 1). It was a sub-study of the MARKO project published elsewhere (5). None of the participants had a history of chronic respiratory disorders or cardiovascular or other significant systemic diseases. The testing was conducted at least four weeks after an acute respiratory episode and participants were instructed to restrain from smoking, eating, drinking, and taking any medicines at least two hours before and during the testing.

The diagnostic workup included medical history, physical examination, baseline EBT, and EBT at 5, 15, 30, 45, and 60 min after having smoked a cigarette, and lung function measurements followed by a bronchodilator test. In a random subsample of 12 participants EBT measurements were repeated at the same time on another day to test the repeatability of EBT dynamics. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethics committees of the Srebrnjak Children’s Hospital (No. 4/2010) and the University Hospital Center Osijek (No. 25-1:10359-4/2014). All patients provided written informed consent.

### Lung function

Lung function was measured with spirometry using a computerised pneumotachograph (Jaeger®, CareFusion, Yorba Linda, CA, USA) according to the ATS/ERS guidelines (6), and the record included the best of three technically satisfactory attempts. The bronchodilator test was done by repeating spirometry 20 min after salbutamol (400 µg) inhalation using an inhalation chamber. Spirometric indices – forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), FEV<sub>1</sub>/FVC ratio, peak expiratory flow (PEF), and forced expiratory flow at 75 % of FVC (FEF<sub>75</sub>) – were recorded as absolute values, percentages of the predicted values, percentiles, and z-scores according to Quanjer (7, 8).

### Exhaled breath temperature

EBT was measured using an X-Halo® device (Delmedica Investments, Singapore) according to a previously validated method (9, 10). We measured multiple expirations, with the device signalling the end of measurement when EBT reached thermal equilibrium. Details about the measurement have been described elsewhere (3). In short, patients inhaled through the nose and exhaled into the device in a tidal breathing pattern through the mouth. Room temperature was 22–25°C and relative humidity 30–60 %. According to Popov et al. (10), measurement precision is 0.01 °C and reproducibility 0.99 (intra-class correlation coefficient).

### Data analysis

For statistical analysis we used STATISTICA version 12 (StatSoft, Inc., Tulsa, OK, USA). The minimal sample size of 39 for multivariate analysis of up to five independent variables was calculated using the expected R-squared of 0.36, statistical power of 90 %, and alpha of 0.05. Numerical data are expressed as means and standard deviations (SD) or as medians and interquartile ranges, depending on the type of distribution. Normality of distribution was tested with the Kolmogorov-Smirnov test. Categorical data are expressed as frequency and proportion (%). Numerical data

**Table 1** Baseline characteristics of the participants (n=55)

	Mean	SD	Range	
Age (years)	41.8	9.2	28.5	61.9
Women (%)*	43 (78.2)			
BMI (kg/m <sup>2</sup> )	24.54	4.09	17.53	33.46
Smoking (years)	20.7	8.8	6.0	42.0
Cigarettes per day	15.9	7.7	5	35
Cigarette smoking (pack-years)**	15 (7-24)		10.0	71.8
Systolic blood pressure (mmHg)	123	10	110	150
Diastolic blood pressure (mmHg)	76	8	60	100
Hearth rate per minute	71	8	58	91

\* results expressed as frequency (%). \*\* results expressed as median (interquartile range). SD – standard deviation; BMI – body mass index

not following normal distribution were normalised. Repeated measurements of EBT changes from baseline were tested with the analysis of variance (ANOVA). EBT changes from baseline until minute 60 were also calculated as the area under the curve [EBT<sub>AUC</sub>, expressed in °C\*minutes (°C<sub>min</sub>)] for each participant and analysed as a dependent variable. The repeatability of EBT<sub>AUC</sub> was tested using concordance correlation in a group of 12 participants and expressed as an intra-class correlation coefficient (ICC). The group was also divided into two subgroups regarding the EBT<sub>AUC</sub> (increase vs. decrease in EBT). The two subgroups were compared using Student's *t*-test. The association between EBT<sub>AUC</sub> and independent variables was assessed with univariate and multivariate regression analysis. Independent variables showing an association with EBT<sub>AUC</sub> of  $p < 0.10$  were used for a multivariate regression model using a stepwise approach. The final regression model was checked against significantly associated variables with variance inflation factor checked.  $P < 0.05$  was considered statistically significant for all tests, corrected for multiple comparisons.

## RESULTS

Table 2 shows lung function measurements in all participants. At baseline, mean EBT of all participants was  $33.42 \pm 1.50$  °C, then rose to its highest  $33.84 \pm 1.25$  °C 5 min after the smoked cigarette ( $p = 0.003$ ), and dropped back to  $33.51 (1.53)$  °C ( $p = 0.999$ , Table 3) 60 min after the smoked cigarette. This pattern, expressed as area under the curve (EBT<sub>AUC</sub>), showed significant repeatability (ICC = 0.85,  $p < 0.001$ ).

The participants, however, exhibited two distinct patterns: 37 had an increase in EBT after having smoked a cigarette, and 18 had a decrease (EBC<sub>AUC</sub> was significantly different,  $p < 0.001$ , Table 3), even though these two groups did not differ in baseline characteristics or lung function parameters ( $p > 0.05$  for all).

In univariate analysis, EBT<sub>AUC</sub> was significantly associated with baseline EBT, baseline and post-bronchodilator FEV<sub>1</sub>/FVC (expressed as absolute values, z-scores and percentiles), baseline FEV<sub>1</sub> (expressed as z-score and % predicted), post-bronchodilator FEV<sub>1</sub> (% predicted),

**Table 2** Baseline and post-bronchodilator lung function parameters (n=55)

	Mean	SD	Minimum	Maximum	
Baseline	FVC (% predicted)	96.20	8.19	76.10	113.30
	FVC (percentile)	40.12	21.05	2.45	81.41
	FVC (z-score)	-0.30	0.65	-1.97	0.89
	FEV <sub>1</sub> (% predicted)	98.43	11.70	75.82	128.97
	FEV <sub>1</sub> (percentile)	45.51	27.97	3.76	98.33
	FEV <sub>1</sub> (z-score)	-0.12	0.93	-1.78	2.13
	FEV <sub>1</sub> /FVC	0.83	0.07	0.67	0.95
	FEV <sub>1</sub> /FVC (percentile)	57.06	29.43	2.75	98.25
	FEV <sub>1</sub> /FVC (z-score)	0.30	1.11	-1.92	3.30
	FEF <sub>75</sub> (percentile)	60.93	25.62	19.47	99.13
	FEF <sub>75</sub> (z-score)	0.42	0.92	-0.86	2.38
	Post-bronchodilator	FVC (% predicted)	97.89	8.33	80.87
FVC (percentile)		44.42	22.34	5.85	87.43
FVC (z-score)		-0.17	0.66	-1.57	1.15
FEV <sub>1</sub> (% predicted)		102.22	10.15	80.05	128.14
FEV <sub>1</sub> (percentile)		55.13	24.97	7.04	97.82
FEV <sub>1</sub> (z-score)		0.18	0.80	-1.47	2.02
FEV <sub>1</sub> change (%)		4.16	4.69	-4.77	15.16
FEV <sub>1</sub> /FVC		0.85	0.06	0.71	0.95
FEV <sub>1</sub> /FVC (percentile)		65.61	26.97	9.89	98.27
FEV <sub>1</sub> /FVC (z-score)		0.60	1.02	-1.29	3.20
FEF <sub>75</sub> (percentile)		69.84	20.70	23.10	98.84
FEF <sub>75</sub> (z-score)		0.67	0.75	-0.74	2.27

SD – standard deviation; FVC – forced vital capacity; FEV<sub>1</sub> – forced expiratory volume in 1 second; FEF<sub>75</sub> – forced expiratory flow at 75 % FVC

**Table 3** Changes in EBT after smoking a cigarette (n=55)

	All (n=55)				Increase in EBT (n=37)		Decrease in EBT (n=18)	
	Mean	SD	Range		Mean	SD	Mean	SD
Baseline EBT (°C)	33.46	1.49	27.94	35.19	33.18	1.66	33.92	1.15
EBT 5 min after a cigarette (°C)	33.86	1.23	28.39	35.47	33.81	1.37	33.97	1.11
EBT 15 min after a cigarette (°C)	33.84	1.43	28.90	35.16	33.95	1.37	33.50	1.71
EBT 30 min after a cigarette (°C)	33.84	1.44	28.76	35.43	33.89	1.49	33.67	1.58
EBT 45 min after a cigarette (°C)	33.79	1.42	28.76	35.40	33.81	1.58	33.67	1.33
EBT 60 min after a cigarette (°C)	33.51	1.53	28.14	35.33	33.58	1.61	33.26	1.61
EBT <sub>AUC</sub> (°C <sub>min</sub> )	18.83	44.15	-101.73	179.23	37.36	41.94	-17.59	23.64

EBT – exhaled breath temperature; SD – standard deviation; AUC – area under the curve

and baseline and post-bronchodilator FEF<sub>75</sub> (expressed as percentile) (p<0.05 for all, Table 4). In multivariate analysis, EBT<sub>AUC</sub> correlated independently with age, BMI, number of cigarettes smoked a day, baseline EBT, and baseline FEF<sub>75</sub> (R<sup>2</sup>=0.39, p<0.001 for the model, Table 5).

## DISCUSSION

The main result of our study in “healthy” smokers was the sensitivity and discriminative power of EBT<sub>AUC</sub> as a measure of airway reaction to acute cigarette smoke exposure, that is, of individual susceptibility of the airways to cigarette smoke toxicity.

The individual pattern of EBT change from baseline to one hour after a smoked cigarette (EBT<sub>AUC</sub>) independently correlated with age, and inversely with BMI, baseline EBT, number of cigarettes smoked per day, and lung function (index representing small airways). Although on average EBT reached maximum and plateaued between 5 and 30 min after smoking, this response was not uniform for all participants. In fact, there were two distinct responses,

**Table 4** Significant univariate associations with EBT<sub>AUC</sub> (n=55)

Variables	r	p-value
Baseline EBT	-0.441	0.001
FEV <sub>1</sub> /FVC	-0.370	0.005
PB FEV <sub>1</sub> /FVC	-0.334	0.013
FEV (z-score)	-0.268	0.048
FEV (% predicted)	-0.272	0.044
FEV <sub>1</sub> /FVC (z-score)	-0.343	0.010
FEV <sub>1</sub> /FVC (percentile)	-0.339	0.011
FEF <sub>75</sub> (percentile)	-0.275	0.042
PB FEV <sub>1</sub> (% predicted)	-0.268	0.048
PB FEV <sub>1</sub> /FVC (z-score)	-0.296	0.028
PB FEV <sub>1</sub> /FVC (percentile)	-0.334	0.013
PB FEF <sub>75</sub> (percentile)	-0.269	0.047

EBT – exhaled breath temperature; AUC – area under the curve; SD – standard deviation; FVC – forced vital capacity; FEV<sub>1</sub> – forced expiratory volume in 1 second; PB – post-bronchodilator; FEF<sub>75</sub> – forced expiratory flow at 75 % FVC

significantly associated with participants’ demographics, acute (cigarettes per day) and chronic cigarette smoke exposure (age, pack-years), and lung function. This was, however, visible only from regression analysis because this kind of analysis exhibits greater statistical power. These findings suggest that a specific combination of genetic and epigenetic factors makes some individuals more prone to the adverse effects of cigarette smoke. The integrated expression of such a trait (cigarette smoke sensitivity phenotype) could be identified by assessing the change in EBT after smoking a cigarette (a cigarette challenge test).

These findings also support our earlier ones in smokers at risk of developing COPD (4), in whom the rise in EBT from baseline to minute 5 after smoking turned out to be a significant predictor of newly developed COPD over two years of follow-up (4).

Tobacco smoke is a complex mixture of more than 4000 compounds, most of which toxic, and is considered the major cause of COPD (11). According to Tuder et al. (12), cigarette smoke damages lung tissue in three stages: 1) initial tissue damage, 2) injury progression, and 3) propagation of cell damage (12). In the initial stage, tobacco smoke damages the cells of the alveolar septum through oxidative stress, apoptosis, and inflammation. In the second stage, continued exposure causes destruction of the alveolar walls and the development of emphysema. In the final stage, already damaged tissue causes its own destruction by activating signalling pathways which amplify the reuptake of pro-inflammatory cells and the expression of chemokines and cytokines (12).

Changes in EBT in this study seem to be associated with changes in vascularity (vasodilation or vasoconstriction). Numerous studies have tried to elucidate the development of COPD, but gaps remain in our understanding of the role of the airway vasculature, most likely because it is methodologically difficult to measure bronchial blood flow (13). Although earlier research suggests that pulmonary circulation is the one responsible for heat exchange in the airways between air and mucosa (14–16), McFadden et al. (17) believe that it is submucosal bronchial circulation that controls the temperature of exhaled air and causes the airways to narrow. Still, it is not clear if increased or

**Table 5** Multivariate regression analysis for EBT<sub>AUC</sub> (n=55)

	<b>B</b>	<b>SE (of B)</b>	<b>b</b>	<b>SE (of b)</b>	<b>t (49)</b>	<b>p-value</b>
Intercept			448.426	119.586	3.750	0.000
Age (years)	0.268	0.121	1.304	0.586	2.224	0.031
BMI (kg/m)	-0.291	0.120	-3.187	1.313	-2.427	0.019
Cigarettes per day	-0.202	0.114	-1.173	0.658	-1.782	0.081
Baseline EBT (°C)	-0.364	0.113	-10.846	3.374	-3.215	0.002
FEF <sub>75</sub> (percentile)	-0.246	0.114	-0.411	0.190	-2.165	0.035

Regression summary for the dependent variable EBT<sub>AUC</sub>, R=0.625, R<sup>2</sup>=0.391, F(5,49)=6.291, p<0.001. AUC – area under the curve; B – standardised regression coefficients; b – raw regression coefficients; BMI – body mass index; EBT – exhaled breath temperature; FEF<sub>75</sub> – forced expiratory flow at 75 %FVC

decreased vascularity is associated with the development of COPD. Two histological studies showed diminished bronchial vasculature in a COPD population (18, 19), which was later confirmed by more recent studies (20, 21). On the other hand, based on the presence of chronic inflammation of the airways, a vascular proliferation could be expected, at least in some COPD phenotypes (22).

The inverse association with the number of cigarettes per day found in our study could point to two distinct mechanisms: 1) lower intrinsic reactivity, or 2) too short washout time from the last smoked cigarette in participants with higher cumulative daily exposure (23). The second mechanism is supported by the inverse association of baseline EBT with EBT<sub>AUC</sub>. Higher baseline EBT is associated with lower reactivity to repeated acute exposure to cigarette smoke or an already present level of inflammation and higher vascularity like in other inflammatory disorders of the airways (23–25). Our participants, however, did not show any pathology suggesting COPD. Lower EBT and EBT dynamics in patients with COPD can suggest lower heat exchange between air and airway mucosa because it is obstructed by hypersecretion of mucus and/or reduced vascularity as a consequence of morphological changes of the blood vessels (26).

The finding of significant inverse association between EBT<sub>AUC</sub> and BMI in our participants may be owed to increased arterial stiffness found in obese population and therefore lower vascular reactivity (27).

Hogg et al. (28) reported contribution of the small airways to the total airway resistance in normal lungs, but also a four to forty-fold increase in small airway resistance in patients with emphysema. Several studies have confirmed that pathological changes in the small airways do not necessarily entail spirometric abnormalities consistent with COPD diagnosis, so these pathological changes are also known as the “silent zone” of the lungs (29, 30). Although mid-expiratory flow rates have been used to detect small airway dysfunction, they were not used for follow up because of a high degree of variability, which is why little has been known about the role of small airway dysfunction in the development of COPD until quite recently (31, 32). The ability to distinguish between the small airway damage and emphysema has been improved by the recent development of parametric response mapping, which allows

information from all lung voxels in an inspiratory multiple detector CT scan to be assigned to voxels present on an expiratory scan, making it possible to identify parts of the lungs with functional small airway disease (33). Boes et al. (34) used parametric response mapping analysis to monitor the progression of functional small airway disease and emphysema over a year and concluded that it was a transitional stage between normal lung and emphysema. Our results show inverse association between EBT<sub>AUC</sub> and the lung function parameter representing small airway dysfunction (FEF<sub>75</sub>), which suggests that EBT<sub>AUC</sub> could serve as a non-invasive marker of early pathological changes in smokers.

The limitations of our study lie in a relatively small sample, cross-sectional design of the study, and the use of spirometry to measure lung function parameters. However, the protocol using EBT<sub>AUC</sub> showed to be highly reproducible and in line with other research of early changes in COPD, including our own follow-up study (4).

Our current findings suggest that the dynamics of EBT after smoking a cigarette could be associated with bronchial vasculature and small airway dysfunction, which corroborates the results of our previous study from a different perspective and supports that EBT has a potential as a non-invasive early risk predictor of COPD in smokers.

#### Conflict of interest

None to declare.

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### Presječna studija dinamike temperature izdaha nakon popušene cigarete i njezina povezanost s promjenama plućne funkcije u pušača prediktivnima za rizik od KOPB-a

Temperatura izdaha (EBT) biomarker je upale i vaskularizacije dišnih putova za koji je utvrđeno da može predvidjeti nastanak KOPB-a. Cilj ove presječne studije bio je procijeniti potencijal EBT-a u identifikaciji "zdravih" pušača čiji su dišni putovi osjetljivi na toksični učinak duhanskoga dima uz rizik od nastanka KOPB-a. Taj se cilj planirao postići utvrđivanjem povezanosti dinamike EBT-a nakon popušene cigarete s demografskim karakteristikama (dob, spol, pušačka navika) i plućnom funkcijom ispitanika. U ispitivanje je bilo uključeno 55 aktivnih pušača obaju spolova u dobi od 29 do 62 godine, čiji je medijan izloženosti duhanskom dimu bio 15 (10 – 71,8) pušačkih godina (*pack-years*). EBT je mjereno na početku te 5, 15, 30, 45 i 60 minuta nakon popušene cigarete. Plućnu funkciju mjerili smo spirometrijski, uz susljedni bronhodilatacijski test. Za analizu dinamike EBT-a koristili smo se analizom varijance te smo izračunali površinu ispod krivulje u odnosu na početno mjerenje ( $EBT_{AUC}$ ) te  $EBT_{AUC}$  upotrijebili kao zavisnu varijablu. Multivarijatna regresijska analiza korištena je za utvrđivanje povezanosti  $EBT_{AUC}$  s karakteristikama ispitanika, posebice s plućnom funkcijom. Prosječni ( $\pm$ SD) izmjereni početni EBT bio je  $33,42 \pm 1,50$  °C, a najveće značajno izmjereno povećanje zabilježeno je 5 minuta nakon popušene cigarete ( $33,84 (1,25)$  °C,  $p=0,003$ ). Bilo je potrebno 60 minuta kako bise EBT vratilo na početnu vrijednost. Utvrđena je značajna ponovljivost  $EBT_{AUC}$  (ICC=0,85,  $p<0,001$ ). Ispitivanjem je utvrđeno je da je  $EBT_{AUC}$  značajno nezavisno povezan s dobi, indeksom tjelesne mase, brojem popušanih cigareta dnevno, početnim EBT-om te s početnim  $FEV_{75}$  ( $R^2=0,39$ ,  $p<0,001$  za model). Rezultati ove studije sugerišu da EBT nakon popušene cigarete može biti koristan kao rani prediktor rizika od promjena koje su povezane s kroničnom izloženosti duhanskom dimu.

KJUČNERIJEČI: temperatura izdaha; pušenje cigareta; rizik od KOPB-a; disfunkcija malih dišnih putova; toksičnost duhanskoga dima