Dynamic Changes of Nasal Airflow Resistance During Provocation with Birch Pollen Allergen

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Abstract. Over 500 million people suffer from allergic rhinitis around the world. This huge problem causes, in addition to individual impacts, a substantial economic burden to societies. There is a lack of an objective measurement method producing a reliable, accurate and continuous measurement data about the dynamic changes in nasal function. Here, a method to assess the nasal airflow resistance as a continuous signal is proposed and used to compute resistance values during the birch pollen provocation test. The required pressure recording is measured using a nasopharyngeal catheter and the flow recording is measured using respiratory effort belts calibrated with the new method. Ten birch pollen allergic and eleven non-allergic volunteers were challenged with control solution and allergen solution. Continuous nasal airflow resistance signals were computed and analyzed for the dynamic changes in the nasal airflow resistance. The derived signals show in great detail the intensity and timing differences in subjects' reactions. Quantitative results of resistance changes indicate that allergic and non-allergic subjects can be differentiated in a statistically significant degree using the proposed method. The method opens entirely new possibilities to research accurately the dynamic changes in non-stationary nasal function and could increase the reliability and accuracy of diagnostics and assessment of the effect of nasal treatments.

Keywords: Allergy · Challenge · Nasal resistance · Provocation test · Respiration · Polygraphic recorder · Spirometer

1 Introduction

Allergic rhinitis is a major global health problem due to its prevalence, impact on quality of life, along with the impact on work/school performance and productivity. It is also a substantial economic burden to societies. Allergic rhinitis is a systemic inflammatory condition which is inheritable and links with other illnesses like asthma [1–3]. Patients from all countries, ethnic groups and ages suffer from allergic rhinitis, and the prevalence is increasing in most countries of the world to the extent that in some countries over 50 % of adolescents are reporting such symptoms [4]. Using a conservative estimate, over 500 million people suffer from allergic rhinitis around the

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world. Therefore, specific guidelines and programs on the problem have been released, for example by European Union and World Health Organization [5–7].

Allergic rhinitis is diagnosed when the patient has allergic symptoms and specific antigens are detected in the blood. Typical symptoms include nasal obstruction, rhinorrhea, nasal itching, sneezing and eye irritation [6]. The presence of the allergy can also be verified by nasal provocation tests in which subjects are challenged with the suspected allergen. After provocation, changes in their subjective feelings of symptoms are recorded and the amount of secretions and the respiratory function of the nose are measured. Visual Analogue Scale (VAS) is commonly used as a method to measure subjective feelings of nasal obstruction [6]. Nasal provocation tests are done for example in the diagnosis of chronic rhinitis, at the beginning of desensitization and in the diagnosis of work-related respiratory diseases (occupational asthma, occupational rhinitis). To rule out non-specific nasal hyper-reactivity, the nasal mucosa is usually challenged with a control solution before the actual allergen solution.

Nasal function is difficult to quantify directly by clinical examination, which calls for objective measurement methods. Examples of these include peak inspiratory flow measurement (PNIF), acoustic rhinometry and rhinomanometry [8, 9]. PNIF is a noninvasive method that measures the nasal airflow during maximal forced nasal inspiration. Acoustic rhinometry, in its turn, assesses nasal geometry by measuring cross-sectional area of the nose as a function of the distance from the nostril. Rhinomanometer involves the simultaneous measurement of pressure and airflow from the values of which nasal airflow resistance is determined [10]. The resistance is characteristically described as a number that derives from one or more breathing cycles of data. In nasal provocation tests, the major response to measure is the rise in nasal airflow resistance. The rise is rapid (seconds or minutes) and the timing differs in different individuals. This makes it difficult to be detected with a rhinomanometer. One possibility is to determine the resistance with the rhinomanometer in certain time-intervals, but this has been indicated to give inconsistent and variable results with low reproducibility [11–13].

There is thus clearly a demand for a measurement method giving a reliable, accurate and continuous measurement data about the nasal airflow resistance. This kind of measurement could provide much more information about the fast changes in nasal function for instance during provocation tests.

In this paper, a new method to assess nasal function is proposed that produces nasal airflow resistance as a continuous signal at any sampling frequency allowing for analysis of dynamic changes in the resistance. The method is used to study nasal responses of test subjects from birch pollen allergic group and control group.

2 Methods

2.1 Study Subjects

The study protocol was approved by the institutional Ethics Committee of Oulu University Hospital. In Finland, the birch pollen is a common cause of the allergic symptoms such as intermittent seasonal allergic rhinitis for which reason it was chosen

as a substance for provocation tests. Ten (seven males) birch pollen allergic and eleven (eight males) non birch pollen allergic adult volunteers were recruited. They gave written informed consent and their background information was gathered using a questionnaire. The mean (SD) age of the allergic and non-allergic subjects was 24 (1) and 24 (3) years, respectively. The subjects had to be free of heart diseases, brain circulatory disorders and surgical operations of nose. Pregnant ones were rejected as well. The subjects were not allowed to be under medication that affects the function of their nose during a specific time period before the measurement. Additionally, they had to be free of any acute respiratory symptoms during the prior two weeks to the measurements. Before measurement, they were not allowed to have a smoke for four hours and heavy meal, caffeine or other stimulants for two hours.

Measurements were carried out in the spring time before the birch pollen season. An ear, nose and throat specialist examined all the subjects. Before measurements, the total IgE and the specific IgE for birch pollen were determined from blood to verify their allergy or non-allergy status (Table 1). Allergen specific IgE value under 0.35 kU/l means negative result for allergen. Values 0.35–0.69 kU/l, 0.70–3.49 kU/l, 3.50–17.4 kU/l and values above 17.5 kU/l represent the low level, the moderate level, the high level and the very high level of allergen specific IgE, respectively. As can be seen from Table 1, allergic subjects had different levels of allergy.

Table 1. Total IgE and specific IgE for birch pollen values [kU/l] for both groups.

Allergic subject	Total IgE	Specific IgE	Non-allergic subject	Total IgE	Specific IgE
1	119	1.58	1	12	0.00
2	143	55.70	2	6	0.00
3	504	66.00	3	9	0.00
4	59	26.20	4	9	0.02
5	68	51.20	5	27	0.00
6	128	13.20	6	13	0.00
7	95	16.50	7	19	0.18
8	24	3.23	8	3	0.00
9	60	2.18	9	8	0.00
10	165	57.40	10	24	0.00
			11	9	0.00

2.2 Measurement Devices

The pressure and respiratory effort belt signals were recorded with a polygraphic recorder (TrackIt, Lifelines Ltd, Hampshire, UK) with the sampling frequency of 100 Hz. The pressure recording was measured with a 1-mm diameter nasopharyngeal catheter (CH 06, Unomedical A/S, Denmark). The differential pressure sensor (Braebon Ultima Dual Airflow Pressure Transducer) referenced to the atmospheric pressure was connected to the catheter. A sterile filter (Minisart, Sartorius Ltd, Epsom, Uk) was used for protection in between the catheter and the pressure sensor. The pressure data

of the recorder was calibrated to physical units (Pascal). Respiratory effort belts (Ultima SmartBelt, Braebon Medical Corp., Ogdensburg, NY, USA) were attached to the subjects' rib cage and abdomen. For calibrating the signals from respiratory effort belts, simultaneous respiratory airflow signal was recorded with a spirometer (SpiroStar USB, Medikro Oy, Kuopio, Finland).

2.3 Challenge Protocol

An immunologically standardized, water-based commercial 1:10 000 SQU/ml extract of birch (Allergologisk Laboratorium A/S, Copenhagen, Denmark) was used in the nasal provocation test. The diluent solution of the allergen extract was used as a control solution (ALK, A/S, Copenhagen, Denmark). Both solutions were administered into the nasal cavities (bilateral challenge) by pump spray.

At first, the rib cage belt was placed on the xyphoid process and the abdominal belt near the umbilicus. Then, the subjects sat peacefully for a period of 30 min prior to the measurement to adapt themselves to the environment. They were instructed to sit in back upright position avoiding movements and speaking during all measurements. First, flow and respiratory effort belt signals were recorded for one minute with the spirometer and polygraphic recorder, respectively (Fig. 1). The data was used for calibrating the respiratory effort belt signals to flow signal as described in Sect. 2.4. The respiratory effort belts were kept on during the whole measurement protocol.

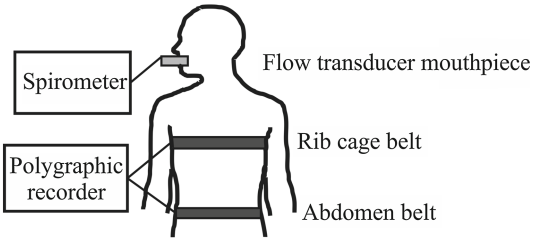

Fig. 1. Measurement of airflow and respiratory effort belt signals for belt calibration

Next, the spirometer was removed from the subject. A nasopharyngeal catheter was inserted 8 cm deep along the floor of nasal cavity into the nasopharynx, the tip of the catheter lying 1 cm anterior from the back wall of the nasopharynx. Air was blown with the syringe through the catheter to inhibit the nasal secrete blocking it. This was done before each protocol phase and every time that the catheter blocking was detected. Measurement setup of the signals needed for the computation of the nasal airflow resistance is depicted in Fig. 2.

At the first protocol phase, the baseline was recorded for 10 min. At the second protocol phase, to rule out nonspecific nasal hyper-reactivity, the nasal mucosa was challenged with a control solution sprayed carefully on the anterior nasal mucosa of both nasal cavities. After that, pressure and airflow were recorded for 5 min. At the third protocol phase, the allergen solution was inserted carefully on the anterior nasal mucosa of both nasal cavities, after which pressure and airflow were recorded for 20 min. After inserting the solution, the

recording was started as soon as possible but first waiting for the reactions such as sneezing to settle. After every phase, the subjects were asked about their worst sensation of obstruction in VAS scale during the phase. The VAS scale was from zero (totally open) to seven (totally obstructed). Finally, the nasopharyngeal catheter was removed and the calibration data collection was repeated with the spirometer.

After recording, all the signals were validated manually by using specially-made visualization software. All detected disturbances, originated for example from sneezing, snuffling, mouth opening and moving, were deleted from signals before analysis. Specific care was taken to maintain the correct synchrony between the signals.

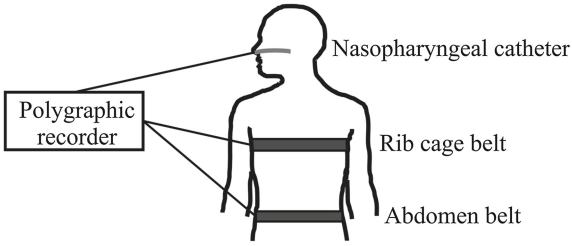

Fig. 2. Measurement of the nasal pressure and respiratory effort belt signals for the nasal airflow resistance computation.

2.4 Calibration Method of the Respiratory Effort Belts

A prediction of the respiratory airflow ŷ is commonly calculated from the dimensional changes of the respiratory effort belt signals by applying the method of multiple linear regression [14]. The conventional model is established by fitting the following model to the time-synchronized signals:

$$y = \beta_1 x_1 + \beta_2 x_2 + \varepsilon, \tag{1}$$

where the respiratory effort belt signals x_1 and x_2 from the rib cage and abdomen, respectively, are the predictor variables, parameters β_1 and β_2 are regression coefficients and ε is a zero-mean Gaussian error. In this model, one sample of each predictor variable is used at a time to predict the response variable y.

In this study, we use our previously published calibration method [15], which is based on the MISO (Multiple-Input Single-Output) system model consisting of a polynomial FIR (Finite Impulse Response) filter bank and a delay element, see Fig. 3.

This method extends the conventional one in an important way: it uses a number of N consecutive signal samples and linear filtering for each prediction. In the model representation, vector notation (bold letter type) is used below to denote that N consecutive signal samples of each predictor variable are included as components, and that the parameters are now vectors of dimension N. The calibration model can be established as follows:

$$y = \boldsymbol{\beta}_1^T \boldsymbol{x}_1 + \boldsymbol{\beta}_2^T \boldsymbol{x}_2 + \varepsilon, \tag{2}$$

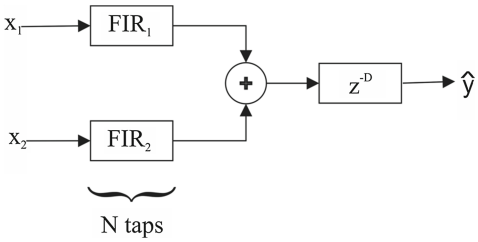

Fig. 3. Extended respiratory effort belt calibration method as a MISO system.

where $\boldsymbol{\beta}_1^T$ and $\boldsymbol{\beta}_2^T$ denote the N tap coefficients of filters FIR_1 and FIR_2 on Fig. 3, respectively. $\boldsymbol{x}_1$ and $\boldsymbol{x}_2$ are vectors including N consecutive samples from the rib cage signal and abdomen signal, respectively: $\boldsymbol{x}_1 = [x_{11}, x_{12}, \ldots, x_{1N}]^T$ and $\boldsymbol{x}_2 = [x_{21}, x_{22}, \ldots, x_{2N}]^T$. Superscript T denotes matrix transpose in the formula.

The spirometer signal and simultaneous respiratory effort belt signals are input to the regression analysis which yields optimal tap coefficients ($\boldsymbol{\beta}_1^T$ and $\boldsymbol{\beta}_2^T$) and minimal prediction error for both filters. During the calibration, tap coefficients are estimated with the method of least-squares.

There is always a delay between the spirometer signal and the respiratory effort belt signals due to two reasons. Firstly, spirometer measures airflow from mouth and respiratory effort belts signals are measured from the rib cage and abdomen. A delay occurs due to the time it takes for the airflow to propagate from the mouth to the lungs and vice versa. Secondly, each measuring device has internal delays. For these reason, the delay element z^{-D} is included at the output, see Fig. 3. The filter tap coefficients were solved for each feasible delay candidate as described above. The minimum error ε in the respiratory airflow prediction determined the optimal delay value.

In our previous study [15], the 0.3 s time window of FIR filters was found to produce the best respiratory airflow prediction. Thus, we used the same window size for FIR filters in this study as well.

2.5 Calculation of Continuous Nasal Airway Resistance Values

Our present measurement system acquires the pressure signal by using a small naso-pharyngeal catheter and the flow signal from the calibrated respiratory effort belts [16–19]. As the pressure signal is measured from inside the nose and the flow estimate signal from the rib cage and abdomen, a small lag between the signals occurs. The cross-correlation function between the signals with a predefined range of lag values is calculated and the maximum peak is found for correcting the misalignment.

In principle, the resistance R is defined by Ohm's law as $R = P / Y$, where P and Y denote pressure difference and flow, respectively. In rhinomanometry, the resistance is read out at a certain reference pressure value such as 75 Pa or 150 Pa. Mathematical models, such as Broms [20], offer parametric means to describe the nonlinear pressure/flow relationship. In this work, we adopted the model of Broms, see Fig. 4.

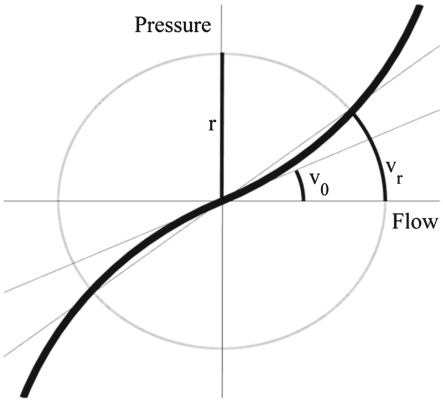

Fig. 4. A diagram of Broms model.

In the model, the pressure/flow relationship is considered to follow the equation

$$v_r = v_0 + cr, \tag{3}$$

where v_r is the angle when radius is r, v_0 is the angle in the origin and c is a constant describing the curvature of the trace. The resistance in radius r, indicated by R_r, is given by

$$R_r = x \tan v_r, \tag{4}$$

where x is a normalization factor depending on the data in hand. It was set to 10 by Broms, because it was best suited for their data [20]. In our study, we adapt x to signal variability (as explained below) and set

$$x = \frac{\sigma_P}{\sigma_Y}. \tag{5}$$

The pressure values can be several orders of magnitude smaller than the flow values. This often makes calculations unstable with noisy data, because the constant c and the angle v_r vary in a relative small range. Therefore, before calculations, we first normalize the pressure and flow values by dividing them with the corresponding standard deviations σ_P and σ_Y of the signals. The normalized data are used in the calculations and the original units are finally restored by using (5) in (4).

The Broms model is applied such that all the measurement data are used for identifying the model parameters in order to calculate a resistance value. Thus, the model expects the data to be stationary, while the nasal system is not stationary. We propose an extension to the Broms model such that it can be used for calculating a continuous nasal airflow resistance value through model adaptation to varying signal statistics.

We use the least-mean-square (LMS) algorithm to adaptively adjust the parameters v_0 and c in time. The normalized pressure signal P' and the flow estimate signal Y' are

the filter inputs. The filter length of only one time sample was found to be sufficient. The update formulas of v_0 and c are

$$v_0(k+1) = v_0(k) + \mu(k)\{v_r(k) - [v_0(k) + c(k)r(k)]\} \tag{6}$$

$$c(k+1) = c(k) + \mu(k)r(k)\{v_r(k) - [v_0(k) + c(k)r(k)]\}, \tag{7}$$

where

$$r(k) = \sqrt{P'^2(k) + Y'^2(k)} \tag{8}$$

$$v_r(k) = \tan^{-1}\frac{P'(k)}{Y'(k)} \tag{9}$$

The initial values for $v_0(0)$ and $c(0)$ were set as $\pi/4$ and 0.1, respectively. Then, the LMS filter was run with data samples in reversed order to initialize filter coefficients properly. The learning rate parameter $\mu(k)$ was defined as

$$\mu(k) = \frac{10^{-3}}{1 + e^{4-10r(k)+2r^2(k)}}. \tag{10}$$

The learning rate parameter was formulated to dampen the parts of signals, which could potentially produce noisy results. More details can be found in our previous paper [16].

Instantaneous resistance values are calculated over the whole measurement data and shown as dynamic plots over time.

2.6 Statistics

Statistical significance of resistance changes in the test subjects was assessed by Wilcoxon signed-rank test. Statistical significance between the subject groups, in its turn, was assessed by Wilcoxon rank-sum test (Mann-Whitney test). The null-hypothesis for statistical tests was that there are no differences in the medians of given data sets. Statistical dependence between variables of the subject groups was assessed by calculating the Spearman's correlation coefficient. It is a measure of statistical dependence between two variables.

3 Results and Discussion

3.1 Dynamic Changes in Nasal Airflow Resistance

Pressure and respiratory effort belt signals were recorded 10 min in baseline, 5 min after the control challenge and 20 min after the allergen challenge. At first, the respiratory effort belts were calibrated from the first 1 min calibration recording. Then, continuous nasal airflow resistance signals were computed from the pressure and

respiratory effort belt signals. Small gaps in the signals can be seen in the figures due to removing of the artifacts during manual validation.

An example case of the continuous resistance signals of birch pollen allergic subject is shown in Fig. 5. The subject shows a non-specific response after having been challenged with the control solution. After the reaction in the beginning, the resistance curve returns approximately to the same level as it was at the *baseline* (about 60 Pa/dm^3/s). After having been challenged with the allergen, a significant allergic reaction occurs. The resistance curve rises immediately and continues rising still about 8 minutes before settling down at about the level of 550 Pa/dm^3/s.

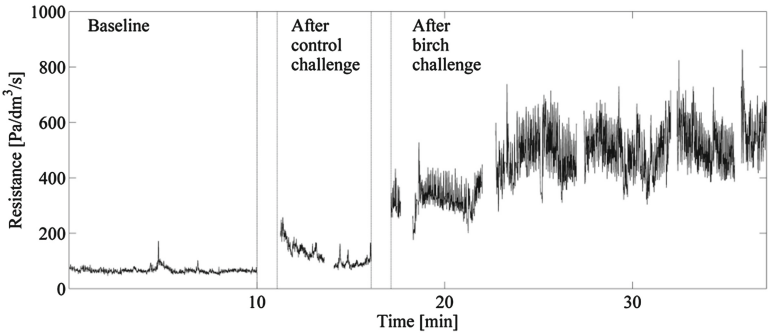

Fig. 5. Resistance curve for allergic subject with a short non-specific response to the control solution and fast and significant reaction to the birch challenge. Each pair of vertical bars marks the period of a challenge.

An example of continuous resistance signal from another birch pollen allergic subject is shown in Fig. 6. After the birch challenge, there is a much slower rise in the resistance than in the previous case (Fig. 5). The resistance rises about 11 min from the level of 150 Pa/dm^3/s in the *baseline* and *after control challenge* to the level of about 500 Pa/dm^3/s.

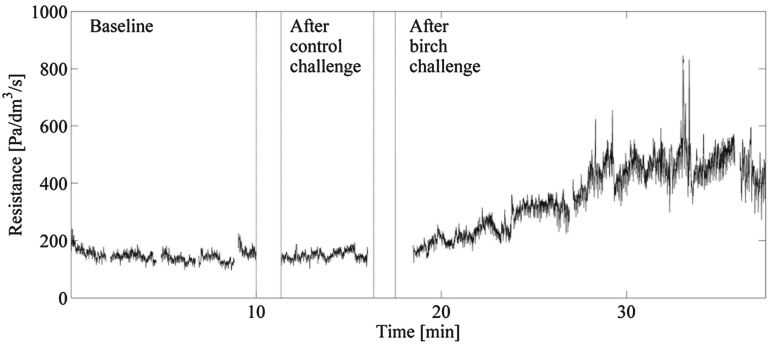

Fig. 6. Resistance curve for allergic subject with a slower significant reaction to the birch challenge.

In this study, we had a unique opportunity to assess also the rise times of resistance and relative rise of resistance after the challenge because we had accurate continuous resistance curves at our disposal. In the group of birch pollen allergic subjects, the median rise time of resistance before it settled to the stable level after the allergen challenge was 9 min. Median of relative rise of resistance after the birch challenge was 76 % and the rise varied from 17 % to 511 %. There was only weak correlation between the rise time and relative rise of resistance after the birch challenge (R = 0.318) confirming the fact that subjects react differently in intensity and in timing to the challenge.

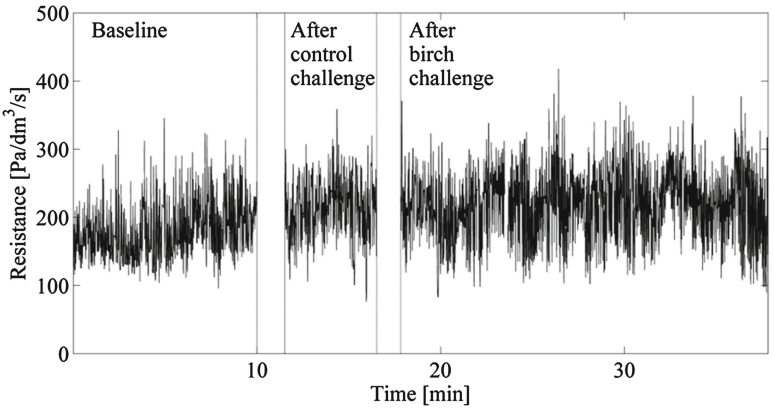

Fig. 7. Resistance curve for non-allergic subject with no reactions during the measurement.

Next, two cases of resistance curves from non-allergic subjects is presented. In Fig. 7, no reaction to either of the challenge solution is detected, but the resistance stays in about 200 Pa/dm^3/s during the whole measurement protocol. In Fig. 8, a short initial reaction in the resistance curve is obvious immediately after the control challenge and the allergen challenge. After the reactions, stable resistance curves follow. These reactions can be non-specific reactions: the nose reacts immediately to any manipulation.

3.2 Resistance Level Changes Between Protocol Phases

First, the respiratory effort belts were calibrated from the first 1 min calibration recording. The continuous nasal airflow resistance was then computed for the last two minutes of all phases: *baseline*, *after control challenge* and *after allergen challenge*. The last two minutes was chosen to get stable parts of the data and also to exclude the short-term non-specific reactions from the analysis. Tables 2 and 3 present the VAS values and mean nasal airflow resistances for each birch pollen allergic subject and non-allergic subject in the three phases, respectively. Group medians instead of means are given because data size is small and non-normal.

In the group of birch pollen allergic subjects, there was a statistically significant change in the resistance values between the *baseline* and *after allergen challenge*

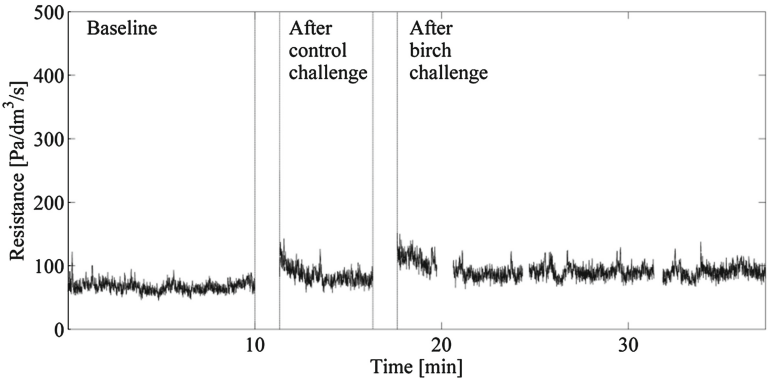

Fig. 8. Resistance curve for non-allergic subject with short non-specific responses after control challenge and after allergen challenge.

Table 2. VAS and nasal airflow resistance values for allergic subjects.

Subject	Baseline		After control challenge		After allergen challenge	
	VAS	Resistance [Pa/dm^3/s]	VAS	Resistance [Pa/dm^3/s]	VAS	Resistance [Pa/dm^3/s]
1	1	151	1	131	3	194
2	2	68	2	60	5	177
3	1	138	1	154	3.5	511
4	2	163	2	205	4	407
5	1	63	1	88	3	545
6	1	146	1	156	4	478
7	2	337	2	535	5	653
8	1	87	1	103	2	168
9	2	131	3	111	3	142
10	1	172	1	179	3	279
Median	1	142	1	143	3.3	343

($p = 0.005$) and in the resistance values between the *after control challenge* and *after allergen challenge* phases ($p = 0.005$). There was no statistically significant change in the resistance values between the *baseline* and *after control challenge* phases ($p = 0.202$). Respectively, in the group of non-allergic subjects, there was no statistically significant change in the resistance values between the *baseline* and *after allergen challenge* ($p = 0.068$) and in the resistance values between the *after control challenge* and *after allergen challenge* ($p = 0.248$). However, there was a statistically significant change in the resistance values between the *baseline* and *after control challenge* phases ($p = 0.005$). Both groups included subjects for whom resistance values increased transiently after control challenge: 50 % in the allergic group and 70 % in the control

Table 3. VAS and nasal airflow resistance values for non-allergic subjects.

Subject	Baseline		After control challenge		After allergen challenge	
	VAS	Resistance [Pa/dm^3/s]	VAS	Resistance [Pa/dm^3/s]	VAS	Resistance [Pa/dm^3/s]
1	1	402	1	462	1	374
2	1	70	1	80	1	92
3	1	131	2	150	1	130
4	1	128	1.5	134	1	124
5	1	178	1	314	1	299
6	1	212	1	214	1	235
7	1	76	1	89	1	108
8	1	114	1	176	1	150
9	1	187	1	211	1	193
10	1	54	3	54	4	71
11	2	216	2	277	1.5	217
Median	1	131	1	176	1	150

group, respectively. These individuals may have non-specific reactions to any nasal manipulations. With this small group size, a statistically significant resistance change in the group mean can easily occur due to random variation which may explain the result with the control group. To summarize the most important finding, the allergic group showed a large change in absolute resistance values during the provocation test, while the non-allergic group did not.

In the *baseline*, the median resistance was 142 Pa/dm^3/s and 131 Pa/dm^3/s for the allergic and non-allergic group, respectively. There was no statistically significant difference in the resistance between the two groups ($p = 0.756$). *After control challenge*, the median resistance was 143 Pa/dm^3/s and 176 Pa/dm^3/s for the allergic and non-allergic group, respectively. There was no statistically significant difference in the resistance between the two groups ($p = 0.512$). *After allergen challenge*, the median resistance was 343 Pa/dm^3/s and 150 Pa/dm^3/s for the allergic and non-allergic group, respectively. In this case, there was a statistically significant difference in the resistance between the two groups ($p = 0.020$). To summarize, the two study groups differ only in the responses to the allergen challenge.

Next, resistance changes of individual subjects are considered. The median change in the subjects' resistance between the *baseline* and *after allergen challenge* was 177 Pa/dm^3/s and 17 Pa/dm^3/s for the allergic and non-allergic group, respectively. There was a statistically significant difference in the resistance change between the two groups ($p = 0.000$). The median change in the subjects' resistance between the *after control challenge* and *after allergen challenge* was 118 Pa/dm^3/s and −15 Pa/dm^3/s for the allergic and non-allergic group, respectively. There was a statistically significant difference in the resistance change between the two groups ($p = 0.001$). The median change in the subjects' resistance between the *baseline* and *after control challenge* was 13 Pa/dm^3/s and 19 Pa/dm^3/s for the allergic and non-allergic group, respectively.

There was no statistically significant difference in the resistance change between the two groups ($p = 0.349$). To summarize, the individual subjects of the allergic group showed large changes in the absolute resistance values during allergen challenge, while individuals from the non-allergic group did not.

The median of relative change in the subjects' resistance between the *baseline* and *after allergen challenge* was 122 % and 11 % for the allergic and non-allergic group, respectively. There was a statistically significant difference in the relative resistance change between the two groups ($p = 0.002$). The median of relative change in the subjects' resistance between the *after control challenge* and *after allergen challenge* was 81 % and −7 % for the allergic and non-allergic group, respectively. There was a statistically significant difference in the relative resistance change between the two groups ($p = 0.000$). The median of relative change in the subjects' resistance between the *baseline* and *after control challenge* was 9 % and 15 % for the allergic and non-allergic group, respectively. There was no statistically significant difference in the relative resistance change between the two groups ($p = 0.426$). To summarize, large relative changes in the individual resistance values occurred only with the allergic group and in the allergen challenge phase.

There was no statistically significant difference in the VAS values of the *baseline* and *after control challenge* between the two groups ($p = 0.251$ and $p = 0.809$, respectively). Instead, there was a statistically significant difference between the groups in the VAS values of the *after allergen challenge* ($p = 0.0003$). When the change in VAS values between the two phases were studied, no statistically significant difference was found between the two groups in VAS change from *baseline* to *after control challenge* ($p = 0.468$) and statistically significant difference in VAS change from *baseline* to *after allergen challenge* ($p = 0.0006$) and from *after control solution* to *after allergen solution* ($p = 0.00007$). In the group of allergic subjects, a strong correlation was found between the S-IgE value and VAS change from *baseline* to *after allergen challenge* ($R = 0.735$, $p = 0.016$) and also between the S-IgE value and VAS change from *after control challenge* to *after allergen challenge* ($R = 0.735$, $p = 0.016$).

4 Conclusions

Here, a method to assess nasal function was proposed that produces nasal airflow resistance as a continuous signal at any sampling frequency allowing for analysis of dynamic changes in the resistance. The method uses pressure signal from nasopharyngeal catheter and calibrated respiratory effort signals from rib cage and abdomen. An LMS filter extension to the Broms model was presented that computes continuous resistance and adapts to the time-varying characteristics of the non-stationary nasal functioning.

Continuous nasal airflow resistance curves were presented from selected subjects of two subject groups – birch pollen allergic and non-allergic subjects. These curves demonstrate the dynamic changes in the subjects' nasal airflow resistance during the challenge. From the figures, the timing and intensity of the reactions can be seen in great detail. To our knowledge, this is the first time that it is possible to estimate accurately from the nasal airflow resistance: (1) how fast and strong the allergic

response occurs, (2) how long it takes the reaction to settle, and (3) whether short non-specific hyper-reactive responses occur with test subjects.

Quantitative results of nasal airflow resistance changes were presented for two subject groups to demonstrate their reactivity to the birch challenge. The allergic group showed a large change in absolute resistance values during the provocation test, while the non-allergic group did not. The two study groups differ only in the responses to the allergen challenge. The individual subjects of the allergic group showed large changes in the absolute resistance values during allergen challenge, whereas individuals from the non-allergic group did not. It should be noted that large relative changes in the individual resistance values occurred only with the allergic group and in the allergen challenge phase. As a conclusion, allergic and non-allergic subjects can be differentiated with statistically significant difference using the presented method.

The proposed method opens entirely new opportunities to research accurately dynamic changes in non-stationary nasal function. It could increase the reliability and accuracy of diagnostics and assessment of the effect of nasal treatments.

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