Continuous Nasal Airflow Resistance during Birch Pollen Provocation Test

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Keywords: Allergy, Birch Pollen, Challenge, Nasal Resistance, Respiration, Provocation Test.

Abstract: Even 50% of population suffers from allergic symptoms in some countries. There is a need for an objective measurement method giving an accurate, reliable and continuous measurement data about the dynamic nasal function. A novel method to assess unobtrusively the continuous nasal airflow resistance using calibrated respiratory belts is used to produce a continuous nasal airflow resistance during the birch pollen provocation test. Ten birch pollen allergic and eleven non-allergic volunteers were recruited and measured. A statistically significant change in the nasal airflow resistance was found due to the challenge in the allergic group while no statistically significant change was found in the non-allergic group. Unique continuous nasal airflow resistance curves were derived to show the dynamic changes in the nasal airflow resistance during the provocation test. The continuous curves show in great detail fast and slow reactions to nasal provocations, which may be helpful in studying the reactivity of patients. The presented method could increase the reliability and accuracy of diagnostics and assessment of the effect of nasal treatments.

1 INTRODUCTION

Allergic rhinitis is diagnosed when specific antigens can be detected in the blood and the patient has allergic symptoms. For instance, eosionophilic cells can be found in allergic and inflammatory conditions. In Finnish population, about 15-25% of people have allergic rhinitis, while in other countries this value can be even over 50%. Allergic rhinitis is an inheritable disease and patients with allergic rhinitis have about threefold risk to get asthma. Typical symptoms of the allergic rhinitis are nasal obstruction, rhinorrhea, nasal itching, sneezing and eye irritation (Bousquet et al., 2008). In Finland, the birch pollen is a common cause of the allergic symptoms such as intermittent seasonal allergic rhinitis.

The presence of nasal allergy can be verified by nasal provocation tests in which subjects are challenged with the suspected allergen. After that, changes in their subjective feelings of symptoms, amount of secretions and the respiratory function of nose are measured. Nasal provocation tests are done for instance in the diagnosis of work-related respiratory diseases (occupational asthma, occupational rhinitis), at the beginning of desensitization, the diagnosis of chronic rhinitis and in scientific research.

Examples of objective ways to measure the function of the nose are acoustic rhinometry and rhinomanometry. Acoustic rhinometry assesses nasal geometry by measuring cross-sectional areas of the nasal cavities. Rhinomanometer measures simultaneously pressure and airflow from which nasal airflow resistance is determined (Chaaban and Corey, 2011). Nasal cavities are measured one at a time and the total nasal resistance is calculated based on unilateral resistances. This makes it impossible to determinate the accurate total resistance in a certain time point, as there is an ongoing variation in unilateral nasal resistance with time. Furthermore, the resistance is described characteristically as one number that derives only from a few breathing cycles of data. In nasal provocation tests, the major response is the rise in the nasal resistance. The rise is rapid (minutes) and the timing may vary in different individuals. This makes it difficult to be detected with rhinomanometer. One possibility is to assess the momentary resistance with the rhinomanometer in certain time-intervals, but this has been shown to give inconsistent and variable results with low reproducibility (Pirilä et al., 1997); (Pirilä and

M. Seppänen T., Alho O., Laajala A., Rahkola E. and Seppänen T..
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DOI: 10.5220/0004181300050010
In *Proceedings of the International Conference on Bio-inspired Systems and Signal Processing* (BIOSIGNALS-2013), pages 5-10
ISBN: 978-989-8565-36-5

Nuutinen, 1998); (Hohlfield et al., 2010).

There is clearly a need for a method giving an accurate, reliable and continuous measurement data about the nasal function. This kind of measurement could provide more information about the rapid changes in nasal function for instance during allergy provocation tests.

Recently, a novel method was presented to assess nasal airflow resistance in a way that provides a continuous resistance values and applies a minimally obtrusive measurement method (Seppänen et al., 2009; 2010). The pressure recording is produced with a nasopharyngeal catheter and the flow recording is produced with calibrated respiratory belts. The nasal airflow resistance is calculated for each signal sample at any sampling frequency, making it possible to discover rapid changes in resistance. A novel calibration method of respiratory belts was presented in Seppänen et al. (2011). It is an extension to the multiple linear regression method which is conventionally used for calibration of respiratory belts. The new method improves greatly the accuracy of the calibration. In the data used, R^2 increased 9% for piezo belts and 10 % for inductive belts; RMSE (Root Mean Square Error) decreased 36% for piezo belts and 43% for inductive belts. R^2 is a coefficient of determination between the spirometer signal and the flow prediction. RMSE, in its turn, is a measure of the difference between the spirometer signal and flow prediction.

In this work, the above mentioned methods are combined to study nasal airflow resistance changes during a provocation test. The used methods and data collection is first described. Quantitative results of resistance changes are then presented between two subject groups – birch pollen allergic and non-allergic subjects - to demonstrate their reactivity to the different protocol stages. In addition, continuous resistance curves are presented from selected subjects to discuss the dynamic changes in their nasal resistance during the provocation test.

2 METHODS AND DATA

2.1 Study Subjects

Ten (3 female, 7 male) birch pollen allergic and eleven (3 female, 8 male) non birch pollen allergic adult volunteers were recruited. The mean (SD) age of the allergic and non allergic subjects was 24 (1) and 24 (3) years, respectively. A medical doctor examined all the subjects. The specific IgE for birch pollen was determined from blood for all of them to determine whether they are allergic to birch pollen or not. As mentioned in section 1, there are different kinds of allergy symptoms. Some allergic subjects suffer only one of them while, others can have several symptoms. The specific IgE value does not indicate the type of allergic symptoms.

The volunteers had to be free of any acute respiratory symptoms during the prior two weeks to the measurements. They also had to be free of heart diseases, brain circulatory disorders and surgical operations of nose. Volunteers were not allowed to be under medication that affects the function of their nose during a specific time period before the measurement. They were not allowed to have a smoke for four hours and heavy meal, caffeine or other stimulative products for two hours before measurement. Pregnant volunteers were rejected as well.

The study protocol was approved by the institutional Ethics Committee of Oulu University Hospital. All volunteers gave written informed consent. Background information was gathered using a questionnaire. Measurements were carried out in the spring before the birch pollen season.

2.2 Challenge Protocol

The signals were recorded with a polygraphic recorder (TrackIt, Lifelines Ltd, Hampshire, UK) with the sampling frequency of 100 Hz. The pressure recording was produced with a nasopharyngeal catheter (CH 06, Unomedical A/S, Denmark) (diameter 1 mm). Figure 1 shows the setup for the nasal pressure measurement. The pressure data of the recorder was calibrated to physical units (Pascal). Respiratory belts (Ultima SmartBelt, Braebon Medical Corp., Ogdensburg, NY, USA) were attached to the subjects' chest and abdomen. For calibrating the signals from respiratory belts, simultaneous flow signal was recorded with a spirometer (SpiroStar USB, Medikro Oy, Kuopio, Finland), as described below.

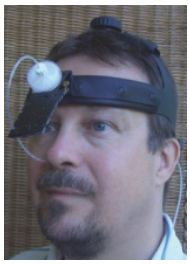

Figure 1: Measurement of nasal pressure signal.

The subjects first sat peacefully for a period of

30 min prior to the measurement. They were instructed to sit in back upright position avoiding movements during all measurements. First, respiratory belt data and flow data were recorded for one minute with the polygraphic recorder and the spirometer, respectively. The data was used for calibrating the respiratory signals to flow signal as described in Section 2.3. The respiratory belts were kept on during the whole measurement protocol.

The spirometer was removed from the subject. A 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. The differential pressure sensor (Braebon Ultima Dual Airflow Pressure Transducer) referenced to the atmospheric pressure was connected to the catheter. Moreover, a sterile filter (Minisart, Sartorius Ltd, Epsom, Uk) was used for protection in between the catheter and the pressure sensor. Air was blown 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.

At the first protocol phase, the baseline was recorded for 10 min. At the second protocol phase, the birch pollen challenge was inserted carefully on the anterior nasal mucosa, after which pressure and airflow were recorded for 20 min. Finally, the catheter was removed and the calibration data collection was repeated with the spirometer.

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

2.3 Calibration Method of the Respiratory Belts

A prediction of the respiratory airflow F_{est} is commonly calculated from the respiratory belt signals by applying the method of multiple linear regression (Tobin, 1992). This conventional model can be established by fitting the following linear model to the time-synchronized signals:

$$F_{est} = \alpha_1 s_{rc} + \alpha_2 s_{ab} + \varepsilon \quad (1)$$

where the predictor variables s_{rc} and s_{ab} are the respiratory belt signals from the chest and abdomen, respectively, and ε is zero-mean Gausian error. In this model, one sample of each predictor variable is used at a time to predict the response variable.

In this study, the calibration of the respiratory belts was based on a special case of the model published previously (Seppänen et al., 2011). Figure 2 depicts a block diagram as a MISO (multiple input, single output) system consisting of two FIR filters and a delay element. In this model, only linear terms of the original filter-bank polynomial are used.

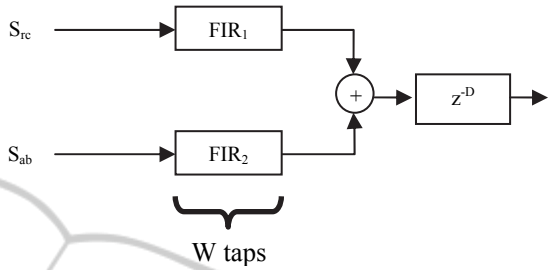

Figure 2: Extended linear model.

The new model is an extension to the conventional model with the option to use the window size of W samples for each prediction. This was found to offer significantly better performance. The calibration model now becomes:

$$F_{est} = \boldsymbol{\alpha}_1^T \boldsymbol{s}_{rc} + \boldsymbol{\alpha}_2^T \boldsymbol{s}_{ab} + \varepsilon \quad (2)$$

Vector notation (bold letters) is used to denote that W consecutive samples are included as components in the predictor variable, and parameters are vectors of dimension W. Terms $\boldsymbol{\alpha}_1^T$ and $\boldsymbol{\alpha}_2^T$ denote tap coefficients of filters FIR_1 and FIR_2 in Figure 2, respectively. Superscript T denotes vector transpose.

During calibration, the W tap coefficients of the FIR units are calculated with the method of least-squares. Respiratory belt signals and the simultaneous spirometer signal are input to regression analysis which yields optimal coefficients and minimal prediction error for both filters.

There is a small delay between the spirometer flow signal and the respiratory belt signals due to 1) the time it takes for the airflow to propagate from the chest to the mouth and 2) the internal delays of the measuring devices. In Figure 2, delay element z^{-D} is included at the output for this reason. The filter coefficients were solved for each feasible delay candidate as described above and the minimum error in the flow estimate was used to determine the optimal delay value.

In Seppänen et al. (2011), the window size 0.3 sec was found to give the best flow estimate and it was used in this study as well.

2.4 Computation of the Continuous Nasal Airway Resistance

A novel method to estimate continuous resistance of the nasal airways using signals from the respiratory effort belts and pressure signal from nasopharyngeal catheter inserted transnasally into the nasopharynx was recently presented by Seppänen et al. (2009; 2010). A least-mean-square (LMS) extension for the model of Broms was developed that adapts to the time-varying characteristics of the nasal functioning. In the model, pressure is presented as a function of flow, and an instantaneous resistance can be calculated from the model after estimating the model parameters at each time instant from the input signals. Although the method allows for setting any reference pressure value used in clinical rhinomanometry, we set it to 25 Pa in this study, since pressure levels do not always achieve the conventional reference values of 75 Pa or 150 Pa, as also pointed out in Naito et al. (1993) and Kohler et al. (2006). Before applying the resistance calculation method, the respiratory belts are calibrated, as described in Section 2.3 above. For further details, refer to the original publication (Seppänen et al., 2009). Instantaneous resistance values are calculated over the measurement data and shown as dynamic plots over time.

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. The null-hypothesis for statistical tests was that there are no differences in the medians of given data sets.

3 RESULTS

3.1 Resistance Level Changes

First, the respiratory belts were calibrated from the first 1 min calibration recording (see Section 2.2). The continuous nasal airflow resistance was then computed for the last 5 min of the *baseline*. Then, the respiratory belts were calibrated from the second 1 min calibration recording (see Section 2.2). Finally, the continuous nasal airflow resistance was computed for the last 5 min of the birch challenge phase. The calibration was performed separately for both phases in order to avoid bias due to possible changes in the breathing style and subsequent mismatch of the calibration model to the data. Especially allergic volunteers had significant changes in their breathing style after the birch challenge.

Table 1 lists the mean nasal airflow resistance for each birch pollen allergic volunteer in the two phases and the group medians. Table 2 lists the mean resistances along with the group medians for non-allergic volunteers. Medians are used because data size is small and non-normal.

Table 1: Resistance values for allergic volunteers.

	Baseline	***After birch challenge***
Subject	***Resistance [Pa/dm^3/s]***	***Resistance [Pa/dm^3/s]***
1	103	145
2	120	245
3	63	111
4	52	441
5	125	246
6	268	637
7	130	382
8	79	124
9	101	120
10	115	134
Median	**109**	**195**

Table 2: Resistance values for non-allergic volunteers.

	Baseline	***After birch challenge***
Subject	***Resistance [Pa/dm^3/s]***	***Resistance [Pa/dm^3/s]***
1	135	211
2	42	43
3	56	59
4	127	196
5	273	205
6	104	108
7	196	163
8	99	72
9	140	103
10	56	69
11	92	92
Median	**104**	**103**

There was a statistically significant change in the resistance values between the *baseline* and *after birch challenge* in the group of birch pollen allergic

volunteers (p = 0.002). Respectively, in the group of non-allergic volunteers, there was no statistically significant change (p = 0.922).

In the *baseline*, the median resistance was 109 Pa/dm^3/s and 104 Pa/dm3/s for the allergic and non-allergic group, respectively. There was no statistically significant difference in the resistance between the two groups (p = 0.860).

After birch challenge, the median resistance was 195 Pa/dm3/s and 103 Pa/dm3/s for the allergic and non-allergic group, respectively. There was a statistically significant difference in the resistance between the two groups (p = 0.015).

The median change in the subjects' resistance (between baseline and after birch challenge) was 85 Pa/dm3/s and 2 Pa/dm3/s for the allergic and non-allergic group, respectively. There was a statistically significant difference in the resistance change between the two groups (p = 0.0017).

The median of the relative change in the subjects' resistance (between baseline and after birch challenge) was 87% Pa/dm3/s and 2% Pa/dm3/s for the allergic and non-allergic group, respectively. There was a statistically significant difference in the resistance change between the two groups (p = 0.0011).

In Figures 3 and 4 below, the differences of the allergic and control groups are depicted with boxplot figures. The central mark is the median on each box, while the edges of the boxes are the 25th and 75th percentiles. In x axis, mark '1' denotes the baseline phase and mark '2' the *after birch challenge* phase.

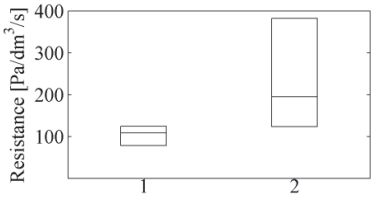

Figure 3: Boxplots for birch allergic volunteers.

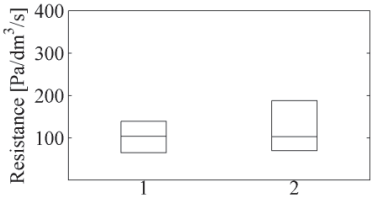

Figure 4: Boxplots for non-allergic volunteers.

In Figures 3 and 4, it can be seen clearly that the deviation of the resistance values after birch pollen challenge is much larger in the allergic group than in the control group. Figure 3 also demonstrates the fact that the birch allergy causes symptoms in the nose in varying degrees in the allergic persons.

3.2 Dynamic Resistance Changes

Pressure and respiratory belt signals were recorded 10 min in *baseline* and 20 min after the birch pollen challenge. Continuous nasal airflow resistance values were computed for these phases. The example figures for continuous resistance signals are presented for a birch pollen allergic and non-allergic volunteer in Figure 5 and 6, respectively. The small gaps in the signals are due to removing of the artifacts. To our knowledge, this is the first time that this kind of continuous resistance curves can be presented for the provocation tests.

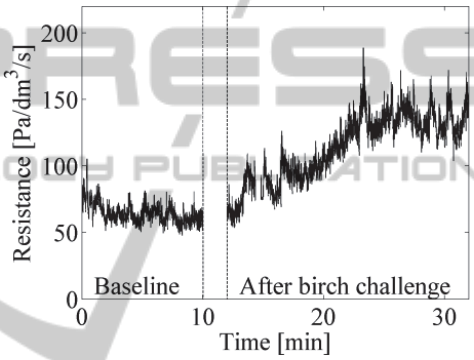

Figure 5: Resistance curve for allergic volunteer.

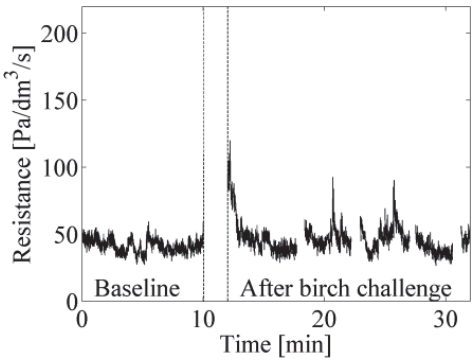

Figure 6: Resistance curve for one non-allergic volunteer.

In Figure 5, the resistance in the *baseline* is quite stable except the initial elevation perhaps due to the insertion of the nasal catheter just a moment ago. After the birch pollen challenge, a significant allergic reaction can be seen. The resistance increases almost linearly for some ten minutes and then settles to a much higher level than in the baseline.

In Figure 6, the resistance in the *baseline* is quite stable. Immediately after the birch pollen challenge,

a clear initial reaction can be observed in the plot. We speculate that this is more due to a transient change in the breathing style than in the nasal resistance. Following the short transition period, a stable resistance curve follows which stays at the same level as the baseline resistance.

4 CONCLUSIONS

A method to estimate continuous nasal airflow resistance during a birch provocation test was presented. The nasal resistance was estimated with a new method that applies LMS filtering technique to the nasal pressure signal and carefully calibrated respiratory belt signals to update adaptively an extended Broms model.

Quantitative results of resistance changes were presented for two subject groups - birch pollen allergic and non-allergic subjects - to demonstrate their reactivity to the birch challenge. In the baseline situation, the median resistance value was similar in the groups. However, due to the birch challenge, statistically significant changes in the individual resistances were observed in allergic group, while no statistically significant differences were observed in the non-allergic group.

Continuous resistance curves were presented from selected subjects to demonstrate the dynamic changes in their nasal resistance during provocation test. To our knowledge, this is the first time this kind of dynamic resistance curves are presented for nasal provocation tests.

Provocation tests like this one may cause changes in the breathing style of subjects. This has the undesired consequence of the fact that the calibration model is not fully accurate all the time. We are currently developing new adaptive calibration methods to enhance the accuracy of flow estimation for situations where the breathing style changes.

Even at present, the method presented above could improve the reliability and accuracy of diagnostics and assessment of the effect of nasal treatments.

ACKNOWLEDGEMENTS

We thank MD Aila Kristo for participating in the collection of the data.

Finnish Cultural Foundation, North Ostrobothnia Regional fund; Allergy Research Foundation; The Research Foundation of the Pulmonary Diseases; and The Finnish Research Foundation of Otology are gratefully acknowledged for having provided financial support for this work.

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