

Re-evaluating the nasal cycle by long-term rhinoflowmetry: most individuals demonstrate a “mixed” nasal cycle*

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Abstract

Background: The nasal cycle seems to be more complex than a strictly alternating swelling of the nasal mucosa. Long-term rhinoflowmetry (LRFM) allows continuous investigation of changes in nasal airflow over 24 hours (24h). We evaluated the various types of nasal cycle with LRFM over 24 hours and investigated the influence of age and gender.

Methods: LRFM was continuously performed over 24h in 55 rhinologically healthy subjects (36 female, 19 male). The LRFM flow curves were examined for phases of the “classical”, “in-concert”, “one-sided” and “no-cycle” cycle types. Subjects were divided into 4 age subgroups (19-29; 30-49; 50-69; >70 years). Correlations of age and gender with the individual cycle forms were analyzed.

Results: 85.5% of the subjects presented a “mixed” nasal cycle within 24h. The “classical” nasal cycle was seen most often (92.7% vs. “in-concert”; 56.4% vs. “one-sided”; 18.2% vs. “no-cycle”; 5.5%). Older age groups significantly more often presented the “no-cycle” type. A tendency was seen towards a mixed nasal cycle with increasing age. The mixed nasal cycle was significantly more often seen in the female subjects.

Conclusions: LRFM is an easy-to-use measurement tool. The “mixed” nasal cycle predominates. However, all 4 different cycle types can be detected, alternating over 24h in each subject. Moreover, the cycle type varies with age.

Key words: nasal mucosa, rhinomanometry, acoustic rhinometry, nasal obstruction, diagnostic techniques, respiratory system, long-term rhinoflowmetry

Introduction

The alternating swelling of the nasal mucosa on both sides is generally known as the nasal cycle^(1,2). This phenomenon was first described in 1895 by Richard Kayser⁽³⁾. Its physiology and function are still not fully understood.

For the past century various studies attempted to describe the nasal cycle and its functions. A variety of diagnostic methods like anterior rhinoscopy, rhinomanometry, acoustic rhinometry, peak nasal inspiratory flow, computational fluid dynamics and magnetic resonance imaging only allows a transient impression of the nasal flow rates, aerodynamic drag, cross section areas as well as nasal cavity volumes⁽⁴⁻⁸⁾. Continuous recording over 24h is not possible. It is necessary to carry out multiple individual measurements over a certain period of time in order to analyse

the nasal cycle, the phases of which can last several hours⁽⁶⁾. Additionally, these measurements cannot be performed during sleep or physical activity. Therefore, continuous flow recording of the nasal cycle over 24 hours (24h) has not been possible until nowadays. Nevertheless, much of today’s knowledge about the nasal cycle is based on these fundamental rhinological diagnostic methods. Literature suggests that a “classical” nasal cycle, consisting of congestion and decongestion of the nasal mucosa on alternating sides of the nose, can be found in 80% of the adult population⁽⁹⁻¹¹⁾. The results vary depending on the measurement method and point in time as well as due to inconsistent definitions of the nasal cycle between 13%⁽⁵⁾ and 100%⁽¹²⁾. Physiologic and pathologic conditions (e.g. sleep, posture, exercise, infections, allergy) influence the nasal cycle^(8,13).

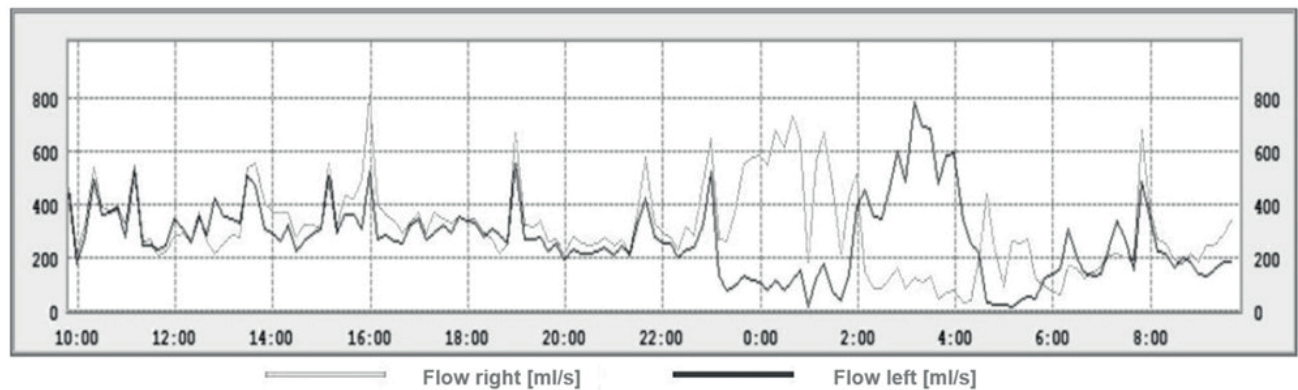


Figure 1. Example of nasal flow curves (ml/s) over the 24h measurement time in grey (right) and black (left) presented by the "Rhino Sys[®]" software. LRFM of a 72year old male subject: in-concert type (10:00-23:00h) and classical nasal cycle (23:00-6:00h).

In 1981 Kern published his study on the so called "non-cycle" nose⁽²⁾. He detected a classical nasal cycle in 36 out of 50 test subjects by repeating rhinomanometrical measurements. From the observations of the remaining 14 subjects, Kern defined 3 types of "non-cycle nose". Type I without any detectable change in resistance on either side (8/14 subjects). Type II with detectable fluctuations on one side of the nose only with constant resistance on the other side (2/14 subjects). Type III with simultaneous fluctuations on both sides ("in concert") without a detectable dominance (4/14 subjects)⁽²⁾. Looking closely, the latter descriptions also suggest a certain rhythm in the fluctuation of nasal airflow in the "non-cycle" subjects. Based on their experience with long-term rhinometry, Mlynski et al. also proposed a more complex system that did not focus on the "classical" nasal cycle⁽¹⁴⁾.

With the development and establishment of a portable long-term rhinoflowmetry (LRFM) a new diagnostic tool is available allowing the investigation of nasal air flow and therefore the nasal cycle under everyday conditions without interruption over a period of 24h⁽¹⁵⁾.

Until today only very few publications on the investigation of the nasal cycle using the LRFM are available^(10,15-17). Additionally, data on the influence of age and gender is scarce. Literature suggests that the nasal cycle might change with age^(18,19).

Considering the large variety of results in previous studies, the aim of this study was to describe and analyse the changes in nasal airflow under everyday conditions in a larger group of healthy subjects using LRFM continuously over 24h. Furthermore, differences in age and gender were considered.

Materials and methods

The study protocol was approved by the ethics committee of the University of Ulm, Germany.

Subject recruitment

55 healthy subjects (36 women, 19 men) aged between 19 and 80 years (mean age: 37.4 ± 18.2 years) were interviewed using a questionnaire. Those without any nasal symptoms or complaints, allergic rhinitis, or regular intake of medication that might interfere with the function of nasal mucosa (e.g. antypertensive drugs, psychotropics, or hormones), underwent anterior rhinoscopy and nasal endoscopy. Prick testing was negative in all subjects.

Exclusion criteria were structural anomalies of the inner or external nose, nasal polyps as well as a history of nasal trauma and surgery of the nose or the paranasal sinuses. Children and adolescents under 18 years, smokers, pregnant women, and individuals with chronic bronchial asthma as well as a calculated body mass index > 25 were excluded.

Long-term rhinoflowmetry (LRFM)

The portable measuring system Rhino-Move[®] (Happersberger Otopront GmbH, Hohenstein, Germany) with attached nasal cannulas allowed a continuous detection of changes in nasal airflow (ml/s) over 24h for each side of the nose, respectively. The nasal cannula has a separation between the left and right sides of the nose and is color-coded for correct assignment of air tube to nose side and air tube to device connection. It was individually adjusted to the face so that the curved air tubes comfortably rested loosely at the base of the vestibulum nasi. It was tolerated very well. The examination did not have to be interrupted or even terminated in any case.

Since the ratio of measured dynamic pressure to nasal flow depends on the size and shape of the nasal inlet, each subject had to be calibrated before recording. This was done using a rhinomanometer integrated into the "Rhino-Sys[®]" unit. LRFM by means of "Rhino-Move[®]" allows the recording of nasal flow velocities for the left and right side separately (ml/s), the nasal respiratory minute volume (l/min), as well as the parameters respiratory rate (1/min).

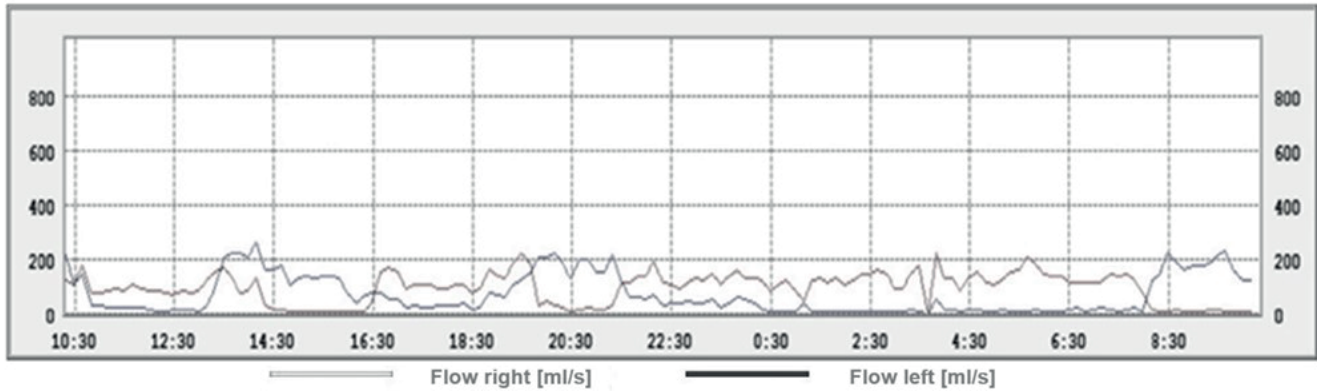


Figure 2. Example of nasal flow curves (ml/s) over the 24h measurement time in grey (right) and black (left) presented by the "Rhino Sys[®]" software. LRFM of a 24-year old male subject: classical nasal cycle over 24h.

After calibration and instruction for use, the measuring system recorder was started. Each subject was instructed to pursue their normal daily activities and to wear the recorder also at night without any interruption.

All measurements were performed according to the manufacturer's recommendations. The medical device "Rhino-Sys[®]" meets all provisions of the directive 93/42/EEC which apply to it. The device is commercially available for purchase.

Evaluation of the data

The "Rhino-Sys[®]" software (software version 1.8.2, Happersberger Otopront GmbH, Hohenstein, Germany) generated an automatic display of the determined nasal flow values as line charts. Figure 1 shows the maximum inspiratory flow values (ml/s) of the right (grey) and left side of the nose (black) over time. Each of these flow curves are generated from mean values of the maximum inspiratory flow velocities determined at 10-minute intervals.

Definition of types of the nasal cycle

Based on the observations in this study and the descriptions by Kern ⁽²⁾, Fisher ⁽²⁰⁾ and Mlynski et al. ⁽¹⁴⁾, we defined 4 types of cyclic changes in nasal airflow:

1. "Classical type": A reciprocal change of dominant airflow on both sides of the nose was called the "classical" nasal cycle. By definition, the side with lower airflow is resting, while the other side of the nose is in a working phase. The beginning and end of a phase are defined by the intersection of the curves "flow left" (black) and "flow right" (grey) (figure 2).
2. "In-concert type": Simultaneous increase and decrease of nasal airflow on both sides of the nose without one detectable dominant side was called the "in-concert type".
3. "One-sided cycle type": The "one-sided cycle type" was defined by the cyclic increase and decrease in flow values occurring only on one side of the nose, while the other side

did not present any significant changes in air flow. Therefore, a change of the working and resting phases occurred only on one side of the nose.

4. "Non-cycle type": Phases with no detectable changes of the flow values on either side of the nose were called "non-cycle type". The cut-off value used to define a "cycle" or "non-cycle" on both sides of the nose was 20% deviation from the mean.
5. "Mixed nasal cycle": Many subjects presented multiple different cycle types during the 24h measurement period. We therefore defined the "mixed nasal cycle" in contrast to the nasal cycle consisting of only one of the mentioned cycle types.

Statistical analysis

The statistical analysis was performed using the "IBM[®] SPSS[®] Statistics Version 25" (IBM Corporation, Armonk, USA). The correlation of nasal cycle type, age and sex was tested using the chi-square test and the Fisher's exact test, when the expected frequencies were below 5. Significance was accepted at $p < 0.05$. For further analysis the subjects were divided into groups by gender (36 females, 19 males) and 4 groups by age: (I) 18 – 29 years ($n = 31$; 23 females, 8 males), (II) 30 – 49 years ($n = 7$; 4 females, 3 males), (III) 50 – 69 years ($n = 11$; 6 females, 5 males), (IV) > 70 years ($n = 6$; 3 females, 3 males).

Results

Cycle type in 24 hours

LRFM was performed in 55 healthy subjects. The changes in nasal airflow of every subject were examined for the cycle patterns as mentioned before. Figure 3 shows the overall detectability of the different cycle types. Within the average measurement time of 23.28 ± 1.34 hours we were able to detect a "classical nasal cycle" in 51/55 subjects (92.7%). Only 4 subjects (7.3%) did not present with a "classical" nasal cycle type. The "in-concert type" was detected in 31 subjects (56.4%), and the "one-sided

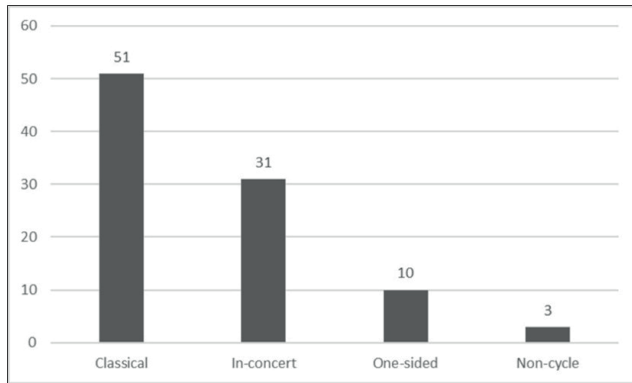


Figure 3. Total number of the different cycle types detected in the LRFM of 55 subjects over 24h measurement time.

cycle type" was detected in 10 subjects (18.2%) during the 24h measurement time. Phases with the "no-cycle type" were only seen in 3 subjects (5.5%).

The LRFM of every subject showed at least one of the mentioned cycle types. Only 7 subjects (12.7%) had a purely "classical nasal cycle" during the 24h measurement period (Figure 4). 1 subject only (1.8%) presented with an "in-concert nasal cycle". The vast majority of subjects (47; 85.5%) showed 2 or more of the previously mentioned types of cyclic swelling over the 24h measurement and therefore had a "mixed nasal cycle" by definition.

Cycle type and age

The 55 subjects were divided into 4 age subgroups as described in the methods section. LRFM results were then examined for a correlation between the age group and the appearance of the different cycle types, respectively. The detectability of the cycle types during the 24h measurement by age is shown in Table 1. There was no significant difference between the age groups concerning the detectability of the "classical", "in-concert" and "one-sided nasal cycle type". However, older age groups had a significantly higher point prevalence of presenting the "no-cycle type" ($p = 0.023$; chi-square test and Fisher's exact test). In the youngest age group (18-29 years) only 8 subjects showed one single nasal cycle type during the entire measurement period, while the rest of all subjects presented with at least two different cycle types. This difference was very close to significance ($p = 0.088$; chi-square test and Fisher's exact test).

Cycle type and gender

As shown in Table 2, we were not able to find a significant difference when looking at the appearance of the different cycle types according to gender. However, we were able to significantly more often detect a "mixed nasal cycle" in the female subjects compared to the male subjects (94.4% vs. 68.4%; $p = 0.016$; chi-square-test and Fisher's exact test).

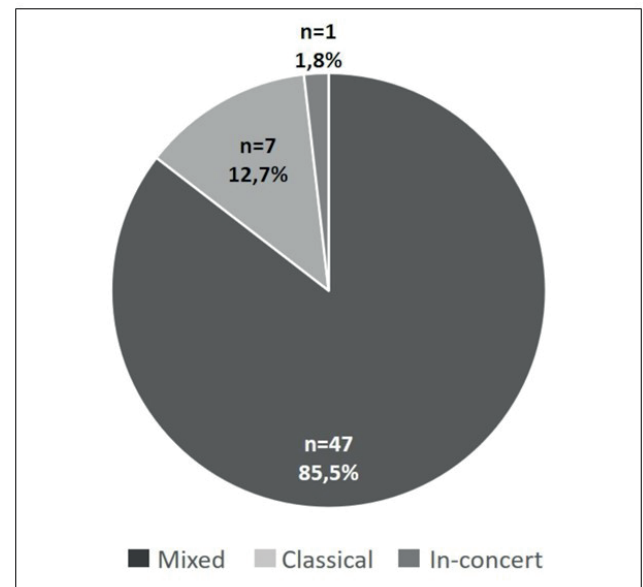


Figure 4. Mixed vs. single nasal cycle type: total number and percentage of subjects that showed one single nasal cycle type or a mixed nasal cycle over the 24h measurement time.

Discussion

The "classical nasal cycle" is a physiological phenomenon based on a mutual change in the swelling state of nasal mucosa⁽²⁾. According to current knowledge, the nasal cycle is considered to have a not to be underestimated impact on the respiratory and immunological function of the nose⁽²¹⁻²³⁾. It has been suggested that the cyclic swelling of the mucosa of the turbinates and septum plays an important role in the regulation of the amount and humidification of air passing through the nose⁽²⁴⁾. Alternating congestion and decongestion create a temperature gradient and therefore allow humidity to pass from mucosa to the air⁽²²⁾. The filling and drainage of the mucosal venous sinusoids create a plasma exudate as part of the nonspecific immune response of the upper airway system⁽²¹⁾.

The current knowledge on the nasal cycle is mainly based on single measurements, which are repeated over a certain period of time in order to meet the phases of the nose cycle, some of which may last for several hours. A continuous measurement over 24h has not been possible for a long time.

The LRFM offers a new opportunity to continuously detect changes in the nasal airflow and therefore characterise the nasal cycle over 24h without any interruption. So far, there have only been few studies on using LRFM to determine the nasal cycle. Mlynski et al. had been involved in the development of the LRFM measurement tool and presented its qualities in 6 exemplary subjects. They were able to detect the "classical nasal cycle" with a duration of 90 minutes to 10 hours⁽¹⁵⁾. In the previously conducted studies with individual measurements, a measurement period of 8 hours often was not exceeded. Therefore, a

Table 1. Age differences in prevalence of the different nasal cycle types and an overall mixed cycle over 24h measurement time, NS = not significant.

| Nasal cycle type | | Age, years; n (%) | | | | P value |
|-------------------|-----|-------------------|------------|-------------|----------|---------|
| Detectable in 24h | | 18-29, n=31 | 30-49, n=7 | 50-69, n=11 | >70, n=6 | |
| Classical | Yes | 29 (93.6) | 7 (100) | 9 (81.8) | 6 (100) | NS |
| | No | 2 (6.4) | 0 (0) | 2 (18.2) | 0 (0) | |
| In-concert | Yes | 22 (71.0) | 6 (85.7) | 10 (90.9) | 5 (83.3) | NS |
| | No | 9 (29.0) | 1 (14.3) | 1 (9.1) | 1 (16.7) | |
| One-sided | Yes | 6 (19.4) | 1 (14.3) | 3 (27.3) | 0 (0) | NS |
| | No | 25 (80.6) | 6 (85.7) | 8 (72.7) | 6 (100) | |
| No-cycle | Yes | 0 (0) | 0 (0) | 1 (9.1) | 2 (33.3) | 0.023 |
| | No | 31 (100) | 7 (100) | 10 (90.9) | 4 (66.7) | |
| Mixed overall | Yes | 23 (74.2) | 7 (100) | 11 (100) | 6 (100) | NS |
| | No | 8 (25.8) | 0 (0) | 0 (0) | 0 (0) | |

Table 2. Gender differences in prevalence of the different nasal cycle types and an overall mixed cycle over 24h measurement time, NS = not significant.

| Nasal cycle type | | Gender; n (%) | | P value |
|-------------------|-----|---------------|--------------|---------|
| Detectable in 24h | | Male, n=19 | Female, n=36 | |
| Classical | Yes | 16 (84.2) | 35 (97.2) | NS |
| | No | 3 (15.8) | 1 (2.8) | |
| In-concert | Yes | 14 (73.7) | 30 (83.3) | NS |
| | No | 5 (26.3) | 6 (16.7) | |
| One-sided | Yes | 3 (15.8) | 6 (16.7) | NS |
| | No | 16 (84.2) | 30 (83.3) | |
| No-cycle | Yes | 1 (5.3) | 2 (5.6) | NS |
| | No | 18 (94.7) | 34 (94.4) | |
| Mixed overall | Yes | 13 (68.4) | 34 (94.4) | 0.016 |
| | No | 6 (31.6) | 2 (5.6) | |

nasal cycle with very long phases might not always have been detected.

In 2005, Ohki et. al. carried out examinations on 20 subjects between the age of 24 and 77 using a portable rhinoflowmeter from the company Rhinometrics A/S, Smørum, Denmark, and were able to demonstrate a classical nasal cycle in 14 subjects within the 12-hour measuring period⁽¹⁷⁾. In 2012, Braun et. al. investigated the effects of oxymetazoline nasal spray on the nasal cycle by LRFM (Happersberger Otopront GmbH, Hohenstein, Germany) in 30 healthy subjects⁽¹⁶⁾, and in 2014 Rohrmeier et. al. studied the nasal cycle over 24 h in relation to body position⁽¹⁰⁾. In the latter one, a classical nasal cycle was detected in 50% of the 20 subjects during wakefulness, and in 75% during sleep. The phases were significantly prolonged during sleep⁽¹⁰⁾. In our study, the distribution of the nasal cycle types also appears to vary at different times of the day. A closer correlation of the data with activity is still pending.

In this study, LRFM was conducted in 55 healthy subjects. It proved to be easy to use without restricting the subjects in their daily activities. We therefore believe that it is a valuable addition to the existing measurement methods in everyday

clinical practice not only in the research of the nasal cycle, but also as a tool in planning surgery. The subjects were interviewed with a specially designed questionnaire as mentioned in the Materials and Methods section followed by anterior rhinoscopy and nasal endoscopy. In order to further standardize the selection of subjects in following studies, validated rhinologic questionnaires, such as the SNOT-22, should be applied in order to more clearly define normal "rhinologic conditions"⁽²⁵⁾. Based on his experience with the LRFM, Gunter Mlynski proposed the categorization of the nasal air flow into 4 cycle types⁽¹⁴⁾. We can confirm this observation: we were able to categorize the nasal airflow of every single one of the 55 subjects in the 4 mentioned cycle types. Even more striking is the fact that only few subjects had one single cycle type during the measurement period of 24 hours (7 "classical", 1 "in-concert"). 47 of the 55 subjects (85.5%) presented 2 or more cycle types and therefore a "mixed nasal cycle". This is very much in contrast to most of the studies in the literature, in which the detectability of a nasal cycle was purely based on the reciprocal swellings of the nasal mucosa^(2,26). Most of these studies found the "classical nasal cycle" in around 80% of their subjects⁽⁹⁻¹¹⁾. In this study we confirm the "classical

nasal cycle" as the most common cycle type (92.7%), followed by the "in-concert type" (56.4%). This difference from the so far published data may give an indication of the importance of measurement timing and attention to periods of rest and activity. In general, the 4 types of nasal cycle are simplifications to visually capture the construct of the nasal cycle. In this context more, studies applying LRFM in larger study groups would be desirable in order to get more insight in the complexity of the nasal cycle. A so called "irregular" nasal cycle type ("mutual alteration in nasal volume without a defined pattern and a constant total nasal volume")⁽⁸⁾ was not detectable in our study group due to the fact that we did 24h measurements. Compared to other studies, we did really continuous measurements instead of selective point of times measurements.

We were not able to detect a significant difference between the age groups when looking for the "classical", "in-concert" and "one-sided nasal cycle type". However, older age groups had a significantly higher point prevalence of presenting the "no-cycle type". In addition, we were able to see a close to significant accumulation of subjects with only one single cycle type as in comparison to the mixed cycle in the youngest age group. Older studies proposed that the nasal cycle changes with age.

By investigating 48 children and adolescents in the age of 3-17 years using repetitive rhinomanometry, Mennella and Beauchamp⁽²⁷⁾ described a transition from parallel or random patterns in younger subjects to predominantly classical reciprocal cycle forms in the older ones. The absence of a classical nasal cycle in neonates and infants was also confirmed in studies by van Cauwenberge⁽²⁸⁾ and Baczek et al.⁽²⁹⁾

Mirza et al.⁽¹⁸⁾ and Williams and Eccles⁽¹⁹⁾, conducted similar studies in adults with repetitive measurements. Similar to our results, they saw a decrease in the reciprocity of nasal airflow with increasing age. This study was the first one to investigate the connection between the cyclic changes of nasal air flow and age using LRFM over 24h.

In the presented study, no significant differences were found in the appearance of the different cycle types according to gender. These results confirm the observation of Mirza et al. who did not find gender-specific differences either⁽¹⁸⁾. However, we were able to detect a "mixed nasal cycle" significantly more often in the female subjects compared to the male subjects. Data on the

influence of gender on the nasal cycle so far is still scarce.

A closer examination of the correlation of physical activity with the cyclical changes of our test subjects is still pending. A hormonal influence is also conceivable.

Additionally, it should be considered that measurement devices could influence the nasal cycle, although the nasal cannula is not deeply inserted into the nose. As a next step, 48h measurements are planned in order to investigate the nasal cycle longer than 24h, as suchlike data are still missing.

Conclusion

We conclude, that LRFM is an easy-to-use measurement tool for the investigation of the changes in nasal airflow over a 24h period without interruption due to physical activity or sleep. With 4 different cycle types the nasal cycle is much more complex than previously depicted in the literature. Most strikingly, it seems that the nasal cycle is of a mixed character most of the time. Therefore, we believe that not every person can be attributed "one" certain type of nasal cycle. It rather seems that the nasal mucosa reacts to influence factors like physical activity, sleep, hormonal changes, age or nasal pathologies. Thus, further studies using LRFM need to be conducted in the future to explore the physiology as well as internal and external clocks. Medical indications might include hypertrophy of the turbinates before turbinate surgery, unclear nasal obstruction during the night with/-out anatomical correlates, sleep apnoea, allergic rhinitis (e.g. dust mite, occupational allergies), Empty Nose Syndrome or regular intake of medication that might interfere with the swelling condition of the nasal mucosa.

Authorship contribution

JL: design of the study, conducting the study, manuscript preparation; EFR: conducting the study, statistical analysis, manuscript preparation; CW: subject acquisition, conducting the study; TKH, MOS, FSo, FSt: conducting the study, manuscript proofreading.

Conflict of interest

The authors declare no conflicts of interest.

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