

Continuous investigation of the nasal cycle over 48 hours

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Abstract

Background: Previous results on the nasal cycle refer to measurements over up to 24h. The long-term rhinoflowmetry (LRFM) allows continuous observations over a longer period. The aim of the study was to observe the nasal cycle for the first time over 48h under everyday conditions.

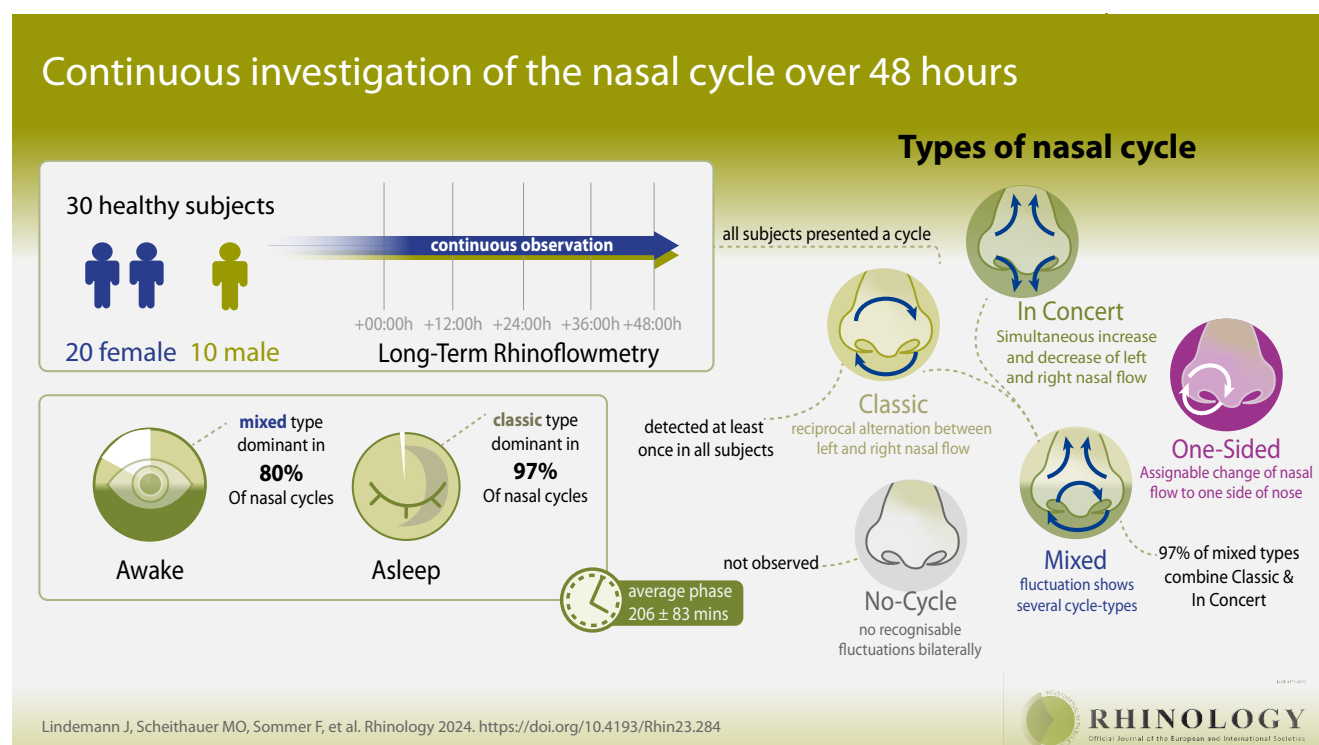
Methodology: The LRFM was continuously applied to 30 rhinologically healthy subjects (20 female, 10 male) over 48h. The different types of nasal cycle were classified as follows: "classic", "in concert", "one-sided" and "mixed". The focus of this study was on the results over the entire 48 hours. The comparison of the two consecutive days was also made.

Results: A nasal cycle could be detected in 100% of the subjects over 48h. With 97%, the mixed type most commonly occurred as a combination of classical and in concert components. In all subjects, classical cycle components could be detected at least once. The no-cycle type was not observed. In the awake state, the mixed type dominated (80%), as a combination of classical and in concert parts. In the sleep state, the classical type was the most common type (97%). The average phase duration was 206 ± 83 minutes.

Conclusions: In the very first continuous 48-hour study on the nasal cycle, 100% of the subjects presented a nasal cycle. The LRFM method is the only one that offers the possibility to perform continuous measurements over a longer period during daily routine. The results of previous single-stage examination methods should thus be questioned.

Key words: nasal cycle, rhinomanometry, nasal mucosa, respiratory system, nasal turbinates

Graphical abstract



Introduction

The nasal cycle is the physiological waxing and waning of the nasal mucosa ⁽¹⁾. This phenomenon was first defined by Richard Kayser in 1895 ⁽²⁾. To date, however, the nasal cycle has not been fully researched.

The nasal cycle is centrally regulated: the state of the nasal erectile tissue is subject to adrenergic innervation, i.e., it is controlled by the autonomic nervous system. A vasoconstrictor effect and consequently the swelling of the nasal mucosa as well as a decrease in airway resistance occurs due to the release of noradrenaline ⁽³⁻⁵⁾.

The task of the nasal cycle is to regulate the amount of inhaled air, which is determined by the state of swelling of the nasal mucosa. In addition, it has a regulating influence on temperature and humidity of the inhaled air and causes regeneration of the nasal mucosa. The nasal cycle is also an important part of the body's defense system through mucociliary clearance ^(3,6-9).

So far, the nasal cycle has been studied using different examination methods. Most studies are based on single-stage methods, such as anterior rhinoscopy, rhinomanometry and acoustic rhinometry or magnetic resonance imaging. These methods are limited when it comes to the examination of the nasal cycle, as they are single-stage procedures. Continuous measurements over a longer period of time under everyday conditions, such as during physical activity or sleep, were not possible with such methods ⁽¹⁰⁻¹⁴⁾.

Continuous recordings of the nasal cycle that go beyond snapshots can only be carried out using the long-term rhinoflowmetry (LRFM) method, which is not often applied so far ⁽¹⁵⁾. Grützenmacher et al., Kimura et al. and Rohrmeier et al. already used the LRFM method ⁽¹⁵⁻¹⁷⁾. LRFM was also applied in a previous 24-hours study by the authors ^(18,19).

Studies of the nasal cycle generally show a wide variance in results due to the different measurement methods and definitions.

Since 1927, based on the results of Heetderks applying an anterior rhinoscopy, it has been generally assumed in the literature that 80% of people have a nasal cycle ^(10,11,17,20). Overall, results in the literature vary widely. Studies with repeated individual measurements speak of the classical nasal cycle in 13% ⁽²¹⁾, 21% ⁽²²⁾ and 100% ⁽²³⁾; per LRFM, 93% ⁽¹⁸⁾ speak of the classical type.

There are also strong deviations with regard to the phase durations, which range from 243 min ⁽¹⁹⁾ to 110 min ⁽²⁴⁾ and 91 min ⁽¹⁷⁾. However, the studies agree that there already is a high intraindividual variance in the phase durations, which can, for example, be associated with postural changes of the body or different phases of physical activity ^(1,17,24).

To date, there are no measurements over a period of time of more than 24 hours. Most of the results so far are based on repetitive single measurements. Only rarely the LRFM method has been applied.

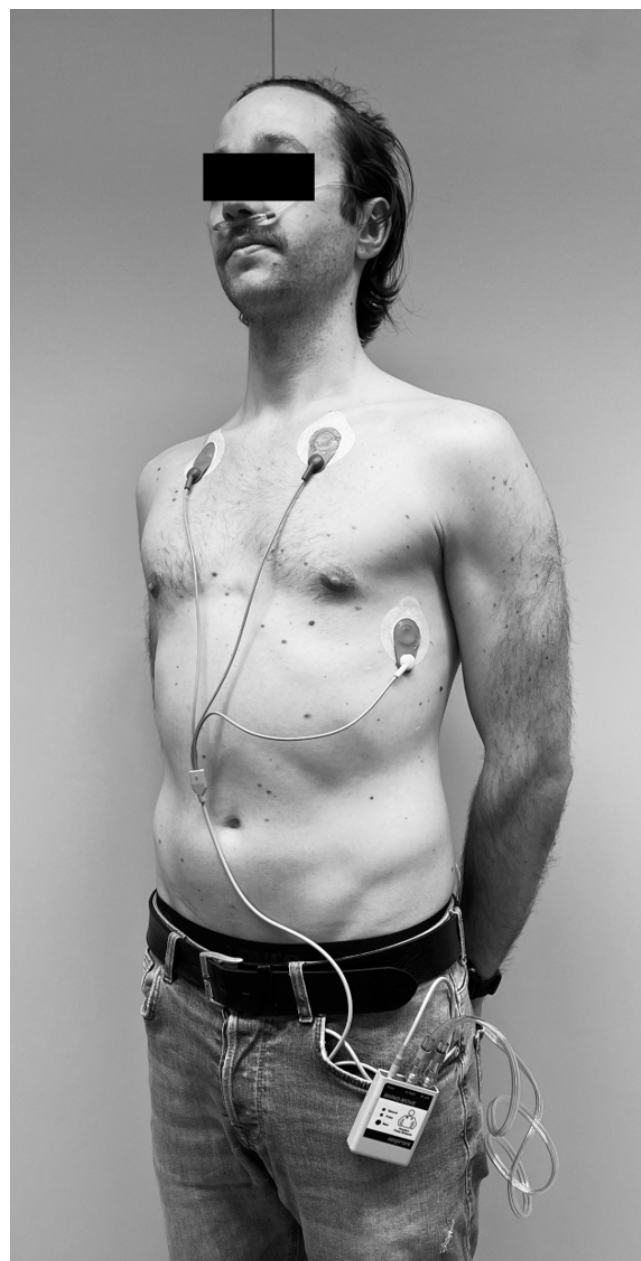


Figure 1. Test person wearing the portable Rhino-Move device with inserted nasal cannula and adapted ECG electrodes.

Therefore, the aim of this study was to conduct continuous LRFM measurements of the nasal cycle over a period of 48 hours for the first time. One aim was to simultaneously observe the nasal cycle for any regularities on two consecutive days. Furthermore, the nasal cycle was examined with regard to the states "awake" and "asleep". In addition, the effect of various activities such as "physical rest", "physical exertion" and "eating" on the nasal cycle in the awake state was explored as well as the phase duration.

Methods

The study protocol was approved by the ethics committee of the University of Ulm, Germany (approval ID number 127/21). All

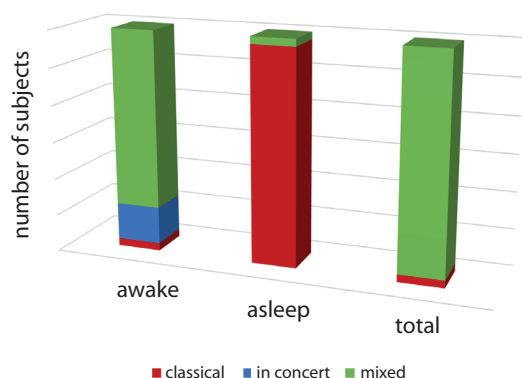


Figure 2. Total number of the different cycle types detected in the LRFM of 30 subjects over 48 hours measurement time during wakefulness, sleep and in total over the entire measurement period.

study participants were informed about the study and signed a written informed consent form before participation.

Subject recruitment

30 rhinologically healthy subjects (20 women, 10 men) between the age of 21 and 62 (mean age of 27 ± 9 years) were interviewed about their health and medication intake using a medical history form and the SNOT-22 questionnaire. Additionally, an inspection of the external nose, an anterior rhinoscopy as well as nasal endoscopy were performed to exclude any compromising anatomical pathologies. Exclusion criteria were a SNOT-22 score ≥ 25 , rhinological diseases, objective and subjective impairment of nasal breathing, structural changes of the nose, previous nasal trauma or surgery, medications with nasal side effects, allergies and existing respiratory infections. The minimum age of the participants had to be 18 years.

Long-term rhinoflowmetry (LRFM) and evaluation of the data

The LRFM measurement method and data analysis were performed as described in detail in a previous study (18). 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 48 hours for each side of the nose. The system was tolerated very well by all study participants during all day and night times activities. The device is portable and does not hinder in everyday life. Figure 1 shows a test person wearing the measuring system.

The examination did not have to be interrupted or prematurely terminated in any case. LRFM by means of "Rhino-Move®" allows the separate recording of nasal flow velocities for the left and right nasal side (ml/s), the nasal respiratory minute volume (liters/min), as well as the respiratory rate (breaths/min) and

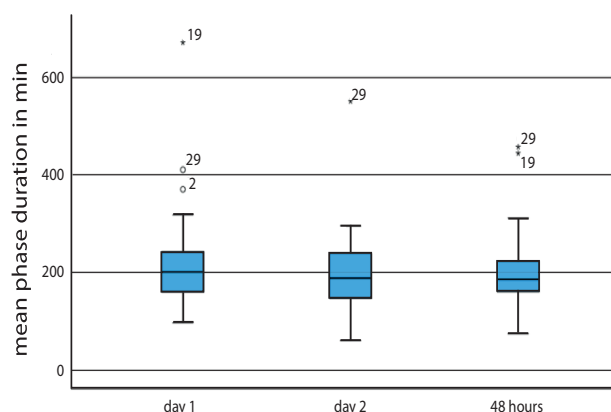


Figure 3. Boxplot comparing the average phase duration for day 1, day 2 and over the whole 48 hours.

heart rate (beats/min). 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 for 48 hours.

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.

Definition of types of the nasal cycle

The following classification of types of the nasal cycle was applied according to our previous study (18):

1. Classical type: the reciprocal alternation between left and right nasal flow. The resting phase is characterized by low flow velocities, the working phase by high flow velocities. The intersection of the two flow curves defines the beginning and end of a phase.
2. In-concert type: the simultaneous increase and decrease of the left and right nasal flow and thus an almost parallel curve.
3. One-sided cycle type: the clearly assignable change of the nasal flow to one side of the nose. The resting and working phases are only visible on one side of the nose, the other side shows no significant changes.
4. No-cycle type: cycle type without recognizable fluctuations on both sides.
5. Mixed nasal cycle: a fluctuation that shows several of the above-mentioned cycle types (1 to 4).

Line graphs were created based on the measured flow rates of both nasal sides over 48 hours. In the line diagrams, the nasal flow on the right and left side was shown in ml/s as well as heart rate in 1/min. The respective activity at a certain point in time was highlighted in color. As soon as a phase $\geq 50\%$ occurred

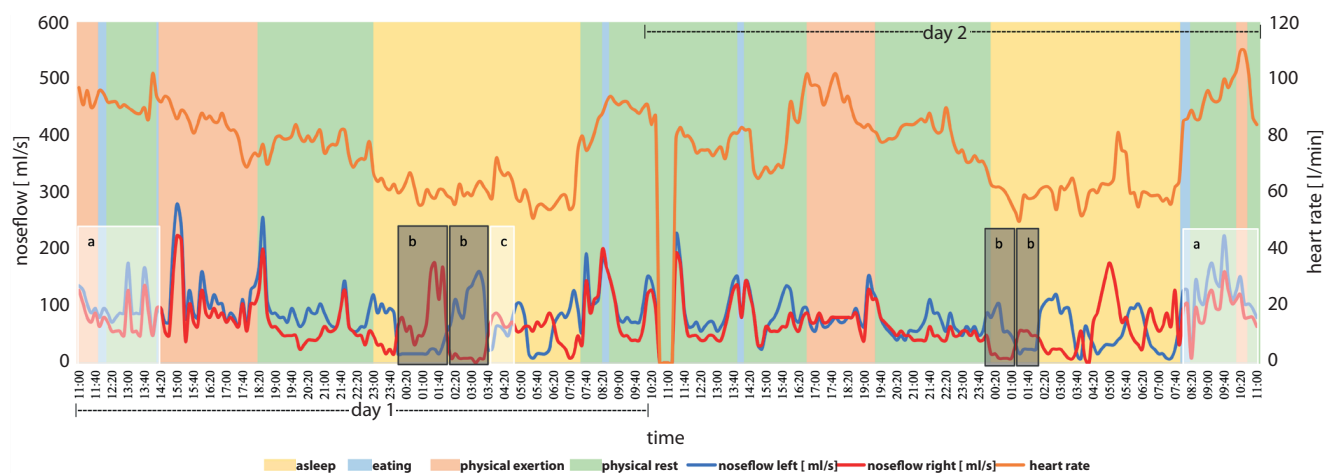


Figure 4. Example of nasal flow curves over 48 hours. LRFM of a 62-year-old male subject: Cycle type awake state: in concert (examples marked as white boxes with an "a"). Cycle type sleep state: mostly classical (examples marked as black boxes with an "b"); one short in concert part during the sleep during the first 24 hours (marked as a white box with an "c"). Cycle type total: mixed.

during the "sleep" activity, it was assigned to it entirely. At <50%, it was consequently considered part of the awake state. Thus, the different cycle types were categorized depending on the activities of the test person. Absolute flow values are not decisive for the classification of the respective cycle type. Subjects can of course have the same cycle types with different flow values. The flow cut off rate was defined as ≤ 800 ml/s.

Statistical analysis

Statistical analysis was performed using the program "IBM SPSS Statistics Version 29" (IBM Corporation, Armonk, USA). The evaluation of the data according to the cycle types is mainly descriptive. Comparisons of the average phase duration during day 1 and day 2 in total, during wakefulness and sleep were performed using the paired t-test. To find out about dependencies of the cycle type on the state of activity, analyses were carried out by means of cross-tabulation and chi-square test. Statistical significance was accepted at $p < 0.05$.

Results

Long-term rhinoflowmetry over 48 hours

LRFM was performed in 30 rhinologically healthy subjects under everyday conditions over 48 hours. With an average measurement duration of 47.4 ± 0.7 hours, a present nasal cycle could be observed in all subjects.

The classical cycle type occurred at least once in each of the test subjects during 48 hours. In 96.7%, a mixed type, in the sense of a combination of classical and in-concert proportions, was present over the entire measurement period. 3.3% showed the classical type over the entire recording duration. No one-sided or no-cycle parts were observed (Figure 2). No relevant difference was found between genders.

Nasal cycle during awake and sleep states

The measurements were subdivided according to awake and sleep states.

During the awake state, 80.0% of the test persons showed a mixed cycle type, which is a combination of classical and in-concert components. 16.7% showed a pure in-concert type and 3.3% the classical cycle type.

During sleep, 100% of the subjects presented classical cycle parts. 96.7% were of the pure classical type, while 3.3% showed a mixed type as a combination of classical and in-concert parts. The one-sided cycle type was not recorded in the study group.

Nasal cycle during different activities in the awake state

The awake state was further subdivided into the categories "awake and physical rest", "awake and physical exertion" and "eating".

During physical rest, the mixed type, which was a combination of classical and in-concert components, was most frequent (80.0%) over the 48-hour period. During physical effort the in-concert type was observed in 67.9%. For the category "eating", the mixed type was observed most frequently (50.0%) and was again a combination of classical and in-concert components.

Comparison of the two consecutive measurement days

As the 48-hour measurement was carried out on two consecutive days, it was possible to compare day 1 and day 2. Overall, 96.7% of the subjects had the same cycle types on both days.

Phase duration over 48 hours

The mean phase duration over the entire measurement period of 48 hours was 206 ± 83 minutes with a median value of 186 minutes. For day 1, the mean phase duration was 224 ± 111

Table 1. Nasal cycle types of the 30 subjects for the states "awake", "sleep" and "total" for day 1, day 2 and over the entire measurement period of 48 hours.

subject number	day 1 total	day 2 total	48 hours total	day 1 awake state	day 2 awake state	48 hours awake state	day 1 sleep state	day 2 sleep state	48 hours sleep state
1	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
2	classical	classical	classical	classical	classical	classical	classical	classical	classical
3	mixed	mixed	mixed	in concert	in concert	in concert	mixed	classical	mixed
4	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
5	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
6	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
7	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
8	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
9	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
10	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
11	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
12	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
13	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
14	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
15	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
16	mixed	mixed	mixed	in concert	in concert	in concert	classical	classical	classical
17	mixed	mixed	mixed	mixed	in concert	mixed	classical	classical	classical
18	mixed	mixed	mixed	in concert	in concert	in concert	classical	classical	classical
19	mixed	mixed	mixed	mixed	classical	mixed	classical	classical	classical
20	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
21	mixed	mixed	mixed	mixed	classical	mixed	classical	classical	classical
22	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
23	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
24	mixed	mixed	mixed	in concert	in concert	in concert	classical	classical	classical
25	mixed	mixed	mixed	in concert	in concert	in concert	classical	classical	classical
26	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
27	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
28	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
29	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical
30	mixed	mixed	mixed	mixed	mixed	mixed	classical	classical	classical

minutes, on day 2 201 ± 91 minutes. Since $p > 0,05$, the null hypothesis "there is no significant difference between the phase durations for day 1 and day 2" was retained. In the awake state phase duration was 154 ± 65 minutes, in the asleep state 249 ± 108 minutes (Figure 3).

There were also single subjects with just one switch of nasal cycle per day, one subject even showed one type without a change in one day. The minimum phase duration was 60 minutes during the awake state, the maximum duration 670 minutes during the sleep state.

For illustration purposes, Figure 4 shows an exemplary LRFM

result of a 62-year-old male test person over the entire 48-hour measurement period. The various daily activities are marked by colors (asleep, eating, physical rest, physical exertion). During the awake state, an in concert type can be seen. The sleep state characteristically shows a classical cycle type with one short in concert part during the sleeping period of the first 24 hours. Thus, a mixed cycle type can be determined for the 48 hours. Of course, individual nasal flow curves can be created for all study participants over the entire measurement period.

Table 1 presents the different cycle types of the 30 test persons for the states "awake", "sleep" and "total" for day 1, day 2 and over the entire measurement period.

Discussion

The nasal cycle describes the physiologically alternating swelling of the nasal mucosa ⁽²⁵⁾. According to the current state of knowledge, a respiratory and immunological function can be attributed to the nasal cycle ^(6,26-28).

However, current results are mainly based on repetitive single measurements. Continuous measurement methods have rarely been applied so far. Therefore, only a few studies of a measurement period of up to 24 hours are available ^(15-19,24). Continuous recordings are only possible using LRFM, which allows valid and detailed observations ⁽¹⁵⁾.

The aim of this study was to perform continuous measurements over a period of 48 hours for the first time using this method without any interruption. This method allows for an increase in knowledge about the nasal cycle in general and the different nasal cycle types under everyday conditions on two consecutive days. Another aspect was to compare the newly collected 48-hours results with those from the continuous 24-hour measurements. For the present study, a portable rhinoflowmeter was applied in 30 healthy volunteers for 48 hours without interrupting everyday life.

Since Heetderk's study in 1927 applying rhinoscopic investigation it has generally been assumed that 80% of the healthy population have a nasal cycle. Conversely, this means that no nasal cycle can be detected in 20% of the healthy population ⁽¹¹⁾. These "historical" data are usually still presented in publications on the nasal cycle.

In contrast, the measurement results of our presented study showed that a nasal cycle was present in 100% of the study participants over a 48-hour period. The majority (97.5%) showed a mixed cycle type as a combination of classical and in-concert proportions. In addition, classical cycle parts were even recorded at least once in each of the test subjects during 48 hours. At no time a no-cycle type was recorded. In the awake state, the mixed type dominated (80%). During sleep, the classical type occurred most frequently (97%), with classical cycle components being observed in 100%.

Based on the same classification and measurement method of current studies by Lindemann et al. ^(18,19), a comparison of the 24-hour and 48-hour measurement results is possible. Over the entire measurement period, 100% of the participants in the present study showed a nasal cycle over 48 hours. In the 24-hour study, 93% of the participants showed a nasal cycle. While the mixed cycle type was most frequent (80%) in the awake state over 48 hours, the mixed and in concert type were present most frequently and almost equally often over 24 hours.

Since the study subjects were physiologically healthy individuals and the present cycle types are also considered to be physiological, it also seems plausible that all of the test persons showed

a nasal cycle. The fact that the no cycle type was only found in 5.5% in the study over 24 hours suggests, that probably all subjects could have a nasal cycle over 48h or even longer.

In the asleep state, the classical cycle type dominated both over 48 and 24 hours. Overall, a no-cycle type was not observed in any of the participants over the 48 hours, whereas it was present in three study subjects over the 24 hours. Therefore, the no cycle type seems to be a rare individual case.

It should be noted, however, that more subjects participated in the 24-hour study (55 vs. 30), and the mean age was higher than in the present study (37 ± 18 years vs. 27 ± 9 years) ^(18,19). Therefore, there was no relevant difference depending on age this time. The current study group was significantly younger. There was also no relevant difference between the genders in the 24-hour as well as 48-hour study.

In a study also applying LRFM, Ohki et al. observed the classical nasal cycle type in 14 of 20 subjects ⁽²⁴⁾ and Kimura et al. in 19 of 20 subjects over 24 hours ⁽¹⁶⁾.

Rohrmeier et al. also divided into the states "awake" and "asleep" and found the classical type in 50% in the awake state and in 75% in the asleep state ⁽¹⁷⁾.

In contrast, based on the new results of the present study classical components were observed significantly more often, both during awake state and during sleep.

The fact that no no-cycle type was observed in any of the rhinologically healthy subjects over the 48 hours, but only classical, in concert or mixed types occurred, supports the statement according to Mlynski et al, that states that the classical and in concert types are physiological states ⁽²⁹⁾.

The fact that classical components could be observed during sleep in all subjects seems plausible as fewer external influences occur in this period.

The in-concert type was most frequently observed during physical effort in the 24-hour study as well as in the 48-hour study ⁽¹⁸⁾. Physical exertion is usually accompanied by an increase in flow velocity on both sides of the nose and an increase in heart rate ⁽³⁾. This shows an adaptation of the nasal cycle: the nasal mucosa decongests on both sides in order to compensate for the increased oxygen demand. On the other hand, the classical type can be observed in phases of physical rest. In particular, this pattern can also be transferred to the sleep state ^(30,31). However, during physical rest over 48 hours the mixed type was predominant (80%), this might be explained by the fact that the body position is also decisive for the present type of the nasal cycle ^(17,32-34). Of course, LRFM does not allow to draw any conclusions about this correlation, and the protocols of the study participants also allow only limited conclusions to be drawn.

In the present study the mixed type dominated (50%) in the category "eating". A comparison is not possible since none of the

studies referred to this so far.

Comparing the two days one must consider that the nasal cycle is extremely dependent on various intrinsic and extrinsic factors among others⁽³⁾. Therefore, no specific rhythm could be expected when comparing the two consecutive measurement days. In particular, the states "awake" or "asleep" and the activities "awake and physical rest" or "awake and physical exertion" influence the cycle types in most cases. The state "eating" was often considered as a transition between rest and exertion phase or vice versa. Therefore, it is difficult to define one particular cycle type for an individual. So far, there is no published data available for comparison, as this is the first study of the nasal cycle over 48 hours.

In the presented study the phase duration was determined for classical cycle phases since a phase change can be determined in the classical type. The beginning and end of a phase was defined via intersections of the two flow curves. A mean phase duration over the 48-hour period (206 ± 83 minutes) could be measured in all subjects. During the awake state the mean phase duration was 105 ± 65 minutes for 23 subjects and 238 ± 92 minutes for 30 subjects during sleep. The low patient number is a possible limitation of the study and includes the possibility of misleading as beta-error could lead to non-significant results. For comparison, over the 24-hour period a mean phase duration of 208 ± 74 minutes was recorded. During the awake state it was 139 ± 53 minutes and during sleep 248 ± 112 minutes^(18,19). According to Ohki et al., the mean phase duration during the day was 110 minutes, although there were large intra-individual variations⁽²⁴⁾. According to a previous study by Atanasov, the range of phase durations during sleep is from about 1.5 to 4.5 hours.⁽³⁵⁾ Rohrmeier et al. was able to record a cycle phase duration of 91 ± 65 minutes in the awake state and 178 ± 93 minutes during sleep in 23-hour LRFM measurements⁽¹⁷⁾. According to Kahana et al., the cycle phase length was 2.0 ± 1.7 hours in the awake state was significantly lower than in the sleep phase of 4.5 ± 1.7 hours⁽³⁶⁾. Kimura et al. determined an average phase duration of 234 ± 282 minutes⁽¹⁶⁾.

The phase durations vary inter- and intra-individually to a significant extent. The mean phase durations presented in this study are comparable to the literature. The wide range of phase

durations is very well reflected in the high standard deviation, analogous to the previous results of the 24-hour study and proves the individual differences in cycle phase duration^(18,19).

The various studies agree that the phase durations during sleep are significantly longer than during the awake state^(17,36).

In general, phase durations are dependent on both extrinsic and intrinsic factors, such as climate, season, age or activity, and can therefore explain the wide range and fluctuations.

Conclusions

Overall, LRFM is a reliable and feasible measurement method to continuously record the nasal cycle without interruption over 48 hours. Previous results, especially those based on single measurements, are being questioned. One-time examination methods are considered outdated. The fact that a nasal cycle could be observed in 100% of the study subjects challenges the established number of 80% in the literature. An exact evaluation of the nasal cycle is only possible with a continuous recording of the nasal air flow. It is therefore quite conceivable, that a change in the cycle type was not detected in previous studies with non-continuous measurement methods. Additionally, it must be considered that with non-continuous measurement methods, a detection of the nasal cycle during activity or during sleep could not be investigated. In our opinion, not every person can be attributed "one" certain type of nasal cycle as the cycle is influenced by too many factors. The nasal mucosa is reacting to various factors like physical activity, sleep, eating, climate, hormonal changes, age, nasal pathologies and many more.

Authorship contribution

JL: design of the study, conducting the study, manuscript writing and preparation; MOS, FSo, TKH, JHa: conducting the study, manuscript proofreading; JF: design of the study, conducting the study, manuscript writing and preparation.

Conflict of interest

The authors declare no conflicts of interest.

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