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Biological Rhythmicity of Nasal Airway Patency: A Re-examination of the 'Nasal Cycle'

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Rhinomanometric observations of nasal airway patency were obtained for each nasal passage every 10 min throughout an uninterrupted 8-h session. The 49 airflow observations for each nasal passage were subjected to autocorrelation analysis, a statistical technique for quantifying periodicities in a temporal sequence of observations. No significant periodicities were found in any of the 16 subjects when the autocorrelation functions were interpreted by conventional statistical criteria. However, when less stringent criteria were applied, we found suggestive evidence for rhythmicity in one (7 subjects) or both nasal passages (2 subjects). The relationship in patency between the two sides of the nose was characterized with correlation coefficients. These correlations were significantly negative in 7 subjects, indicating bilateral reciprocity of patency. In addition, the correlations were significantly positive in one, and nonsignificant in 8 subjects. Only a minority of subjects (13%) displayed the classical nasal cycle, i.e., rhythmicity in both nasal passages as well as reciprocity of patency between passages. *Key words: ultradian rhythms, nasal airflow, rhinomanometry.*

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Since the observations of Kayser in 1895 (1) the otorhinolaryngological literature has frequently referred to a 'nasal cycle'. This phenomenon is said to consist of rhythmic and bilaterally reciprocal alternations of nasal airway patency such that total airway resistance remains constant. The period of the nasal cycle has been reported to range from 0.8 to 5.5 h (Table I). The rhythmic changes in patency are due to dilation and constriction of the venous cavernous tissue in the mucosa of the conchae and septum. The nasal cycle is thought to occur in about 75% of healthy adults (2, 3, 4).

Despite its general acceptance, the nasal cycle concept is a problematic one. In its strongest form it requires that each nasal passage exhibit rhythmic alterations in patency, and that these patency changes be reciprocal across the two sides of the nose. It is often emphasized that the reciprocal changes be of equal amplitude in the two air passages, thereby producing side to side alternations in the side of greatest airflow, with total flow remaining constant (2, 5). Thus, in the idealized cycle, the left and right sides have identical periods, are 180° out of phase, and have similar mean airflow and amplitude. In practice, however, many subjects fail to show all three characteristics. For example, patency changes can be rhythmic in the absence of reciprocal bilateral alternation (e.g., Stoksted (6), Fig. 4, subject 17). Such subjects create a dilemma. They can be disregarded in order to consider only 'pure' nasal cycles, or they can be incorporated, but at the cost of blurring the classic nasal cycle definition.

This dilemma has been exacerbated by differing definitions and methods of quantifying rhythmicity. Some investigators measure cycle length as the interval between recurring points within a single nasal airway (7) while others take it to be the interval between graphical crossings of the two airway functions (8). A common practice is to estimate period from visual inspection of the plotted data (9). The potential subjectivity of this technique is rarely countered by the use of multiple raters, or raters who are blind to the hypothesis. The potential for bias increases when cycle length is approximated by extrapolation (6, 10).

In this study we attempted to confirm the nasal cycle phenomena using the objective, quantitative techniques of time series analysis, as they are typically applied in biological rhythms research (for reviews, see 11, 12). We addressed three basic issues: (1) Can rhythmicity be objectively detected and quantified in one or both sides of the nose? (2) Do the nasal passages alternate reciprocally, irrespective of detectable rhythmicity in either passage? (3) If both sides of the nose are rhythmic, do they have the same period and do they have a characteristic phase relation?

To answer these questions, we obtained standard rhinomanometric observations of nasal patency and used autocorrelation analysis in order to identify and characterize rhythmicity. Correlation analysis was used to characterize bilateral reciprocity.

METHODS

Subjects

We examined 10 male and 6 female adults (ages 18 to 34), all unmedicated non-smokers, with no evidence of active head cold or nasal allergy, grossly impaired sense of smell, deviated septum, broken nose, or history of nasal surgery or disease. A written statement of informed consent, approved by the University of Pennsylvania Committee on Studies Involving Human Beings, was signed by each subject after the experimental procedures had been fully explained. Subjects were paid for their participation.

Procedure

Nasal patency was measured under standardized conditions by means of active anterior rhinomanometry (measurement of air flow at the external nares). A Connell Rhinometer (J. T. Connell, Englewood, NJ) was used to measure the airflow in one nasal passage at a

Table I. *Summary of previous studies on the nasal cycle*

	Estimated period (h)			Obs length (h)	Sampling period (min)	*N*
	Mean	SD	Range			
Heetderks, 1927 (3)	2.5	–	0.8–4.0	2+	10	60
Stoksted, 1952 (5)	–	–	1.5–2.25	2–3	30	10
Stoksted, 1953 (6)	2.5	–	1.5–5.0	2.5–3.5	30	26
Principato & Ozenberger, 1970 (19)	–	–	–	4–24	15	–
Hasegawa & Kern, 1977, 1978 (2, 20)	2.9	0.5	1.0–6.0	6	15	50
Eccles, 1978 (8)	–	–	1.0–2.5	10[a]	30	2
Cole et al., 1979 (9)	–	–	3.0–4.0	4	20	16
Juto & Lundberg, 1984 (7)	–[b]	–[b]	–[b]	4	20	14
Van Cauwenberge & Deleye, 1984 (21)	1.0	–	–	6.25	15	26[c]
Lenz, Theelen & Eichler, 1985 (4)	2.3[d]	1.1[d]	1.0–5.5	8	30	40
Gilbert & Rosenwasser, this study	4.3	1.3	2.4–7.3	8	10	16

[a] Observed 10 hours on each of 7 days.
[b] No cycles detected.
[c] Aged 3–6 years.
[d] Estimated from figure.

time. Plastic tubes were placed gently on (not in) the external nares, and the subject inhaled and exhaled through the tubes in a natural manner. This technique was nearly effortless for the experimental subject, and frequent measurements were easily obtained over many hours. Flow rate ($cl\,s^{-1}$) was recorded during inspiration at a differential pressure of -1.5 cmH_2O. Each determination of airflow was calculated as the mean of three observations, with the side of first reading alternated between measurements. Readings were taken with the subject in an upright sitting position. The subject held the tubes to his or her own nostrils, and a technician recorded all values. Any value more than 10 $cl\,s^{-1}$ different from the other two values was replaced by taking another reading.

Subjects arrived at 8:30 a.m. for a 30-min interview and instruction period that allowed them to acclimatize to the temperature and humidity of the test room. Beginning at 9 a.m., nasal airflow measurements were taken every 10 min until 5 p.m., for a total of 49 measurements. Measurements continued through a 45-min lunch period that began at 12 noon. In an attempt to minimize vascular artifacts, only room temperature food was served, and no caffeinated beverages were allowed. Vigorous exercise (e.g., climbing stairs) was not allowed.

Autocorrelation analysis

Rhythmicity in a time series is confirmed by the presence of significant values in the autorcorrelation function which repeat at multiples of some critical lag; this lag provides an estimate of the period of the rhythm (11, 12). Autocorrelation values greater than $2/\sqrt{N}$ are significantly different from zero at the 95% confidence level (13). Given that $N=49$ in the present case, values of $r>0.29$ were considered significant. We computed all autocorrelograms using the SPSS^{x} Box-Jenkins procedure (14).

Given the sampling density (6 per hour) and observation length (8 h) of the present experiment, the minimum detectable period according to the Nyquist relation is 0.3 h (11). There is no similarly strict definition of the maximum detectable period. However, the maximum period that could be detected with reasonable confidence would be $N/4=12.25$ lags, or about 2 h (13). Period estimates between 2 and 4 h are less statistically reliable, and estimates greater than 4 h should be considered extremely unreliable, given that fewer than two complete cycles could occur during the experiment, and thus no second peak could be detected in the autocorrelogram.

Occasional, isolated, significant autocorrelation values are expected by chance even in a time series composed of random numbers (13). To empirically assess the baseline level of such spurious significance in our time series, we employed a Monte Carlo simulation, i.e., we randomized each sequence of observations and reapplied the time series analysis.

Analysis of bilateral reciprocity

A correlation coefficient (r) was calculated for each series of 49 pairs of left and right nasal airflow values. Values of $r<-0.29$ or >0.29 were considered statistically significant (df = 47, $p<0.05$, two-tailed). Significant positive internostril correlations indicate parallel changes in the two sides of the nose, while significant negative correlations indicate bilateral reciprocity, i.e., airflow through one is high while flow through the other is low.

RESULTS

At least one significant autocorrelation value was found in 17 of 32 individual nasal passages, representing 13 of the 16 subjects. Applying a strict criterion (i.e., the presence of repeated significant autocorrelation values) to these 17 time series, no statistically significant periodicities could be detected. We re-examined the autocorrelation results using a less stringent criterion of rhythmicity, namely, the occurrence of regularly repeated autocorrelation peaks, whether at a statistically significant level or not. This re-analysis yielded evidence of rhythmicity in one nasal passage of 7 subjects (one left, six right), and in both passages of 2 subjects. The estimated periods based on the less stringent criterion are listed for each subject in Table II.

The estimated periods ranged from 3.9 to 7.3 h (mean 5.5±1.7 h) in the left nostril ($n=3$), and 2.4 to 5.3 h (3.8±0.9 h) in the right ($n=8$). For all 11 periodic nasal passages, the mean period was 4.3±1.3. Mean flow rate measured during inspiration at a differential pressure of -1.5 cmH_2O was 25±14 and 23±12 $cl\,s^{-1}$ in the left and right sides respectively.

Seven subjects displayed significant negative bilateral correlations, indicating reciprocity in airflow between the two nasal airways. One subject showed a significant positive correlation, indicating that airflow changes occurred in parallel in the two sides. Eight subjects showed no significant correlation. Bilateral correlation coefficients for each subject are listed in Table II. All 7 subjects displaying reciprocity also showed at least one rhythmic nasal passage, as can be seen by comparing the relevant columns in Table II. In fact, reciprocity was present in 7 of the 9 subjects showing rhythmicity, and none of the 7 non-rhythmic subjects, suggesting that bilateral reciprocity is closely associated with nasal rhythmicity.

Fig. 1 shows the airflow data for several representative subjects, demonstrating the range of experimental variation observed. Included in Fig. 1 are individuals showing evidence of bilateral nasal rhythmicity and reciprocity (subjects 1 and 13), unilateral rhythmicity and reciprocity (subject 2), and neither rhythmicity nor reciprocity (subjects 4, 10, and 12). Subject 12 actually showed a significant positive internostril correlation.

Isolated significant autocorrelation values appeared in six air passages in the Monte Carlo simulations. However, none of these six showed repetitive peaks in the autocorrelation function. Therefore, no rhythmicity was detectable in any of the randomized data

Table II. *Demographic characteristics and data for all 16 subjects*

Estimated periods for cycles in the left and right nasal air passages are based on the less stringent statistical criterion described in the text. Inspiratory airflow values taken at a differential pressure of -1.5 cmH_2O

			Estimated period (h)			Mean airflow (±SD) $cl\,s^{-1}$	
Subject	Sex	Age	Left side	Right side	Bilateral correlation (r)	Left side	Right side
1	♂	30	3.9	3.1	−.35	52±10	42±7
2	♀	26	–	2.4	−.53	27±6	17±5
3	♂	25	–	3.3	−.37	15±3	9±4
4	♂	25	–	–	−.10	8±5	37±2
5	♂	25	–	4.2	+.22	6±4	22±1
6	♀	19	–	–	−.05	11±3	18±4
7	♂	30	–	–	+.14	16±3	7±2
8	♂	24	7.3	–	−.57	37±21	16±13
9	♂	34	–	4.3	−.45	32±7	32±11
10	♀	21	–	–	+.11	23±3	20±3
11	♀	30	–	3.4	−.16	40±6	39±8
12	♂	20	–	–	+.32	13±4	12±2
13	♂	20	5.3	5.3	−.87	27±10	19±8
14	♀	18	–	4.3	−.49	23±7	19±4
15	♂	29	–	–	−.02	46±8	42±6
16	♀	24	–	–	−.23	23±4	17±3

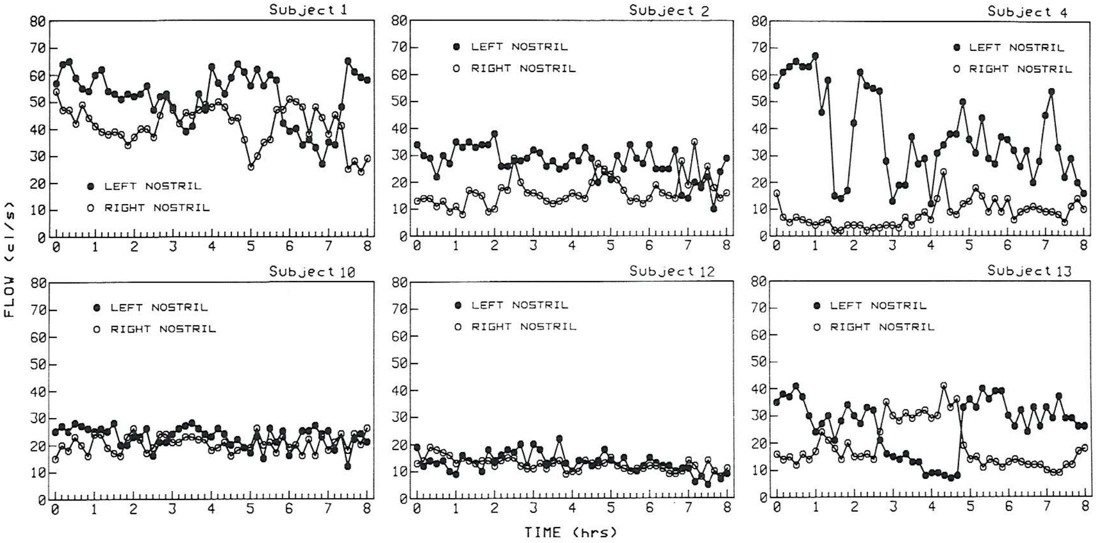

Fig. 1. Flow rate measured during inspiration at a differential pressure of -1.5 cmH_2O for 6 selected subjects. See Table II for other subject characteristics.

sequences, even under the less stringent criterion of rhythmicity. Additionally, none of the randomized data sequences showed significant bilateral correlations. These results suggest that it is unlikely that significant values in the analyses of the original data were due to random variation.

DISCUSSION

Our data resemble in most qualitative respects those previously illustrated in the literature (6). We observed spontaneous changes over time in nasal airway patency of healthy adults. The magnitude of these changes varied widely within and between subjects. We also observed occasional side-to-side alternations in the side of greatest airflow (Fig. 1).

Unlike previous investigators, we took the individual nasal passage as the point of reference for a time series analysis of rhythmicity. No significant periodicities could be detected when the autocorrelation functions were conventionally interpreted (12, 13). Conventional criteria would also require continuous observations spanning approximately four times the expected period of the rhythm (13). Our observation interval was longer than most previous studies, and our frequency of measurement was as high as any previously reported (Table I). Even so, these criteria have not been satisified to date in any study, including our own.

When re-analysed with a less stringent criterion, the autocorrelation functions were suggestive of rhythmicity in one (7 subjects) or both (2 subjects) sides of the nose in 9 of our 16 subjects. Even this re-analysis produced tentative evidence of a patency rhythm in only 56% of normal persons, in contrast to previous estimates of 72% (2) and 80% (4). Bilateral rhythmicity was suggested in only 2 (13%) of our subjects, and thus appears to be a far less common feature of nasal airway physiology than previously believed.

Period estimates of individual air passages suggested by the time series analysis ranged from 2.4 to 7.3 h, with a mean of 4.3±1.3 h. No rhythmicity was detected in the period range of 0.3 to 2.0 h, where our statistical analysis is most robust, and where human ultradian rhythms in physiological and psychological functions such as REM sleep, urine flow, and task performance are most commonly noted (15, 16). Given the variability and experimental uncertainty to date in estimates of nasal rhythmicity, it seems premature of Werntz et al. (17) to conclude that a close relationship exists between nasal patency and other ultradian rhythms.

Despite its persistence in medical textbooks (18) it appears that there is little empirical support for the nasal cycle as strictly defined, that is, as a reciprocal and rhythmically alternating relation between the two nasal passages, with identical periods, mean levels, and amplitudes in each. Bilateral reciprocity was detected in 7 of 16 subjects, indicating that reciprocity is a common, but not universal feature of nasal physiology. Our data, as well as those of most previous investigators, do suggest that spontaneous changes in nasal patency are a major feature of upper respiratory physiology. However, we believe that it may overstate the case to refer to these changes as a nasal cycle. In this respect, we share some of the reservations expressed by Juto & Lundberg (7). But where they reject the validity of the nasal cycle concept, we come to a rather different conclusion. In our view, no study has yet firmly established the presence of a statistically reliable rhythm as implied by a strict interpretation of the term 'nasal cycle'. Indeed, the phenomenon is so unstable in most subjects that it should probably be considered quasiperiodic, or episodic (16).

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