

## ROLE OF HORMONES ON NASAL CYCLE

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### ABSTRACT

#### INTRODUCTION

Nasal airflow is greater in one nostril than in the other because of transient asymmetric nasal passage obstruction by erectile tissue. The extent of obstruction alternates across nostrils with periodicity referred to as the nasal cycle. The nasal cycle is related to autonomic arousal and is indicative of asymmetry in brain function. The main hormone to affect the nasal mucosa is adrenaline and its analogues. However both male and female sex hormones are seen to affect the nasal mucosa with increased levels of nasal secretion and congestion seen in puberty, pregnancy and with menstruation. Early oestrogen rich oral contraceptive pills were seen to cause nasal congestion and squamous metaplasia was seen in the nasal mucosa. This study was designed to know about the role of different hormones acting on nasal mucosa and nasal cycle.

#### KEYWORDS

PEF(peak expiratory flow),allergic rhinitis, pregnancy rhinitis, nasal congestion, NOSE score

#### INTRODUCTION

##### Normal nasal airflow

At rest and low levels of exertion inspired and exhaled air passes through the nasal passages. The nose when considered as an organ is responsible for Olfaction, filtration of the air and the provision of humidification and heating of the air flowing through it<sup>1</sup>

The nasal valve is the narrowest point of the nasal passage; it is made up of the cartilage at the end

of the nasal vestibule and the start of the bony cavum and the erectile tissues of the inferior turbinates and septum.<sup>2</sup>Work by Haight and Cole (1983)<sup>3</sup> has shown the site of greatest resistance to lie at the level of the end of the inferior turbinate in the first few millimetres of the bony cavum, whilst noting that the tip of the inferior turbinate can extend by around five millimetres when engorged<sup>3</sup>.As air enters the narrowing of the nasal valve it accelerates and once it enters the larger cavity of the nose decelerates again disturbing the airstream in a phenomenon called orifice flow<sup>2</sup>.

The nasal cavity has a rich arterial blood supply. The nasal septum and inferior turbinates of the nose both contain venous erectile tissue made up of venous sinusoids.<sup>4</sup>The drainage of blood from the venous sinusoids is controlled by longitudinal muscle fibres in distal veins. This allows for shunting of blood through the system as well as pooling of blood and therefore venous congestion<sup>5</sup>.Both the nasal septum and inferior turbinates are components of the nasal valve so filling of these vascular structures will increase the resistance to airflow at the nasal valve. It is worth noting that the venous sinusoids are particularly well developed in these areas to the point where they may be able to obstruct the nasal airway<sup>6</sup>.

##### Control by the autonomic nervous system

The filling of the venous sinusoids is under the control of the autonomic nervous system and predominantly the sympathetic component. Sympathetic activity causes vasoconstriction and drainage of the venous sinusoids.

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The influence of the autonomic nervous system is traditionally seen as causing an alternating reciprocal pattern of congestion and decongestion of the venous tissues of the nasal cavity referred to as the nasal cycle.

### **Defining the nasal cycle**

The first reported description of the nasal cycle is attributed to Kayser<sup>7</sup> despite the fact that he did not use the term “nasal cycle”. There is some disagreement in the published literature about who first used the term “nasal cycle”, but the earliest reference found on a Pubmed search is that of Stoksted's 1953 paper “Rhinometric measurements for determination of the nasal cycle”<sup>8</sup>. Using this term Stoksted referenced Kayser's original observations that “the nasal cavities are subject to continuous alternating changes in the lumen and this cycle had no effect on the total nasal passage”<sup>8</sup>.

### **Function of the nasal cycle**

Certain possibilities have been excluded, such as an effect on the humidification of inhaled air, as no relationship between nasal patency and humidification of 6 nasally inhaled air is seen<sup>10</sup>. It has been suggested that the nasal cycle may allow a side to “rest” whilst the other predominates in function<sup>11</sup> and a possible beneficial effect on olfactory acuity<sup>9</sup>. There is evidence that there is increased plasma production in the decongested nostril, likely related to vasoconstriction of the venous sinusoids. This leakage of plasma fluid rich in immunoglobulins is likely to have an immune function as well as providing a physical flushing mechanism to remove pathogens<sup>12</sup>. The physiological vasoconstriction and resultant decongestion of a nasal passage which is seen in the nasal cycle is maintained in upper respiratory tract infections to the point where there is only a 30% increase in total nasal resistance seen, so maintenance of the nasal airway in disease may be a key function of the nasal cycle<sup>9</sup>. Studies have shown variation in mucociliary clearance times, with this being slightly increased in the more

congested nostril.

### **Factors affecting nasal cycle**

#### **EXERCISE**

There would be bilateral vasoconstriction within the nasal cavity abolishing the nasal cycle to allow improved airflow and decrease the work of breathing. However this is only likely to be significant in low to moderate exercise before mouth breathing predominates. The vasoconstriction induced by exercise is also able to overcome the congestion caused by exposure to freezing temperatures.<sup>14</sup>

#### **POSTURE**

Adopting a supine posture has an amplification effect on the nasal cycle, but this is a filling effect related to changes in the Jugular venous pressure and not down to any neural response<sup>9,14</sup>. Haight and Cole in 1986<sup>15</sup> showed that in response to adopting a lateral recumbent position for a prolonged period (over 12 minutes) the nasal cycle was reversed with congestion of the nostril on the dependent side and decongestion contra laterally.

#### **SLEEP**

Studies of the nasal cycle during sleep using a portable rhino flow meter suggest that in addition to the postural changes, the duration of cycle length increases<sup>16,17</sup> and the amplitude of changes in nasal congestion increase<sup>16</sup> the latter probably remains an effect of posture rather than sleep itself.

#### **SLEEP AND NASAL CYCLE**

Funk and Clarke in 1980<sup>18</sup> reported that right nostril predominance for one subject and left nostril predominance for a second during the main meals of breakfast and lunch which both fell on a regular schedule, based on observations over a month.<sup>18</sup>

#### **Temperature and nasal airflow**

Exposure to the cold particularly where an acute temperature change occurs can cause an overall

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increase in nasal resistance to airflow, due to increased nasal venous congestion<sup>19</sup>

#### **Humidity and nasal airflow**

Increased humidity may increase nasal cavity volume and therefore airflow, as suggested by an acoustic rhinometry study using nasal nebulisers to simulate humidity changes<sup>20</sup>

#### **Disease and nasal airflow**

Mucosal disease can occur acutely e.g. upper respiratory tract infection (URTI) or chronically e.g. allergic rhinitis. Both result in the release of a mix of inflammatory mediators and the predominating result is vasodilatation and nasal congestion.

#### **REVIEW OF LITERATURE**

Yasim Basal et al noted that TR-a1 and TR-b1 receptors were shown to be increased in the epididymitis of rats suffering from hypothyroidism.<sup>21</sup> Thyroid hormone receptors were shown to be increased in the pituitary glands of rats with hypothyroidism when compared to normal euthyroid rats.<sup>22</sup> Also, an raise in thyroid hormone receptors was seen to be determined in the brains of rats in which hypothyroidism was created.<sup>23</sup> An increase in edema findings was determined together with TR-a1 and TR-b1 in the larynges of rats in which hypothyroidism was created when compared to the normal group.<sup>24</sup> In that study, inflammation, edema, and vascular proliferation were seen to be more in amount in the group with hypothyroidism when compared with the control group. Hypothyroidism was found to lead to increasing inflammation, edema, and vascular proliferation; these findings were consistent with the literature. It was identified that the thyroid hormone receptors in sebaceous glandular structures were present in the study. Thyroid hormone receptors were shown to have an anti-inflammatory effect in one study.<sup>25</sup>

Eva Ellegård et al noted that in a randomised, cross-over, placebo-controlled clinical trial, that there was no connection between treatment with recombinant human growth hormone and nasal congestion expressed as change in nasal

PEF(peak expiratory flow). Neither was there any change in lung function, as expressed by PEF-values, attributable to GH. Blockage index, which compensates for individual variations in lung function, also failed to show any effect of rhGH treatment upon the degree of nasal congestion. Because of the low intra-individual variation in nasal PEF, it would have been possible to detect differences of 22 l/min, which is half of the difference previously found to be clinically significant (Ellegård and Karlsson, 1994). PEF values were lower than predicted by sex, age and body height, possibly because of low body weight as part of short bowel syndrome, indicating chronic malnutrition and muscle wasting in several of the patients. They demonstrated earlier that raised serum levels of estrogen cannot possibly be a causative factor in nasal congestion of menstruation (Ellegård and Karlsson, 1994). The same holds for pregnancy rhinitis (Ellegård and Karlsson, 1997). They suggested placental growth hormone as the hormone responsible for nasal congestion in pregnancy rhinitis. Weight gain, representing retention of water, does not per se seem to induce nasal congestion but there may still be a local retention, i.e. edema in the mucosa. The theory that growth hormone may induce changes in the mucosa of the upper airways is supported by Skinner and Richards (1988). They reported increased frequency of mucosal hypertrophy and polyp formation in the sphenoid.

Bodil paulsson et al noted Nasal mucosal activity has been thought to be related to variations in female sex hormones (Mackenzie, 1884; Mackenzie, 1898; Mortimer et al., 1936; Zondek and Bromberg, 1947; Armengot et al., 1990). Histological changes in the nasal mucosa have been described during different phases of the menstrual cycle in women with a history of premenstrual tension syndrome, but not in healthy women (Toppozada et al., 1981). However, the syndrome was not defined and the importance of these results is therefore difficult to assess. In other studies, the sensitivity to odours and nasal patency were shown to vary during the menstrual cycle (Le Magnen, 1952; Doty et al.,

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1981). Nasal mucosal changes during the menstrual cycle have been reported to be related to changes in the plasma levels of oestradiol and progesterone, but no measurements of these hormones have confirmed this hypothesis. The present study on regularly menstruating women showed that nasal patency was lower in the morning than in the evening, but there was no difference during the various menstrual phases. There was a tendency towards increased mean peak-flow values at the end of the menstrual cycle, indicating less obstruction on these days. If there was a significant change in nasal obstruction during the menstrual cycle, the nasal peak-flow technique should have detected it. Olcay cem bulut et al noted that there were reports of improved nasal breathing after sexual intercourse for up to 60 minutes and to the same extent as application of nasal decongestant as measured with subjective VAS. This was confirmed by objective rhinometric data as mean nasal flow increased while resistance decreased immediately, 30 minutes, and 60 minutes post-intervention. Three hours after sexual intercourse, nasal breathing was back to the baseline level while it remained improved for longer after nasal decongestant. The effect was significant in patients with some pre-existing nasal obstruction (NOSE score >30).

Although Sigmund Freud and Wilhelm Fliess had described a physiological connection between the nose and the genital area a long time ago,<sup>13 5</sup> that was the first exploratory study investigating sexual activity with climax and its impact on nasal breathing and patency. The strength of this study was the use of both subjective (VAS) and objective (rhinometric) measurements at different time points. Comparison to nasal decongestants were also very informative.

This study however had major limitations. They were not able to collect rhinometric data in all participants. This could be due to the participants' inability to focus on the device before and immediately after intercourse. The participants were all health care professionals. The relatively

high mean NOSE score and average VAS at baseline suggest that they selected participants complaining of nasal obstruction. The collection of data by the participants may not be reliable. As the rhinometric measurements were obtained at the participants' home by themselves, the compliance with the guidelines cannot be guaranteed. Acoustic rhinometric evaluation would have been ideal, but a portable version was unavailable. Also, the results of this study, though interesting, may not be generalizable.

Stimuli leading to changes in nasal breathing include physical exercise, temperature, alterations of body position, changes by hormones, neurologic syndromes and dentistry also have an effect on nasal reflexes.<sup>19 12 16</sup> An increase in nasal patency with exercise is well known and described in the literature.<sup>10 17 19</sup> Hanci et al described a decrease in nasal resistance after exercise in swimmers, runners, and handball players.<sup>20</sup> Studies investigating nasal function and exercise have mostly assessed isometric exercises.<sup>21 22</sup> Wilde et al reported that isotonic exercise causes a drop in nasal resistance and may have a nasal decongestant effect.<sup>22</sup> Depending on the sexual exercise, one may experience isotonic or isometric contractions.

Several studies have focused on the duration of exercises' effects on nasal breathing.<sup>23 25</sup> These report a decrease in nasal resistance up to 30 minutes after exercise. Strohl et al showed that nasal resistance returned to baseline after 30 minutes and was lowest when measured between the first and the fifth minute.<sup>25</sup> This study showed improvements for up to 60 minutes, although diminishing slowly after 30 minutes. Sympathetic reflexes are active in the nasal mucosa, and  $\alpha$ -adrenergic agonists decrease mucosal thickness and increase nasal patency.

Studies suggest that nasal airflow resistance decreases with intensity but not duration of exercise.<sup>10</sup>



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Other interesting studies have reported links between specific physical activities and nasal function. Hasegawa et al reported that breath holding for 30 seconds decreased nasal resistance.<sup>26</sup> Immersion of both feet in warm water (42 °C) may have a transient positive effect on nasal resistance.<sup>27</sup> Performing 5 minutes of axillary pressure (crutch reflex) leads to contralateral increase in nasal vasoconstriction.<sup>28</sup> Jang et al showed that in nasal septal deviation, the mucosal response is more prominent in the concave nasal cavity.<sup>21</sup> Incorporating these findings could potentially synergistically improve nasal function even more.

If further studies prove that masturbation alone has similar positive effect, there might be a potential natural substitution for nasal decongestant application in some cases. Headaches secondary to sinus problems might benefit from such “natural means.” Freud and Fliess “naso-genital” reflexes may not be due to genital spots located on the nasal turbinate.

Leonardo Balsalobre et al noted that topical corticosteroids are the first-line therapy of choice for Allergic rhinitis (AR). These drugs act locally on the nasal mucosa, primarily by regulating protein synthesis, leading to inhibition of various pro-inflammatory cytokine productions<sup>26</sup> and, consequently, reduced nasal congestion. A recent randomized placebo-controlled study showed a significant improvement in nasal obstruction and AHI in patients with OSA following a 1 month course of intranasal fluticasone.<sup>27</sup> Although this study did not include patients diagnosed with OSA, only subjects with AR, the initial evaluation of the effect of a 28 day course of intranasal Budesonide showed a significant improvement in subjective nasal obstruction (VAS-visual analogue scale and NOSE-nasal obstruction scoring evaluation), corroborating these findings. It is worth noting that there was no statistically significant improvement on post-treatment and pre-treatment comparison of these individuals through objective parameters (PNIF-peak nasal

inspiratory flow).

Brian Kennedy et al noted Higher levels of Nor Epinephrine are found in the blood of one arm versus the other, and the ratio of concentration in the two arms alternates over time. The earlier studies of the ultradian rhythms of NE<sup>12,13</sup>, I<sup>14</sup>, E<sup>13,14</sup>, and DA<sup>14</sup> using humans were all done by sampling blood from a single site, thus eliminating the possibility of discovering this differential activity. The approximate periodicities of dominance on one side of the body in our study, varied between 60-150 min. They are similar to the 75-188 min. (mean 107 min.) cycles reported by Levin et al.<sup>12</sup>. In other studies with humans there was also similar variations in both the amplitude and frequency components of these neurotransmitters<sup>13,14</sup>. Levin and Natelson<sup>13</sup> found that Nor Epinephrine and Epinephrine correlated well in 9 out of 12 subjects when the amplitude trend was considered, but levels correlated in only 6 out of 12 subjects when a statistically significant correlation (in 2 of 3 subjects) between the nasal cycle and NE ratios appears. Since both phenomena reflect gross sympathetic activity, this relationship would suggest a centrally regulated mechanism for the lateralization and coordination of autonomic activity throughout the periphery. The striking similarities in the temporally shifted airflow rhythms and blood flow patterns support the case that both activities are representative of the same overall pattern of autonomic regulation of sympathetic activity.

Haeggström et al noted that The rhinostereometric measurements show the presence of nasal hyperreactivity, on histamine challenge in the mid-cycle phase when oestrogen levels have reached their peak. Oestrogen as a cause of nasal stuffiness is indicated by the fact that topical oestrogen has been used to induce congestion in the nasal mucosa in the treatment of patients with atrophic rhinitis<sup>28,29</sup>. It has also been reported that contraceptive pills with high levels of oestrogen can produce nasal mucosa congestion as a side-effect.

## DISCUSSION

Hypothyroidism causes increased inflammation, edema and vascular proliferation in nasal mucosa as compared with euthyroid subjects. There was no connection between treatment with recombinant human growth hormone and nasal congestion expressed as change in nasal PEF(peak expiratory flow) .Studies suggested placental growth hormone as the hormone responsible for nasal congestion in pregnancy rhinitis. There were reports of increased frequency of mucosal hypertrophy and polyp formation in the sphenoid in case of recombinant growth hormone in one study. Changes in the nasal mucosa have been described during different phases of the menstrual cycle in women with a history of premenstrual tension syndrome. Nasal mucosal changes during the menstrual cycle have been reported to be related to changes in the plasma levels of oestradiol and progesterone. Improved nasal breathing after sexual intercourse for up to 60 minutes and to the same extent as application of nasal decongestant was also seen. A decrease in nasal resistance after exercise was noted due to endorphins. Corticosteroids cause reduced nasal congestion. Oestrogen can cause nasal stuffiness.

## CONCLUSION

Contradictory studies are seen in case of recombinant growth hormone relations with nasal mucosa. Several studies contributed to the importance of female sex hormones like progesterone and estrogen effecting the nasal cycle and emergence of diseases associated with it. Nor epinephrine and epinephrine play a role too, but its relation is still unclear. Corticosteroids are widely used drug as nasal decongestant due to its properties. More extensive studies are required to determine the role of hormones in nasal cycle in order to know about their effects.

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