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Title page:

The role of nasal congestion as a defence against respiratory viruses

Running title; nasal congestion and respiratory viruses

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Abstract

Introduction; This review discusses how nasal congestion may have benefits as a mechanism of defence against respiratory viruses.
Methods; A literature research was conducted on respiratory viruses and nasal congestion, following a recently published review on how temperature sensitivity is important for the success of common respiratory viruses.
Results; The literature reported that common respiratory viruses are temperature sensitive and replicate well at the cooler temperatures of the upper airways (32ºC), but replication is restricted at body temperature (37ºC). The amplitude of the phases of congestion and decongestion associated with the nasal cycle was increased on infection with respiratory viruses and this caused unilateral nasal congestion and obstruction. Nasal congestion and obstruction increase nasal mucosal temperature towards 37ºC and therefore restricted the replication of respiratory viruses.
Conclusion; Nasal congestion associated with the nasal cycle may act as a mechanism of respiratory defence against infection with respiratory viruses

Key Points

- Nasal congestion is considered a disturbing symptom, but it may have benefits as a mechanism of defence against respiratory viruses
- Common respiratory viruses are temperature sensitive and replicate well at the cooler temperatures of the upper airways (32ºC), but replication is restricted at body temperature (37ºC)
- The amplitude of the phases of congestion and decongestion associated with the nasal cycle is increased on infection with respiratory viruses and this causes unilateral nasal congestion and obstruction
- Nasal congestion and obstruction increase nasal mucosal temperature towards 37ºC and therefore restricts the replication of respiratory viruses
- Nasal congestion associated with the nasal cycle may act as a mechanism of respiratory defence against infection with respiratory viruses

Key words; nasal cycle, congestion, common cold, temperature sensitivity,

Introduction

“Respiratory tract infections are the most common infections to afflict mankind and are responsible for an enormous burden of disease, ranging from trivial mild common colds, to severe fatal pneumonias”[(1)] The nose is the main site of infection of common respiratory viruses as the filtration function of the nose ensures that matter containing viruses is deposited in this area of the upper airways[(2)]. The nose has several defence mechanisms to neutralise respiratory viruses and the first is mucocilary clearance which clears inhaled viruses towards the acid environment of the stomach where acid sensitive respiratory viruses are destroyed[(3)]. The nasal cycle of alternating airflow and congestion has been proposed to be important for respiratory defence by creating a plasma exudate which has been described

as a “first line respiratory mucosal defence” [4, 5]. The nasal cycle is a phenomenon which has generated interest over some 125 years since it was first described by Kayser in 1895[6] and recently reviewed by Pendolino et al. (2018)[7]. An alternating congestion and decongestion of the nasal turbinates, with alternating dominance of nasal airflow (nasal cycle) has been found in all mammals so far studied, including the cat[8], pig[9], rabbit[10], dog[11] and rat[10]. The nasal cycle of alternating congestion is a prominent aspect of nasal physiology that still poses many questions[12]. This review will propose a new mechanism of respiratory defence associated with the nasal cycle, that is related to the congested phase of the nasal cycle causing an increase in nasal mucosal temperature which inhibits the replication of temperature sensitive respiratory viruses.

Search Strategy

References for this review were identified through searches on PubMed using the terms “nasal congestion”, “nasal cycle” linked with “temperature” and “virus”. Searches and the bibliography of a recent review article (Eccles R. Why is temperature sensitivity important for the success of common respiratory viruses? Rev Med Virol. 2020: DOI 10.1002/rmv.2153) were also used. Google Scholar was used to search for references using the same search terms. The bibliographies of articles were searched for relevant references and the Web of Science was used to search for citations to key references.

Why are respiratory viruses the most successful human parasites?

The common respiratory viruses include adenovirus, enterovirus, human coronavirus, human metapneumovirus, rhinovirus (RV), influenza, parainfluenza and respiratory syncytial virus (RSV)[13]. Respiratory viruses are the most common human parasites and the common cold syndrome of disease that they cause is the most common disease of mankind with most school children having 7-10 colds a year, and adults 2-5[14]. Respiratory viruses have easy access to the human airway as an adult breathes in 10,000-15,000 litres of air a day. A two year old child has a respiratory rate at rest of 26 breaths per minute which equals 37,000 breaths each day[15], thus the airway is continuously exposed to potential infection from large volumes of inspired air. As well as providing easy entrance to the body for infection, the nose also provides an easy exit for the virus to infect other hosts[16]. Symptoms of nasal viral infection are runny nose, sneezing and cough[17]. The symptoms are triggered by the host defensive response to the viral infection with the generation of inflammatory mediators such as bradykinin and prostaglandins that stimulate sensory nerves in the upper airway to cause reflex nasal secretions and sneezing by stimulating trigeminal nerve endings in the nose, and cough by stimulating vagal nerve endings in the larynx and trachea[18]. The host response to upper airway viral infection thus provides the exit mechanism for respiratory viruses as they are transmitted in respiratory fluid on fomites that can contaminate hands, and in airway fluid expelled as aerosols by coughs and sneezes[16].

What is viral temperature sensitivity?

All common respiratory viruses replicate best at a temperature close to that of the human upper airway which is between 32ºC-34ºC[16]. Viral temperature sensitivity has been defined as follows;

Virus 'temperature sensitivity' is the property of a virus to replicate poorly or not at all at the normal body temperature of the host (restrictive temperature) but to replicate well at the lower temperatures found in the upper airway of the host (permissive temperature)[16].

The temperature sensitivity of common respiratory viruses restricts the viral replication to the cooler nose and upper airways and means that in most hosts the virus does not infect the lungs where the temperature is at 37ºC. The restrictive nature of temperature sensitivity is best exemplified with the avian influenza virus A/H5N1 which is not successful in spreading from domestic birds to humans despite the many close contacts and occasional human infections, as avian influenza viruses are adapted to replicating in the avian gut at the normal avian temperature of 40ºC[19]. Another example of temperature sensitivity is with live vaccines for human influenza that are made up of temperature sensitive strains of virus, so that the viruses can infect the upper airway at temperatures around 32ºC and cause a mild or asymptomatic disease, and there is no risk of them infecting the lungs to cause serious disease as they have a restrictive temperature of >35ºC[20].

What is the temperature gradient along the human airway?

The inspired air over the wide range of climates from the arctic to the equator is warmed by the nose and upper airway to a temperature of 37ºC at the level of the alveoli[21]. Nasal mucosal temperature during respiration has been studied by Lindemann et al (2002)[22] and mean nasal mucosal temperature ranged from 30.2ºC-34.4ºC in a study on 15 healthy subjects breathing ambient air at 25ºC. Fig.1 illustrates the range of temperature along the human airway from the entrance of the nose at the nasal vestibule (32.5ºC) to the nasopharynx (33.2ºC), and lungs at 37ºC. The nose and upper airway have a great capacity to warm the inspired air, and even at an inspired air temperature of -17ºC the air temperature is 34ºC at the level of the bronchi and reaches 37ºC before the alveoli[23].

Which factors influence nasal mucosal temperature?

The temperature of the nasal mucosa is determined by four factors; firstly, the core body temperature, secondly, the rate of blood flow through the nasal mucosal blood vessels, thirdly, the rate of airflow through the nose, and fourthly, the temperature of the inspired air. These different factors that determine nasal mucosal temperature are illustrated in Fig.2.

1. The core body temperature is normally regulated at 37ºC but fever is common in children with acute upper respiratory tract viral infections[18, 24] and a raised body temperature is found on infection with respiratory viruses[25, 26].

2. The blood flow and filling of the large veins in the nasal turbinates is regulated by the sympathetic vasoconstrictor innervation of the nose[27, 28] and increased blood flow during the congestion phase of the nasal cycle is likely to cause an increase in nasal mucosal temperature whereas during the vasoconstrictor part of the cycle the nasal turbinates decongest, blood flow is reduced, and nasal temperature is likely to decrease.

3. The nasal airflow alternates with the nasal cycle and since the inspired air is normally cooler than the nasal mucosa the higher the airflow the greater the cooling action of the inspired air. In conditions of severe nasal congestion, the airflow will be close to zero and nasal mucosal temperature will be the same as body temperature. After complete cessation of airflow through the nose the nasal mucosal temperature rises to body temperature in a few minutes [29]. Airflow also cools the nasal mucosa by causing evaporation of water from the surface of the mucosa, as the humidity of the inspired air is conditioned by the nose.

4. The temperature of the inspired air will also affect the temperature of the nasal mucosa, but this will be affected by the rate of nasal airflow, as low airflow when the nasal passage is congested will have little capacity to influence nasal mucosal temperature.

The first three of these factors; core body temperature, nasal mucosal blood flow and nasal congestion are all significantly increased on infection with a respiratory virus[26].

How do nasal congestion and the nasal cycle influence nasal mucosal temperature?

Nasal airflow is normally asymmetrical due to the spontaneous congestion and decongestion of venous sinusoids in the nasal turbinates and nasal septum[7]. The hypothesis put forward in this review is that the nasal cycle is associated with congestion and decongestion of the nose and that during the congestion phase of the nasal cycle the temperature of the nasal mucosa is increased towards body temperature (37ºC) and that this temperature restricts the replication of respiratory viruses. The amplitude of the congestion and decongestion phases of the nasal cycle is increased in patients with common cold as illustrated in Fig.3, which shows that in the patient with common cold the congested side of the nose has almost no airflow whereas the decongested side of the nose compensates with greater airflow to maintain normal breathing resistance[30]. In this subject the congested side of the nose maintained an almost completely obstructed state for around three hours, and this will raise the nasal mucosal temperature close to body temperature (37ºC [29].

In health and disease, the partitioning of nasal airflow caused by the nasal cycle is influenced by posture, so that when assuming the lateral recumbent position the dependent nasal passage is congested and the upper nasal passage is decongested[31]. In subjects with common cold, adoption of the lateral recumbent posture will cause total obstruction of the dependent nasal passage and this may restrict viral replication by elevating nasal mucosal temperature. In subjects with common cold changing from the sitting position to supine has been shown to cause complete unilateral nasal obstruction in 5/12 subjects[32], and although this is a widely accepted occurrence in subjects with common cold it has not been documented in the literature.

Discussion

The common respiratory viruses are temperature sensitive and replicate well at the normal temperature of the nasal mucosa (32ºC) and poorly or not at all at body temperature (37ºC)[16]. This review proposes that unilateral nasal congestion and obstruction associated with the nasal cycle is a mechanism of defence against infection with respiratory viruses as it

raises the nasal mucosal temperature to a restrictive temperature of 37ºC. The nasal cycle allows nasal breathing to continue at normal levels of ventilation even though one nasal passage may be obstructed as illustrated in Fig.2, and total resistance to airflow remains relatively unchanged from normal[30].

The idea that a rise in nasal temperature may be the first line of defence against respiratory viruses was first proposed by Bende et al. (1989) who conducted some elegant experiments at the Medical Research Council, Common Cold Unit in Salisbury, United Kingdom, just as the research unit ended its 43 years of research on common cold viruses (1946-1989). Common colds were induced by coronavirus challenge and were reported to be very mild colds[26] as is expected from laboratory cultured viruses[33], however they caused the following changes in the volunteers who were infected by the coronavirus;

1. A rise in body temperature of 0.5ºC
2. A 20% increase in nasal mucosal blood flow
3. A 40% increase in total nasal resistance to airflow
4. A 2ºC rise in mean combined nasal mucosal temperature.

Despite the very mild symptoms exhibited by the experimental coronavirus infection the results support the proposal in the present review that nasal congestion associated with common cold causes an increase in nasal mucosal temperature, and the authors concluded that "These observations suggest that a rise in temperature may be the first line of defence against coronavirus infections" [26]. Akerlund & Bende (1989)[25] studied nasal mucosal temperature in healthy subjects and with acute rhinitis and the study reported a mean increase of 2.9ºC in nasal mucosal temperature in subjects with acute rhinitis when compared with healthy subjects and concluded "An increased mucosal temperature was found in patients with acute rhinitis, an effect which is supposed to assist in the defence system against micro-organisms".

If nasal congestion is a defence mechanism against infection are nasal decongestants likely to increase the severity of viral infection? This seems unlikely as nasal decongestants are taken in millions of doses every day, and yet after a literature search no reports have been found in the literature that treatment with nasal decongestants prolongs or exacerbates upper respiratory tract viral infections. One study on the topical nasal decongestant oxymetazoline reported that use of this nasal decongestant reduced viral titres in subjects with induced common colds[34]. It is possible that by the time nasal congestion reaches a level of severity to warrant treatment with a nasal decongestant, viral replication will have passed its peak, and decongestion will not influence the course of the disease but will provide symptomatic relief from congestion.

Conclusion

This review proposes that the periods of unilateral nasal congestion associated with the nasal cycle cause an increase in nasal mucosal temperature that will restrict the replication of respiratory viruses responsible for the common cold syndrome of disease.

Conflict of interest

The author has no conflicts of interest to declare regarding this review article.

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Fig.1. Nasal mucosal temperatures measured during inspiration of ambient air at 25C Drawn from data published by Lindemann et al. (2002).

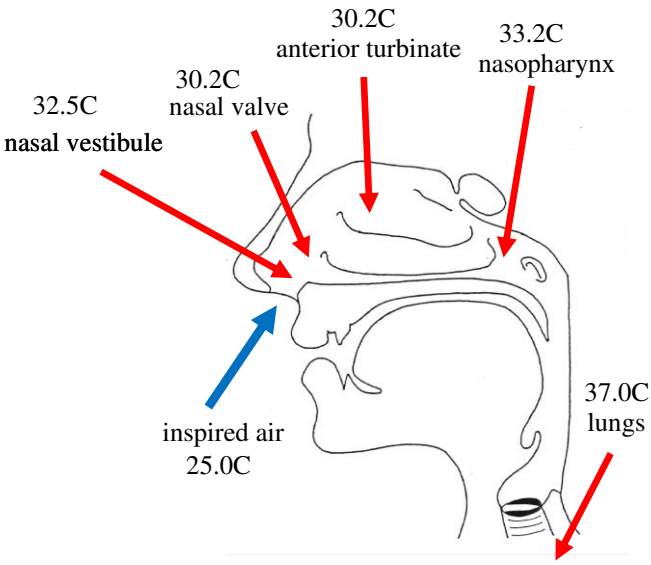

Fig.2. Diagram of nasal passages, illustrating asymmetrical airflow caused by asymmetrical congestion of nasal turbinates and nasal septal blood vessels. The more congested side of the nose illustrated in red has a lower airflow and higher nasal mucosal temperature (37°C) than the less congested side of the nose shown in blue where there is a higher airflow, and the mucosal temperature is lower (32°C). The congested side of the nose has a higher blood flow than the decongested side due to differences in sympathetic vasoconstrictor tone associated with the nasal cycle.

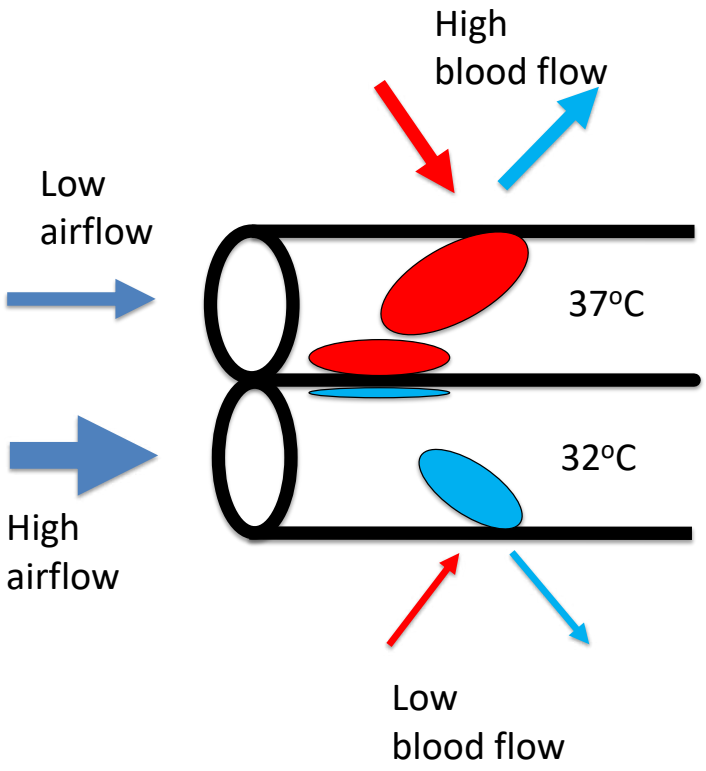
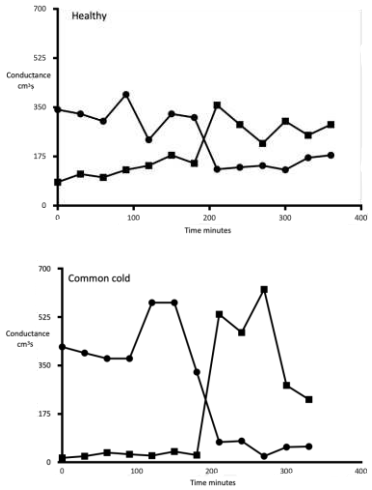
Fig.3. Changes in unilateral nasal conductance, expressed as inspiratory airflow cm^3s at a driving pressure of 75Pa, recorded in one subject during common cold and 6-8 weeks later when healthy. Circle symbols are for right nasal passage and square symbols for left nasal passage. Each point represents mean conductance calculated from 12 breaths. Conductance recalculated from resistance and redrawn from data in publication by Eccles et al. (1996).