



Research Article

Does Covid-19 curtail the Mucociliary clearance in Nose and Paranasal Sinuses?

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ABSTRACT

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Introduction: In the history of mankind 21st century will mark as the era of COVID due to the global pandemic caused by the virus COVID 19. Mucociliary clearance (MCC) is a vital defence mechanism of the respiratory tract, any disturbance in the mechanism leads to stagnations of secretions and secondary infections both lead to prolonged mucociliary clearance time. Disruption in mucociliary clearance may be either acquired or genetic in origin and can result in chronic infections affecting the nose, paranasal sinuses and respiratory tract.

Aim and objectives: To evaluate the effect of COVID 19 disease on the mucociliary clearance in the nose and paranasal sinuses.

Materials and methods: An observational study was conducted on 40 RT-PCR-confirmed COVID-19 patients admitted to our tertiary care hospital. Mucociliary clearance was assessed using saccharin transit time test. Patients were enrolled into three different groups based on severity (A: mild/asymptomatic, B: Pneumonia, C: Severe disease with hypoxia/sepsis). Data was collected on basic demographic profile, baseline characteristics and mucociliary clearance time were recorded. Statistical analysis was performed using SPSS v22.0.

Results: The mean MCC time was significantly prolonged compared to the normal values reported (6.7 to 11.7 minutes). The minimum MCC time observed was 16.21 minutes and maximum was 45.39 minutes. Severe cases had the longest clearance times. Six patients (15%) developed fungal sinusitis during follow-up.

Conclusion: COVID 19 disease affects the nasal mucosa at the cellular level by altering the normal homeostasis of the mucosa by reducing the transmucosal potential difference across the mucosa of nose and paranasal sinuses and thus altering the mucociliary clearance. This will further lead to stasis of secretions in nose and paranasal sinuses which would further lead to sinusitis. On follow up, 6 out of 40 patients developed fungal sinusitis which could be attributed to the fact of altered mucociliary clearance.

Keywords: COVID 19, Mucociliary clearance, Saccharin test

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INTRODUCTION

In the history of mankind 21st century will mark as the era of COVID due to the global pandemic caused by the virus COVID 19. The origin of the pandemic was traced back to Wuhan, China where series of cases started in December 2019. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), belongs to the family of SARS-related coronavirus, already known for epidemic outbreak. Coronaviruses are made up of single-stranded, positive sense RNA distinguished by club-shaped spike (S) protein on their surface. The receptor-binding domain of these spikes enables the virus to attach to the angiotensin-converting enzyme 2 (ACE2) receptor, allowing entry into host cells and leading to infection. [1,2].

The virus primarily affects the ciliated epithelial cells, leading to significant increase in multiciliate cells. However, this also raises the number of susceptible cells. Due to its permissive and cytopathic nature, the virus ultimately leads to a reduction of ciliated cells, with mRNA degradation playing a significant role in the loss of respiratory epithelial integrity[3].

Mucociliary clearance serves as crucial first line defence mechanism of respiratory tract with two key components of mucus and cilia. The cilia lining the respiratory tract moves in a coordinated fashion and carries mucus along with trapped foreign particles out of the airways. The mucus layer, produced by secretory cells is rich in antimicrobial components such as defensins, lysozyme, IgA and cytokines that helps in neutralizing pathogens. When mucociliary clearance is impaired, mucus transport is disrupted, resulting in mucus accumulation and plug formation. This creates an environment conducive to bacteria colonization, thereby increasing the risk of sinopulmonary infections.[4]

The predominant upper respiratory tract (URT) symptoms of SARS CoV-2 infection include sore throat, rhinorrhoea, headache and anosmia or hyposmia[5]. Among people infected with COVID-19, lower respiratory tract infections are often linked to co-infections with a range of bacterial, fungal and viral pathogens. Reported bacterial co-infections include *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and less frequently *Enterobacter* species, *Enterococcus faecium*, *Chlamydia*, *Klebsiella pneumoniae* etc. Fungal co-infections are mainly associated with *Aspergillus flavus*, *Aspergillus fumigatus*, and *Candida glabrata*. Additionally, viral co-infections like Respiratory Syncytial Virus (RSV) and Influenza A have also been reported [6]. This study evaluates the impact of COVID-19 on the mucociliary clearance of the nose and paranasal sinuses, assess the extent of mucociliary dysfunction in relation to disease severity, and examine its correlation with the occurrence of co-infections.

METHODOLOGY

Study design and setting

This was a hospital based prospective observational study conducted in a tertiary care centre. The study was carried out after obtaining approval from the Institutional Ethical Committee (Ref No. KIMS/IEC/A057/M/2020) and informed consent was obtained from all participants prior to the enrolment. Due to the exploratory nature of the study and logistical constraints during the COVID-19 pandemic, a convenience sample of 40 patients was included.

The sample size was estimated based on the mean difference expected in mucociliary clearance among severity groups of COVID-19. Assuming a moderate effect size ($f=0.25$), a statistical power of 80% ($\beta = 0.20$) and a significance level of 0.05, the sample size was calculated using one way analysis of variance (ANOVA).

The general formula used for sample size estimation in ANOVA is:
$$N = \frac{(Z_{\alpha} + Z_{\beta})^2 * 2\sigma^2}{\Delta^2}$$

Where: N = total sample size, Z_{α} = standard normal deviate corresponding to the desired significance level (1.96 for $\alpha = 0.05$), Z_{β} = standard normal deviate corresponding to desired power (0.84 for 80% power), σ = standard deviation, Δ = minimum detectable difference between group means

With an assumed standard deviation of 3 minutes and a minimum clinically significant difference of 3.5 minutes, the calculated sample size was approximately 12 patients per group (total ≈ 36). This was rounded to 40 participants for the present study.

$$N = \frac{(1.96 + 0.84)^2 * 23^2}{\Delta 3.5^2} = 11.52$$

Study Population

Person tested positive for COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) were recruited. All study participants were subjected for history taking and a comprehensive ENT examination. **Inclusion Criteria:** Patients aged 18yrs and above, confirmed COVID-19 by RT PCR and willing to participate in the study will be included. **Exclusion Criteria:** Patients under 18yrs, patients with endotracheal intubation and patients presenting primarily with anosmia or ageusia will be excluded from the study.

Participants were categorised into three groups based on clinical severity:[7] Group A (Mild)- Mild case of fever, myalgia, cough and sore throat along with asymptomatic and presymptomatic cases. Group B (Moderate)- Patients with fever and pneumonia. Group C (Severe)- Patients with hypoxia, cyanosis, hypotension, tachycardia, tachypnoea, sepsis or septic shock.

Mucociliary clearance time was measured using Saccharin test, following the method described by Corbo GM (1989).[8] A saccharin pellet was placed on the floor of nasal cavity about 1 cm posterior to the anterior end of inferior turbinate. Participants were instructed to follow the instructions and swallow every 30 seconds and report the first perception of sweet taste. The nature of the test substance was not disclosed to minimize the bias. The time taken to perceive sweetness was recorded as mucociliary clearance time. A normal range of 6.8-11.7 minutes was considered, based on previously reported studies [9,10]. The degree of impairment was assessed and compared across the three groups of disease severity.

Statistical Analysis

Data were coded and entered into MS excel and analysed using Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp. Descriptive statistics were used to summarize demographic and clinical characteristics of study participants. Continuous variables were expressed as mean, standard deviation, while categorical variables were presented as frequencies and percentages. Comparison of mucociliary clearance time between the three groups was performed using one way ANOVA (Analysis of Variance). A p value of <0.05 was considered statistically significant.

RESULTS

Our study enrolled 40 patients comprising of 26 males (65%) and 14 females (35%). The mean age of participants was 38.4 ± 11.2 years and they ranged from 18–60 years. Patients were categorized into three severity groups: Group A (Mild, n=25), Group B (Moderate, n=12), and Group C (Severe, n=3).

Table 1: Demographic and Clinical Characteristics of the study participants

Variable	Group A (Mild) n=25	Group B (Moderate) n=12	Group C (Severe) n=3	Total (N=40)
Age (mean \pm SD, years)	34.6 ± 9.8	41.2 ± 10.5	49.3 ± 8.7	38.4 ± 11.2
Male : Female	16:9	8:4	2:1	26:14
Co-morbidities (%)	20%	33%	67%	28%

Table 2: Mucociliary time among three different severity groups

MCT Range (minutes)	Group A (Mild)	Group B (Moderate)	Group C (Severe)
16–20	14	5	–
21–25	5	4	–
26–30	3	3	–
31–35	3	–	3
36–40	–	–	3
41–45	–	–	3

Mucociliary clearance (MCC) time was significantly prolonged among patients affected with COVID-19 compared to the normal reference range (6.8–11.7 minutes). The minimum observed clearance time was 16.21 minutes, while the maximum was 45.39 minutes.

The average mucociliary time observed in mild cases of COVID-19 was observed to be 21.8 ± 4.2 minutes, whereas Moderate and Severe diseased patients had 24.6 ± 3.9 minutes and 38.7 ± 5.1 minutes respectively. This difference of MCC time across three different severity groups was found to be statistically significant (one-way ANOVA, $F=18.42$, $p<0.001$). Intergroup analysis revealed that severe COVID-19 cases had markedly impaired mucociliary clearance compared to mild and moderate cases. (post-hoc Tukey’s test-Group A vs Group B: $p = 0.12$, Group A vs Group C: $p < 0.001$, Group B vs Group C: $p < 0.001$). On follow-up, it was found that 6 out of 40 patients (15%) developed fungal sinusitis, which could be attributed to the fact of altered mucociliary clearance.

DISCUSSION

The nasal mucosa has been described as a delicate structure since time immemorial. Beyond its respiratory role, it is also involved in olfaction and voice resonance. Its autonomic innervation consists of sympathetic fibres from the superior cervical ganglion and parasympathetic fibres, which utilize co-transmitters like VIP, NPY, Substance P, and nitric oxide that play key roles in modulating vascular tone and secretion. The foremost physiological function of the nasal mucosa is mucociliary clearance, often described as nature’s most efficient “air conditioner”. This mechanism safeguards both upper and lower respiratory tracts by humidifying, filtering and warming approximately 12,000 litres of air flow passing through an adult’s nose daily, It also contributes the reflexes such as sneezing and provides a bacterial defence through nitric oxide production. Additionally, the nasal mucosa contributes to enzymatic activity, including CYP450 metabolism. The mucous film, enriched with immunologically active components such as IgG and IgA, along with its adsorptive capacity and water content, ensures that inhaled air is nearly sterile, sufficiently humidified, and brought to body temperature.[11]Its autonomic innervation is derived from sympathetic fibers of the superior cervical ganglion and parasympathetic fibers, which employ cotransmitters such as vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), Substance P, and nitric oxide (NO). These mediators play crucial roles in regulating vascular tone and glandular secretion.[12]

The foremost physiological role of the nasal mucosa is mucociliary clearance, often described as nature’s most efficient “air conditioner.”[4] This mechanism safeguards both the upper and lower respiratory tracts by humidifying, filtering, and warming the approximately 12,000 litres of air that pass through the adult nose daily.[8,11]It also contributes to reflexes such as sneezing and provides a bactericidal defence through nitric oxide production. Beyond these functions, the mucosa participates in enzymatic activity, including cytochrome P450 metabolism, and maintains an immunologically active surface film enriched with IgA and IgG.[11,12] Together, these features ensure that inhaled air is nearly sterile, adequately humidified, and conditioned to body temperature.Mucociliary clearance is a crucial defence mechanism, any disruption

whether acquired or genetically determined can lead to stagnation of secretions, prolonged clearance and predisposition to secondary infections of the nose, paranasal sinuses, and lower respiratory tract.[13]

In this study, 40 patients (26 males, 14 females; age range 18–60 years) diagnosed with COVID-19 infection were evaluated using saccharin time test. Normal mucociliary clearance values reported in previous literature range between 6.8 and 11.7 minutes [8–10]. Corbo et al. reported a median clearance time of 8 minutes in children with a wide range of 1–40 minutes[14]. The study participants in our study demonstrated a contrast finding with prolonged clearance times, emphasizing the impact of COVID-19 on nasal physiology. This finding of increased clearance time among COVID patients was backed up by several studies. Koparal et al. observed significantly prolonged clearance times in COVID-19 patients compared with health controls, age showed significant correlation whereas gender showed no correlation [15]. Kahraman et al. similarly reported increased mucociliary clearance times in infected individuals [16]. Cecen et al. demonstrated the additive effect of smoking, with the longest clearance times observed in COVID-positive smokers, though the difference was not statistically significant [17]. Pezato et al., observed no difference in mucociliary clearance among asymptomatic individuals, but significant impairment in those presenting with dyspnoea. Other conditions also demonstrate altered clearance[18]. Kumar et al. proved the effect of endoscopic surgery improving the mucociliary clearance among chronic rhinosinusitis patients [19]. Viral infections such as influenza and rhinovirus have been shown to impair mucociliary clearance by disrupting the ciliary beat frequency and epithelial integrity, as described by Wilson et al. [20].

These findings suggest that COVID-19 infection significantly disrupts mucociliary clearance, likely through mechanism similar to respiratory viruses. This impairment may predispose to secondary infections, as reflected in our cohort where 15% developed fungal sinusitis during follow-up. The limitations of this study is the limited generalizability due to single centred study and small sample size. In addition, the saccharin test, though widely accepted, is a subjective measure dependent on patient perception and compliance. These factors should be considered when interpreting the results.

CONCLUSIONS

Since the inception of COVID 19 pandemic, many strains have emerged and are still emerging. Although the pandemic is over it surprises us with a new strain and a new feature. Due to global vaccination against COVID 19, the severity of the disease has reduced and is known to have both short term and long term consequences. In our study, we found out that COVID 19 virus significantly affects the mucociliary clearance of the nose and paranasal sinuses. The exact mechanism of this is not known but it could be due to the altered nasal mucosal homeostasis by causing alteration in transmucosal potential difference. Further studies with multicentric designs would add more strength to the evidence pool.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Suhasini Hanumaiah, Jagannatha Bisanna, Bindya Nayak, Vibhav S. Hegde

Acquisition, analysis, or interpretation of data: Suhasini Hanumaiah, Jagannatha Bisanna, Bindya

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DISCLOSURES

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or

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