

Nasal Mucociliary Clearance in Adenoid Hypertrophy and Otitis Media with Effusion

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Abstract Mucociliary clearance (MCC), which exists in many systems, is the first defensive mechanism of the human body. Nasal MCC has an important role in transporting the secretions of the nasal cavity and paranasal sinuses along with the trapped inhaled pathogens to the nasopharynx. Physiologic or pathologic situations that effect nasal MCC, such as temperature, humidity, nasal obstruction, allergic rhinitis, chronic infections, etc., lead to impaired MCC and related local or circumjacent system disorders. With this perspective, when a unified airway with a multiple disease principle is considered, investigating the relationship between adenoid hypertrophy (AH), otitis media with effusion (OME) and nasal MCC is logical. In this review, histological and physiologic properties of nasal MCC and its possible role involving pathologic situations such as AH and OME is discussed together with recent literature findings.

Keywords Mucociliary clearance · MCC · Adenoid hypertrophy · Otitis media with effusion

Introduction

Human metabolism works continuously with perfect harmony of multiple systems including the respiratory system. Regarding the latter, the unified airway starts with the nasal vestibule and oral cavity narrowing down to the bronchioles, with adjacent paranasal sinuses, the middle ear cavity, and laryngeal structures that are all lined by pseudostratified ciliated epithelium with glandular epithelial cells and submucosal glands [1]. The first and most important defensive mechanism of this unified airway is mucociliary clearance (MCC). Systemic diseases such as cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) may lead to nasal or middle ear disorders by affecting nasal MCC [1, 2]. Local MCC disorders may be induced by local diseases such as chronic rhinosinusitis (CRS), adenoid hypertrophy (AH), and otitis media with effusion (OME), and these disorders might secondarily contribute to the development of each other [3, 4, 5•]. For example, infective and inflammatory situations of AH impair nasal MCC via metaplastic changes and loss of cilia, and this in turn causes OME by affecting the Eustachian tubes (ET) and respiratory epithelium [6, 7], while surgical removal of adenoid tissue restores nasal MCC by normalizing the nasal physiology [8]. Nowadays, the middle ear is also considered to be part of the unified airway with its modified respiratory epithelium [9]. This idea is strongly supported by Nguyen et al. who stated that the middle ear should be included in the unified airway system, and that treatment of middle ear pathologies should involve the modality of avoiding systemic inflammation in the whole unified airway by showing similar cellular and cytokine profiles in atopic OME patients in the samples of bilateral middle ear, ET and nasopharynx [10].

In the light of these findings, structural properties, working principles and possible AH- and EOM-related changes in

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nasal MCC of the rhinopharyngotubal system has been reviewed together with recent literature findings.

What Is Nasal MCC and How Does It Work?

Nasal MCC is the first physiologic defensive mechanism of the pseudostratified ciliated columnar epithelium that lines the nasal cavity, ET, protympanum, anterior mesotympanum, and in some cases promontorium [11]. The whole system endlessly transports the secretions of the nasal cavity and middle ear to the nasopharynx by rhythmic and continuous ciliary beats. Cilia were first discovered by Purkinje and Valentin on the respiratory and uterine mucous membranes of mammalia, birds, and reptiles. Later, Purkinje and Valentin accidentally found the ciliary transport mechanism after they noticed small portions of the mucous membrane of the tube turning round and moving briskly on a recently impregnated fallopian tube. In addition, they stated that this transport mechanism was still active up to 30 h after death when the nasal and windpipe mucosa were covered with blood. Later, Sharpey worked on cilia and defined them as “a peculiar sort of moving organs, resembling small hairs, which are visible with the microscope in many animals”. He also pointed out the clearance function of cilia. Sharpey was the first to show the nasal MCC activity and its pathway by using charcoal powder. He reported that the MCC activity is directed towards the nasopharynx on the inferior turbinate and maxillary sinuses and is directed towards the larynx on the windpipe [12].

Nasal MCC may be affected by various factors such as age, diabetes mellitus, hypertension [13], temperature, menopause [14], moisture, partial oxygen pressure, pH, cigarette, anesthetics [15], radiofrequency radiation [16], nasal obstruction [17], AH and chronic allergy [18], and infections or inflammations of sinuses [3] and the middle ear cavity [5•]. Therefore, adequate knowledge about the physiology and responses of nasal MCC on pathological situations is necessary in order to manage the diagnosis and treatment of diseases.

Nasal MCC transports the rhinopharyngotubal mucous layer over the ciliated epithelium with a constant ciliary beat frequency (CBF) (mean 12.6 ± 2.9 Hz [19]) unrelated to parts of the nasal cavity with various MCC velocities (MCV) (1–2 mm/h at the anterior part of the inferior turbinate and 10 mm/h at the posterior part of the nasal cavity) [20] according to the variety of seromucinous glands and cilia localization and density. MCC starts from the nasal vestibule and involves the Eustachian tube, middle ear, protympanum, anterior mesotympanum and promontorium to direct mucous to the nasopharynx [21, 22] and ends where the lining differentiates to squamous epithelium.

Nasal mucous is transported mainly by two pathways. The first transports maxillary, anterior ethmoid and frontal sinus secretions below the ET orifice. The second transports

posterior ethmoid and sphenoid sinus secretions over the ET orifice [23]. In normal circumstances, secretions of the nasal cavity have no contact with the ET orifice, but AH cause stagnation of the mucus and changes the transport routes leading to transportation over the ET orifice. This increases the contact of the nasal mucous with the ET with resultant bacterial overgrowth and/or increased inflammation that impairs the MCC of the ET. The persistence of the obstruction might overwhelm MCC tolerance of the ET which results in decreased ventilation, drainage and pH of the middle ear which decreases MCC further in a resultant vicious cycle. All these steps of this vicious cycle might cause different disturbances in the MCC by impairing the mucous and cilia structures [24]. Therefore, both mucous and cilia have to be better known to clarify the pathologies and the MCC relationship.

Mucous

The nasal mucous layer is constantly being secreted by seromucous glands and goblet cells and covers the nasal cavity like a carpet, with the function of trapping inhaled particles larger than $0.5\text{--}1\text{ }\mu\text{m}$. Normally, the mucus layer consists of 97 % water and 3 % solid components with various types of mucin having different functions and locations [classified as, gel-forming mucins (GFM): MUC 2, MUC 5AC, MUC 5B, MUC 6, MUC 7, and MUC 8; membrane associated mucins (MAM): MUC 1, MUC 4, MUC 11, MUC 13, and MUC 16] [20, 25], defensins, lysozyme, IgA, secretoglobins, cytokines and protective molecules such as trefoil proteins and heregulin [26]. Mucous is generally being secreted by goblet cells which are found between the microcilia at the epithelium and seromucous glands at the lamina propria layer with mechanical or osmotic stimulus from the presence of appropriate ATP, approximately $0.1\text{--}0.3\text{ mg/kg/day}$ or nearly $600\text{--}1,800\text{ ml/day}$ [21, 27]. There is general acceptance about the mucous layer being a gel on the liquid model. Inferiorly, the liquid layer or sol layer is placed with a depth of $7\text{ }\mu\text{m}$ and permits cilia motion [26, 28]. Superiorly, the gel layer is more viscous with a depth of $0.5\text{--}5\text{ }\mu\text{m}$, usually coming in to contact with cilia only at the fast phase of ciliary motion. Recently, a new model was proposed to explain the relationship of both layers and the coordination of dynamic motion as an alternative to the gel on liquid model. According to this model, an additive periciliary mesh layer that is tightly bound to the cilia, microvilli and epithelial surface consists of spanning forms of MUC1, MUC4, MUC16, and MUC20 and tethered mucopolysaccharides. Thus, this layer provides periciliary stabilization, avoids pathogens which exist in mucous contact with the epithelium and facilitates effective MCC [29]. Therefore, mucins with their effect on MCC and microbial interactions [30] should be investigated in AH- and OME-related nasal MCC impairments.

Ali et al. reported that the most expressed mucin genes in AH were membrane-bound mucins, MUC4, MUC3 and secretory mucin MUC5AC, and suggested that membrane-bound mucins are more responsible for the primary defensive functions of adenoids rather than gel-forming mucins. Due to different mucin distribution, a lack of mucus secretory cells in the majority of hypertrophic adenoids and the rare presence of respiratory epithelium in adenoid samples, they claimed that adenoid tissue is not involved in the MCC process and mucus gel production [31]. However, Elsheikh reported high rates of MUC5AC and MUC 5B up-regulation in OME patients' nasopharynx samples and only MUC5B up-regulation in the middle ear. They speculated that MUC 5B has an important role on middle ear MCC and the up-regulation of MUC5B leads to MCC dysfunction and contributes to OME formation [32].

In infective situations, pathogens bind to respiratory mucins and up-regulate their synthesis with changes in mucus concentration [33]. Kerschner et al. investigated the GFM (*MUC2*, *MUC5AC*, *MUC5B* and *MUC19*) up-regulation in a human middle ear epithelium culture model in an exposure of the most common upper respiratory pathogens [*Streptococcus pneumoniae* (SP), non-typable hemophilus influenzae (NTHi), and moraxella catarrhalis (Mcat)]. The most prominent up-regulation was seen on MUC5AC. They reported that all GFM, except MUC 19, were up-regulated after NTHi exposure [33]. NTHi and Mcat had the most significant impact on *MUC5AC* and *MUC2* whereas SP demonstrated the most significant effect on the *MUC5B* response. Further, they evaluated mucin up-regulation responses to multi-microbial exposure and stated that various GFM up-regulations (most commonly MUC5AC) were seen. As a conclusion, they suggested that mucous stasis due to hypersecretion is responsible for the development of OME. However, Precido et al. reported the increment of pro-inflammatory cytokine Cxcl2, no changes in mucin gene transcripts including MUC5B, and no changes in MUC5B up-regulation in vitro in NTHi-exposed mice ears, and suggested that the mucous hypersecretion in OME is related to cytokine hypersecretion, immune cell recruitment, and middle ear mucosal metaplasia due to chronic bacterial stimulation [34]. Therefore, in infective situations of AH and OME, mucin-related factors may affect mucous characteristics and nasal MCC.

The other mechanism that might affect nasal MCC in AH patients is mechanical obstruction causing mucous stagnation. Linbo et al. investigated the mucous load effect on fully differentiated human bronchial epithelial cultures and full thickness swine trachea by using micro-optical coherence tomography (mOCT) and MCC with intracellular Ca^{+2} , simultaneously [35••]. They showed the dynamic responses of respiratory epithelium to mucous overload and viscosity changes. In the circumstances where the periciliary layer's depth was reduced by compression to 0–1 μm and the maximum CBF

was obtained with a simultaneous intracellular Ca^{+2} increase. However, when the reduction of the depth reached 2 μm , they reported that CBF declined gradually and decelerated the auto-regulatory mechanisms when the reduction of depth exceeded 2 μm . Therefore, when the effect of mechanoreceptors on controlling the viscosity of the mucous was considered [36], stagnation and related mucous overload might lead to periciliary compression and impaired nasal MCC in AH and OME.

Cilia

Cilia are found in multiple systems of the human body like the trachea, paranasal sinuses, middle ear, fallopian canal, ductuli efferentes and ependyma of the brain with similar structures [21, 37]. All cilia have two central microtubules bound with radial spokes to nine peripheral microtubules. The peripheral microtubule connection is achieved by nexin, and all peripheral microtubules have inner and outer dynein arms that have roles in ATP-stimulated basal ciliary activity and its regulation. The other important mechanism about chemical stimulation and coordination of cilia is the ATP-related intracellular Ca^{+2} increment [22]. Epithelial cells contains 50–200 cilia with a length of 5–7 μm and diameter of 0.2–0.3 μm [24, 27] which corresponds to $10^9/\text{cm}^2$ cilia for the respiratory epithelium [38]. However, as stated above in relation to ciliary and goblet cell density in different sites of the rhinopharyngotubal system, MCV may vary. Usually, sinonasal mucosa epithelium is covered by 75 % ciliated cells, 20 % goblet cells and 5 % basal cells [27]. These cilia transport the nasal mucous with fast and slow phases by synchronized (transversally) and metachronized (longitudinal) movements with 9–15 Hz beat frequency, so that nasal mucous might be fully transported within 10 min. The CBF normally has a constant rhythm but external factors might have an effect on both CBF and MCV [39].

Braverman et al. investigated the CBF in chronic rhinosinusitis (CRS) patients and healthy controls. They reported no significant differences at the sinus ostiums and suggested that nasal MCC impairment in CRS is not related to decreased CBF [39]. Cohen investigated the CBF in CRS and healthy controls. The basal CBF among groups were similar; however, in the experiment of ATP-induced CBF change in healthy controls, dynamic responses were increased by 50–70 %, but in CRS patients CBF were decreased by 50 % during 8 min. He suggested that cilia responses were blunted to environmental stimuli in chronic infection situations [24]. Therefore, in the situation of AH with infective etiology, nasal MCC impairment should be seen according to the environmental changes such as hypoxia, decreasing pH and blunted ciliary response when the regulation of the CBF is considered [3].

Maurizi et al. investigated the adenoid tissue changes with scanning electron microscopy and nasal MCC changes with aging. Nasal MCV in patients without AH were increased with age and reached approximately adult values at 10 years. However, correlated with adenoid size, nasal MCV in AH patients were significantly impaired. In a comparison of ultrastructural properties, the absence of the cilia, or scarcely represented cilia (with 'islet' configuration), with unevenness of the mucosal surface, were more commonly seen in AH patients. They linked these changes to inflammation of the mucosal surfaces and obstruction due to lymphoid hypertrophy [7]. Similarly, Demarco et al. studied the nasal mucosal ciliary changes by transmission electron microscopy in CRS patients and showed ciliary edema and bubbles (50 %), compound cilia (27 %), peripheral microtubules (26 %), squamous metaplasia (15 %), and ciliary disorientation (11 %) [2].

As the authors also stated, the ciliary changes that are seen secondary to the inflammatory, infective or obstructive conditions are usually reversible. However, this reversible capacity of cilia is strongly related to the pathologic event's severity and duration, the tolerability of respiratory mucosa and the presence of co-morbidities. Therefore, to demonstrate and follow-up the status of cilia by nasal MCC might be important in deciding, and timing, the surgical intervention for AH and OME.

AH and Nasal MCC

AH might alter nasal physiology by causing nasal obstruction and being an inflammatory and infective reservoir with secondary co-morbidities such as rhinitis, CRS, OME, etc. [6, 40]. Related to this, nasal MCC measurement might be of importance in demonstrating the pathologic changes in AH and related diseases.

Maurizi et al. investigated the nasal MCV of 34 children by a saccharine test before and after adenoidectomy. They showed postoperative MCV scores were significantly improved (from 0.33 ± 0.10 to 0.47 ± 0.11 cm/min) with the correlation of active anterior rhinomanometry findings. With these results, they suggested the use of nasal MCV evaluation and active anterior rhinomanometry in decisions of surgery with their potential for accuracy and objectivity [41].

Ranga et al. studied nasal MCC changes by a saccharine test in 50 adenotonsillar hypertrophy patients. Although higher than the controls, they reported that postoperative nasal MCC times remained in normal ranges (from 16.97 ± 3.1 to 8.7 ± 2.14 min). They suggested the increment of pH and restoring the normal physiology is the main mechanism that is responsible for nasal MCC improvement [42].

Arnaoutakis et al. reported postoperative MCC and MCV improvement in adenotonsillectomy-performed children which demonstrated the correlation of symptomatology and nasal MCC changes. They found that patient symptomatology was correlated with nasal mucociliary dysfunction, mechanic obstruction and the bacterial reservoir role of adenoids and resultant mucous retention. Furthermore, they suggested the treatment of nasal obstructions and the removal of the bacterial reservoir and the possible occurrence of biofilms may restore nasal physiology with normalized nasal MCC and pH increment [8].

In our previous study, we investigated the nasal MCC and MCV in AH with or without OME [5••]. We classified the adenoid size according to an endoscopic view for the obstruction rate to choana as Grade 1: 25–50 %, Grade 2: 50–75 % and Grade 3: 75–100 %. We found that postoperative nasal MCC times were improved in all groups after adenoidectomy. However, when we compared the preoperative nasal MCC times, although nasal MCC in all groups were impaired, statistical significance was present only for Grade 3 AH. However, the effect of adenoid size was not related to MCC improvement. We showed that greater adenoid size is related to increased nasal MCC time preoperatively, but not related to postoperative improvement after surgery.

Recently, Ozkiris et al. used the nasal MCC measurement in a different manner to consider which adenoidectomy technique is useful and recovers nasal physiology earlier. Although, nasal MCC were improved in both groups postoperatively, the coblation technique was found to be superior to the cold curettage technique [43].

OME and Nasal MCC

The middle ear epithelium is a modified respiratory epithelium that is connected to the nasopharynx through the ET [44]. MCC in the middle ear was first demonstrated in dry perforated ears by light microscopy [45], and the nature of mucociliary activity in different sites, cilia number and clearance velocity were reported later in experimental studies [46]. Mucous secreting glands were placed in the ET with an increasing ratio from the tympanic cavity to the nasopharynx. Gland numbers [47] and the ratio of serous to mucous glands [48] were reported to be lower in children as compared to adults, which might be a predisposing factor for OME development. Kajra et al. reported ear and nasal MCC impairments by rhinoscintigraphy in chronic OME patients and suggested primary or secondary MCC disorders might have an important role in the pathophysiology of OME [49]. Cingi et al. reported that the nasal MCC of the ipsilateral nasal cavity in unilateral chronic otitis media patients were significantly impaired among contralateral nasal cavity and control groups, and proposed nasal MCC to be a valuable diagnostic method to reflect

the middle ear and tubal status according to the similar morphologic and functional properties [50].

Gurr et al. found significant differences between mean CBF (7.4 s^{-1}) in OME patients and healthy controls (10 s^{-1}) in the middle ear and did not report a relationship between CBF changes and effusion presence or viscosity. Therefore, they proposed CBF changes to be more important in OME pathophysiology rather than effusion viscosity. In addition, they could not find any significant differences when comparing patients' bilateral ear CBF and they suggested that this bilateral regulation is related to patients' individual MCC mechanism, and the changes in this mechanism and regulation have an important role in disease pathophysiology [51]. The lower rates of OME opposed to the more viscous mucus in CF [52] and the higher presence of OME in primary ciliary dyskinesia [53] are also compatible with the above-mentioned finding of CBF importance rather than mucus viscosity in OME pathophysiology.

With the knowledge of the importance of MCC in OME pathophysiology, mucocurative treatments such as surfactants have been used. Ma et al. used an intratympanic surfactant in the treatment of the experimental OME model and reported that surfactant treatment is useful to protect the cilia at the ET [54]. Later, Zhu et al. used a pulmonary surfactant via the intranasal way and showed significantly more normalized ciliary morphology, lower mucosal edema, and decreased goblet cells (although it is not similar in all regions) at the different parts of the ET. Related to this, they suggested that the usage of an intranasal surfactant in OME treatment is useful according to the protective and hyposcretory effects on ciliary morphology, lowering the surface tension and facilitating the opening of the ET [55].

Nasal MCC in AH with OME

Concomitance of AH and OME were thoroughly examined in previous studies and possible mechanisms such as obstruction, tubal dysfunction, chronic infection and MCC impairment were speculated on [4]. Andreoli et al. measured the CBF in AH, AH + EOM, AH + recurrent OME (ROM) and reported no significant differences in basal CBF among groups (AH: $13.34 \pm 0.75 \text{ Hz}$; AH + EOM: $13.48 \pm 0.85 \text{ Hz}$; AH + ROM: $13.30 \pm 0.80 \text{ Hz}$). However, in the stimulation with isoproterenol, the responses in the AH + EOM group at 2 and 3 h were significantly lower than controls and AH + ROM, respectively (AH + EOM: 20.76 and 10.36 %; controls: 27.49 and 17.70 %). They stated that a chronic inflammatory condition in OME may lead to MCC dysfunction, or impaired MCC may lead to chronic infection and inflammation and subsequent OME [4]. Similarly, Cohen showed a blunted dynamic ciliary response chronic infection and suggested that

this might also have a role in MCC impairment pathophysiology like CBF and mucous changes [24].

Wake and Smallman were the first to report the correlation of nasal and middle ear MCC in AH + OME patients and suggested that nasal MCC is a useful parameter to clinically show the ciliary function in the middle ear [56]. In our previous study, we found that both pre- and postoperative nasal MCC times were significantly impaired in AH + OME patients compared to AH patients. Although MCC times were improved in both groups post-operatively, AH + OME patients' improvement were as good as those of AH patients. Further statistical investigations showed that the most important factors for nasal MCC impairment were cigarette smoke exposure and OME presence [5••]. Another study that investigated the nasal MCC changes in OME was performed by Passali et al. in persistent and intermittent allergic rhinitis. Although they found nasal MCC time increments in both groups, the persistent allergic group scores were significantly impaired compared to intermittent allergic rhinitis. Therefore, they proposed that MCC investigation with the tympanometric test is useful to explore the rhinopharyngotubal clearance and tolerability of the ET in OME especially in allergic etiology [18].

Changes in nasal physiology primarily or secondarily in AH + OME patients can lead to nasal MCC dysfunction. Therefore, MCC is an appropriate method to understand the ciliary or mucous changes and their effect on the disease process of AH + OME. Cilia have the capacity to restore their function up to a certain amount of damage after the pathology has been treated; therefore, nasal MCC might be an accurate method for deciding the operation time before irreversible ciliary dysfunction occurs [57].

Conclusions

In conclusion, AH and OME have multiple etiologic factors that might interfere in the pathologic process. Nasal MCC impairments were seen in both AH and OME with different mechanisms such as infection, obstruction and inflammation; however, the main question concerning these changes is to find whether they are a cause or a result. Furthermore, the possible etiologic factors that might play a role in the occurrence of AH, OME and nasal MCC changes, such as chronic rhinitis, gastroesophageal reflux, local or systemic allergic reactions, cigarette smoke exposure and the recently popularized biofilms relationship, should also be investigated. In conclusion, nasal MCC reflects the nasal physiology and might be of importance in both the treatment and follow-up processes of AH and OME.

Compliance with Ethical Standards

Conflict of Interest Dr. Yazıcı declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors. With regard to the authors' research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

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