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Lung mucus: a clinician's view

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Lung mucus: a clinician's view. W.D. Kim. ©ERS Journals Ltd 1997.
ABSTRACT: Respiratory mucus represents the products derived from secretion of the submucosal glands and the goblet cells. Accumulation of mucus in the airway tree may be caused by an increased volume of mucus produced, and also by decreased clearance due to defects in the ciliary clearance apparatus.

Hypersecretion of mucus contributes to the morbidity of airway diseases by predisposing patients to respiratory infections, and contributing to airflow obstruction and to patients' discomfort. There is a significant association between chronic production of mucus and an increased risk of mortality. Also the degree of airway obstruction is related to the physical properties of the sputum. Observation of chronic bronchitic sputum can reveal important clinical information concerning the type and level of the inflammatory process, the physical properties of the material, the extent of bronchial mucosal damage, and the identification of pathogenic microorganisms that may be present. The management of mucous hypersecretion can be undertaken in two main ways: firstly, improved clearance by physical methods; and, secondly, by pharmacological methods.
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In ancient times, the perceived purpose of respirations was only to cool the blood, and nasal mucus was thought to be a discharge from the brain. Later it was demonstrated that fluids cannot travel from the brain to the nose. It appears that credit for pointing out the medical significance of bronchial secretions and the biological value of the exocrine function of the lungs belongs to Laennec. He described the "chronic idiopathic pituitous catarrh", known today as bronchorrhoea, which is characterized by paroxysms of expectoration. The importance of all this is that airway secretions, and their alterations, became one of the cardinal signs of many respiratory diseases [1].

Secretion of mucus

Respiratory mucus represents the products derived from secretion of the submucosal tracheobronchial glands and the epithelial goblet cells, whereas tracheobronchial secretions include the mucus plus other fluid and solute derived from the alveolar surface and the circulation. Sputum consists of bronchial mucus contaminated by saliva, transudated serum proteins, and inflammatory and desquamated epithelial cells [2]. Sputum represents an increase in normal secretions and is, thus, pathological.

LUCAS and DOUGLAS [3] postulated a double layer of mucus: the bronchial periciliary sol phase, in which the cilia beat; and a superficial blanket of gel which is moved forward by the tips of the cilia. The gel phase contains the bronchial glycoprotein, some serum proteins and protein bound to the bronchial glycoprotein. The sol phase contains any soluble components of bronchial secretion, together with serum proteins.

Mucus is a complex mixture of water, proteins and glycoproteins, lipids and salts. Mucous glycoproteins, or mucins, are important constituents of airway mucus, and are responsible for its viscoelastic properties. Respiratory mucus is usually cleared by airflow and ciliary interactions, and sputum is generally cleared by cough. Airway clearance of mucus depends on the physical properties of the mucous gel, serous fluid properties, and ciliary function.

Respiratory mucus has three important roles: 1) in mucociliary clearance of particulate matter deposited within the respiratory tract; 2) as an antibacterial substance (respiratory mucus contains immunoglobulins, lactoferrin, which chelates iron necessary for the growth of some bacteria, and lysozyme, which destroys bacteria); and 3) as a humidifier of inspired air and in prevention of excessive fluid loss from the airway surface by dint of its hydrophilic nature [4].

Amounts of mucus secreted onto the airways surface in healthy lungs are small. Lavage of airways from normal volunteers recovers little mucin or other macromolecules. The total amount of surface liquid (mucus) in the conducting airways is governed by the rate of mucous secretion, on the one hand, and the clearance of mucus by epithelial reabsorption, evaporation, ciliary transport, and cough transport.

Hypersecretion of mucus

Airway hypersecretion of mucus, if not accompanied by increased clearance of mucus, can lead to the accumulation of airway mucus. Increase in volume of airway

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mucus has several functional consequences. Undesired effects include: airflow obstruction; enhanced deposition of inhaled particulate matter in the tracheobronchial tree; and cough. However, the increased amount of airway mucus may also have a protective role, by: serving as a physical barrier against biologically active inhalants (mechanical screen); preventing bacteria colonizing the airways by adhering to the epithelium (biological screen) and inactivating cytotoxic products released from luminal leucocytes (chemical screen) [5].

Normal subjects may secrete substantial amounts of mucus only if they inhale noxious fumes (*e.g.* ammonia) or irritating substances, such as hypertonic saline, or acquire an acute respiratory tract infection. For laboratory animals as well as humans, chronic irritation or injury induces a state of mucous hypersecretion. Alterations in the quality or quantity of airway mucus, as encountered in many respiratory tract disorders, can result in impaired mucociliary clearance.

Clinical significance of hypersecretion of mucus

Accumulation of mucus in the airway tree may be caused by an increased volume of mucus produced, and perhaps also by decreased clearance due to defects in the ciliary clearance apparatus. Hypersecretion of mucus may be chronic, but increased volumes are produced in exacerbations of chronic obstructive pulmonary disease (COPD), during attacks of asthma, and in bronchiectatic and cystic fibrosis patients with chronic bacterial colonization.

Intraluminal mucus accumulation in the airways associated with hypersecretion of mucus creates a clinical problem in almost all pulmonary and some nonpulmonary diseases. Hypersecretion of airway mucus is an important determinant in the prognosis and clinical features of various pulmonary diseases, such as chronic bronchitis, bronchiectasis and bronchial asthma, in addition to cystic fibrosis.

Hypersecretion of mucus contributes to the morbidity of airway diseases by predisposing patients to respiratory infections, and contributing to airflow obstruction and to patients' discomfort. Results of a mortality survey revealed a significant association between chronic production of mucus and an increased risk of mortality [6].

Hypersecretion of mucus and respiratory infections

Bacterial microorganisms are usually found as a component of sputum in chronic bronchitis. Their origin is either through inhalation or aspiration from the ambient air or oronasopharynx, or as part of the exudate from infected areas of the bronchi. The increased secretions mixed with the products of inflammation would adversely affect mucociliary clearance. With the delayed clearance of bacteria, infection of the bronchial tissue occurs, with establishment of a resident population of pathogens. Conversely, the possibility has been addressed that bacteria and their products could contribute to hypersecretion of mucus by directly stimulating mucus-secreting cells.

Airway hypersecretion and airway obstruction

Chronic bronchitis is a condition associated with chronic productive cough that lasts for at least 3 months of the year for two successive years. Thus, airway hypersecretion is a principal clinical feature in chronic bronchitis. The common association of chronic bronchitis and chronic limitation of airflow leads us to assume that hypersecretion of mucus results in limitation of airflow. Chest physiotherapy has been shown to facilitate sputum expectoration and, therefore, improvement in pulmonary functions [7, 8]. It is also noteworthy that, in the largest population-based studies, presence of chronic mucous hypersecretion is associated with excess decline in forced expiratory volume in one second (FEV_1) [9].

Some epidemiological studies have suggested that chronic bronchitis and chronic obstructive impairment may be considered as separate entities, rather than as manifestations of a single disease [10, 11]. REID [12] had established that the major site of mucous gland hypertrophy was in the large bronchi in chronic bronchitis. On the other hand, HOGG *et al.* [13] showed that the dominant site of irreversible airflow obstruction due to primary airway disease lay in the peripheral airways of less than ~3 mm in diameter. Hence, the major sites of obstruction and hypersecretion appeared to be in different sized airways, a finding that supported the epidemiological evidence for distinguishing the hypersecretory and the obstructive components of bronchial (and bronchiolar) disease.

However, goblet cells can be present in the peripheral airways (bronchioles), where they are not normally present, and this is referred to as goblet cell metaplasia. In chronic bronchitis with airflow limitation, one of the specific bronchiolar changes is goblet cell metaplasia, which can cause mucous plugging and may displace the surface layer of surfactant, allowing the airways to close more easily [14]. Thus, increased mucus production from goblet cells in the more peripheral airways may contribute to obstruction in COPD. For the measurements of intraluminal mucus, AIKAWA *et al.* [15] employed fixation of the lung by immersion instead of intrabronchial instillation of formalin, to prevent wash-out of mucus from the airways. They showed a large amount of mucus in the airways, especially in the peripheral airways, in chronic bronchitis with airflow limitation.

Clinically, it is often observed that patients with bronchial asthma expectorate a significant amount of sputum, especially during an asthmatic attack, and are subsequently released from dyspnoea after the expectoration of a large amount of sputum. Moreover, a large amount of mucous plugging in airways, with an increase in secretory cells, is frequently observed in autopsied lungs of patients with bronchial asthma [16]. This suggests that accumulation of mucus (mucous plugging) in airways, resulting from mucous hypersecretion, contributes to airway obstruction in addition to bronchoconstriction and mucosal oedema in asthma.

Airway hypersecretion and mortality

Some epidemiological reports have indicated that, after controlling for the degree of lung function, airway hypersecretion or phlegm was not significantly associated with death caused by COPD, and they suggested that the hypersecretory disorder is an innocent disease [10]. Nevertheless, other investigators observed a significant association between phlegm (or airway hypersecretion) and all causes of mortality [17].

SAETTA *et al.* [18] reported that asthmatic patients who died suddenly and unexpectedly showed luminal occlusion by mucous plugs, plasma exudate, and inflammatory cells in the peripheral airways of autopsied lungs.

TURNER-WARWICK *et al.* [19] found that half of the patients with idiopathic pulmonary fibrosis (IPF) in their study expectorated a significant amount of sputum. HIWATARI *et al.* [20] revealed that 44% of patients with IPF who survived over 1 yr had mucous hypersecretion and that patients with IPF who suffer from mucous hypersecretion have a shorter survival rate than those without mucous hypersecretion.

Correlation between physical properties of sputum and clinical features

Airway clearance of mucus depends on the physical properties of the mucous gel, serous fluid properties, and ciliary function, as well as interactions between mucus and airflow or mucus and cilia. In cystic fibrosis, sputum hydration and cough clearability are decreased, probably owing to alterations in the surface properties of the mucus resulting from impaired chloride transport into the periciliary fluid layer [21].

Several investigations have demonstrated that the degree of airway obstruction is related to the physical properties of the sputum (*i.e.* the thicker the sputum, the greater the decrease in ventilatory capacity) [22–24].

Clinical assessment of sputum

Sputum is the abnormal material produced by, or expectorated from, the bronchopulmonary system. Production of sputum by a patient is indicative of an ongoing pathological process in the lung. Observation of chronic bronchitic sputum can reveal important clinical information concerning the type and level of the inflammatory process, the physical properties of the material, the extent of bronchial mucosal damage, and the identification of pathogenic microorganisms that may be present [25].

A useful general principle is that the volume of sputum expectorated usually reflects the severity of the chronic bronchitis. The volume should be obtained over a set period. A routine collection that includes a 24 h period is most valuable, since this accommodates the variability among bronchitics in terms of when each one raises their sputum. The volumes expectorated in chronic bronchitis range 1–100 mL·day^{-1}, with a rare individual producing more. The average range is 5–40 mL·day^{-1} when patients are clinically stable, and may double or triple when acute infection is present.

Bronchorrhoea has been defined as a condition in which more than 100 mL of sputum is produced within 24 h. It may be associated with tuberculosis, alveolar cell carcinoma, chronic bronchitis, or asthma, or it may be idiopathic.

The colour and estimation of the specimen's degree of purulence can also provide valuable information concerning the pathology in the bronchopulmonary system. The purulence of the specimen depends on the degree of yellow to green coloration. Macroscopic purulence is due to the content of polymorphonuclear leucocytes and deoxyribonucleoprotein fibres arising from disintegrated cells, particularly from polymorphs. Cell counts are particularly useful on mucopurulent sputum from asthmatic patients, since the pus may consist largely of eosinophils.

The usual implication of purulence in the literature is that this finding is synonymous with the presence of bronchopulmonary infection. ROBERTSON [26] clearly related green coloration to the presence of myeloperoxidase released from degenerated polymorphonuclear neutrophils (PMNs), an enzyme also prevalent in eosinophils. This coloration strongly suggests stasis in the airways of secretions containing PMNs, which allows time for these cells to break down and release their peroxidases. The more peroxidases released, the greener the specimen.

Evaluation of the sputum cellular populations is of considerable value in differentiating chronic bronchitis from bronchial asthma, and in determining the aetiology of acute exacerbations in chronic bronchitics. The PMNs are the preponderant inflammatory cells in chronic bronchitis, and the frequency of eosinophils rarely exceeds 5% during clinically stable periods. In bronchial asthma, PMNs are also usually the preponderant polymorphonuclear cells; the average percentage of eosinophils ranges from 20–40%, depending on corticosteroid dependency, but may be as high as 90%.

The cytological and Gram stain findings can distinguish the likely cause of the exacerbation in chronic bronchitis. The common bacterial species recovered from the sputum of chronic bronchitics during acute bacterial exacerbations are *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*. Less commonly, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* can be found.

Management of mucous hypersecretion

The aim of therapy for bronchial hypersecretion has usually been: to alter the rheological properties of bronchial mucus; to reduce the degree of airways obstruction; to enhance the function of the mucociliary escalator; and to promote expectoration. To reduce the amount of luminal mucus in the airways, three major strategies have been employed. The first is to inhibit mucous hypersecretion using pharmacological agents. The second is to stimulate ciliary activity and improve mucociliary interaction, thereby augmenting ciliary clearance; this is generally also accomplished with pharmacological agents. The third approach is to enhance cough clearance, either by changing the rheological properties of luminal mucus by pharmacological means or by moving mucus physically from smaller to larger airways, from where it can be eliminated by cough clearance.

Dehydration of a patient with severe chronic bronchitis is associated with difficulty in expectorating small amounts of viscid sputum, and rehydration usually eases expectoration. It is not clear whether this effect is on secretory gland activity or on tissue fluid transudate. BLANSHARD [27] showed a reduction in sputum viscosity following an increased fluid intake. These findings are in keeping with the clinical observation that the dehydrated patient in respiratory failure has difficulty in clearing retained secretions, which can be alleviated by intravenous fluids and presumably reflects the dependence of the secretory structures on adequate tissue fluid. CHODOSH [28] also demonstrated that extra oral water

increased the water content and decreased the apparent viscosity of sputum in chronic bronchitis, without increasing the volume expectorated. However, SHIM and KING [29] found no evidence that moderate hydration or dehydration had any significant effect on sputum volume or viscoelasticity in stable chronic bronchitis. Nevertheless, adequate hydration is generally recommended as an essential measure, particularly in more severe conditions.

In practice, the management of mucous hypersecrtion can be undertaken in two main ways: firstly, improved clearance by physical methods, including cough, chest physiotherapy and the more recent method of high frequency oscillation; and, secondly, by pharmacological methods [30]. Pharmacological methods will be discussed later by another author [31].

Physical methods of clearance

Cough is the immediate reserve mechanism when mucociliary clearance is overwhelmed by copious secretions, as in chronic bronchitis. Encouragement should be given to cough from a high lung volume and perhaps augment cough with the forced expiratory technique. Cough is significantly effective in removing secretions from central lung regions, in accordance with theory.

Chest physiotherapy consists of: postural drainage, where secretions are drained with the help of gravity; percussion, with clapping of the chest wall producing a shock wave transmitted through the chest and thought to loosen bronchial mucus; and vibration, with chest shaking, a further means of transmitting phasic energy, usually in expiration. Chest physiotherapy is significantly effective both in removing secretions from peripheral to more central regions and in promoting their final removal from the lungs.

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