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Optimizing Mucociliary Function : The Humidification Story

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ABSTRACT

Temperature and humidity are added to normally inspired gas through the action of the nose and upper airway so that gas reaches the lower airway at body temperature and saturated with water vapor (BTPS). This serves two main functions ; it facilitates gas exchange in the alveoli, and secondly it maintains the optimal function of the mucociliary transport system which helps to preserve lower airway sterility by capturing foreign particles and removing them from the airway. In the mechanically ventilated patient, the upper airway is bypassed by the placement of an endotracheal tube which results in dry ventilator gases being delivered directly to the trachea. Given the various co-morbidities that may accompany the patient's need for intubation and mechanical ventilation, such as a history of smoking and other lung diseases, it is essential that the gas delivered to these patients is conditioned to BTPS so that their mucociliary function is optimized.

Introduction

In the normal healthy human, inspired gases are warmed and humidified in the upper airways until they reach body temperature at atmospheric pressure and are saturated with water vapor (BTPS). Upon exhalation some of the heat and moisture in the gas is recovered. The deficit between what is lost to the gas on inspiration and what is recovered on expiration, is made up from the body's systemic reserves. This simple process continues throughout our lives and for the most part needs no assistance. However, the ability of the airway to condition inspired gases is not unlimited and exceeding its capacity can have serious effects. This happens when the inspired gas is very cold and/or dry and is particularly important when a patient is mechanically ventilated using dry medical gas. It is therefore necessary to understand the process of gas conditioning further so that we can determine what level of gas conditioning results in optimal mucosal performance.

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The Normal Airway

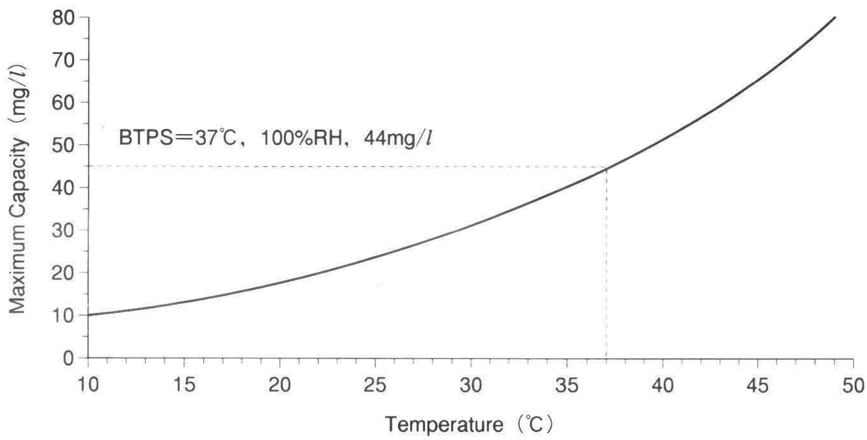
The airway mucosa consists of the layer of cells that line the inside surface of the airway. When inspired gas passes over this well-perfused mucosa the warm blood flow to the cells transfers heat to the gas, while the periciliary fluid and mucus provide a water surface capable of humidifying the gas. Liquid water contained within the mucus and periciliary fluid is converted to water vapor (individual molecules of H_2O in a vapor state) as gas passes over the mucosal surface until equilibrium is achieved and the gas has reached BTPS. The energy given up by the mucosa to convert liquid water into water vapor is called the *latent heat of vaporization* (2414 J/g). This energy loss

DEFINITIONS OF HUMIDITY

As a gas increases in temperature, so does its ability to contain water vapor.

Maximum Capacity (mg/l) —the maximum amount of water vapor a gas can contain at a particular temperature (i. e. 100% relative humidity).
Absolute Humidity (mg/l) —the actual amouot of water vapor a gas contains.
Relative Humidity (%) —the amount of water vapor a gas contains compared to its maximum capacity at the same temperature (100% relative humidity = saturated).

NOTE : Maximum capacity, absolute humidity, and relative humidity should all be stated along with a corresponding temperature.



means the mucosal surface is relatively cool prior to exhalation. As exhaled gas passes over this surface, it cools so that it's temperature falls below its dew point causing the water vapor in the exhaled gas to condense on the mucosal surface. The energy returned to the mucosa is called the *latent heat of condensation* (2414 J/g). This process is not 100% efficient and the amount of water evaporated from the mucosa on each inspiration is greater than the amount of water vapor condensed on exhalation. As a result, there is a net loss of heat and moisture to the environment after each breath and the deficit must be replaced by the body's systemic reserves.

Conditioning of the gas as it moves down the airway towards the lungs is a gradual process. During normal quiet breathing inspired gases are warmed and humidified to 30°C, 95% RH, 29 mgH_2O/l in the upper trachea, and to 34°C, 100% RH, 38 mgH_2O/l in the lower trachea[1)2)]. Hence, the majority of heat and moisture is added in the nasopharynx but the gas does not achieve BTPS until it reaches the fourth or fifth generation of the subsegmental bronchi[1)]. The exact position in the airway where the gas reaches BTPS, the isothermic saturation boundary (ISB), is dynamic, changing depending on the temperature and humidity of the inspired gas.

Table 1 Humidity recommendations from various international standards and authors

Author/Standard	Recommendation
AARC (1992)	33±2°C, 30 mg/l
Chatburn (1987)	32～34°C, 100% RH, 34～38 mg/l
ECRI (1987)	37.6 mg/l
ISO 8185 (1998)	33 mg/l
Shelly (1988)	32°C, 27.3 mg/l
Williams (1996)	37°C, 100% RH, 44 mg/l

When a patient is intubated the endotracheal tube (ETT) bypasses the upper airway and consequently its heat and moisture exchanging properties. This allows dry medical gases to be delivered to the airway 2～4 cm above the carina. Under these conditions, the ISB shifts further down the respiratory tract resulting in severe losses of heat and moisture from the respiratory tract and damage to the airway mucosa. Assessing whether the level of humidity actually delivered to the patient is adequate is commonly based on a clinical outcome, such as, partial or complete occlusion of the ETT, and secretion quantity and quality. In order to avoid such humidity-related complications, minimum levels of temperature and humidity have been stipulated in guidelines published by various international respiratory organizations (**table** 1). However, such complications have still been observed when these guidelines are followed suggesting that higher levels of temperature and humidity are required[3)4)]. Improving the level of humidity after complications have occurred may not prevent additional microscopic damage to the mucosal surface. Therefore, we need to understand what level of humidity is required to avoid these complications, and to do this we need to know what is an appropriate marker for lung health.

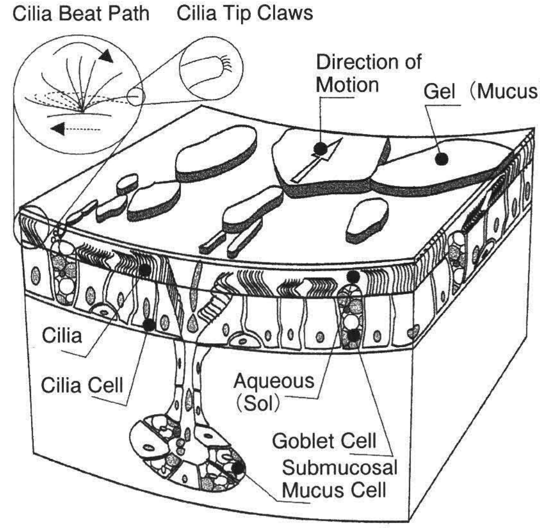


Fig. 1 Schematic of airway mucosa (Reprinted with permission from Williams et al., 1996)

The Mucociliary Transport System

The mucociliary transport system (MTS) can provide information about the function of the cilia, mucus characteristics, and most importantly, cellular dysfunction. The MTS (**figure** 1) lines almost the entire airway surface, from the nose down into the 15th or 16th generation of the airway[5)]. It is made up of ciliated epithelial cells each of which contain approximately 200 cilia, 5～7 μm long which rhythmically beat at 10～20 Hz in a whip-like motion within the periciliary fluid. Interspersed between the ciliated epithelial cells are goblet cells and submucosal glands which produce the mucus which is expelled onto the surface of the airway and then propelled by the beating cilia in a cephalad direction. Contaminants entering the airway are trapped by the mucus and moved out of the airway at a rate of approximately 10 mm/min. Performance of the MTS is affected by genetic abnormalities, disease states, drug therapies, fluid balance, anesthetic agents, and of course, humidity.

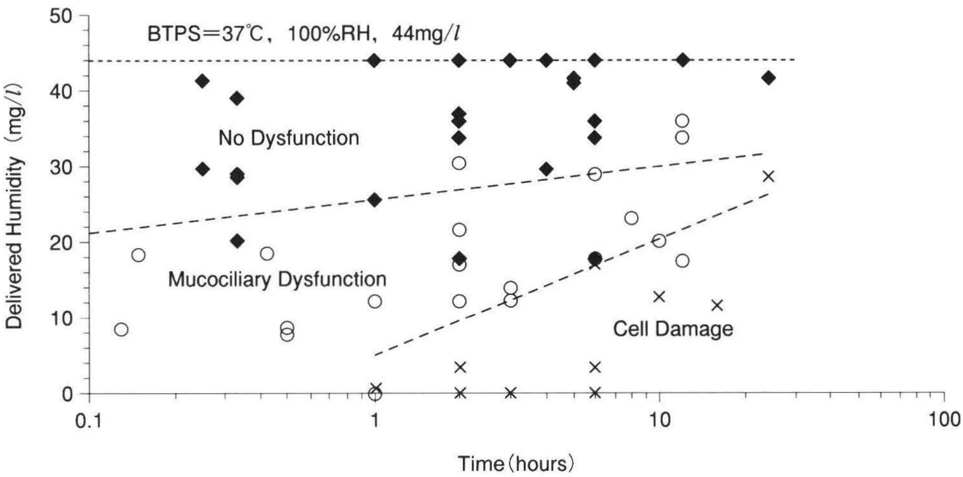


Fig. 2 Delivered humidity versus exposure time

Each data point represents a single measurement from studies examined by Williams et al. Closed diamonds represent no dysfunction, open circles represent a combination of thick mucous, mucociliary transport stopped, and cilia stopped, and crosses represent cell damage. The dashed trend lines separating no dysfunction, mucociliary dysfunction, and cell damage were determined using linear discriminant analysis. This graph shows that the further the delivered gas deviates from BTPS, the faster and the greater the mucosal damage.
(Adapted from Williams et al., 1996)

● Humidity and the MTS

Temperature and humidity affect the performance of the MTS. In a recent review, Williams et al[6] proposed a model which describes the relationship between MTS performance and the humidity of the inspired gas. At any given level of temperature and humidity, either greater than or less than BTPS, mucosal dysfunction was predicted to deteriorate sequentially through the following steps ; 1) thickened mucus, 2) slowed mucociliary transport, 3) mucociliary stasis, and 4) cell damage. The rate of deterioration through these steps was further predicted to be related to the magnitude of the humidity deficit. In addition, the model suggests that this humidity-related mucosal dysfunction may be further compromised by the presence of lung disease. A meta-analysis of the relevant literature by Williams et al[6] broadly supported the model showing that cell damage could occur within 24 hours following exposure to gas conditioned to approximately 30 mgH_2O/l (**figure** 2). This analysis also showed that when gas was conditioned to BTPS no mucosal dysfunction was apparent. Studies by King et al[7][8] which were included in the Williams model, show that gas at BTPS optimizes the performance of the MTS. Airway epithelial function was monitored in anaesthetized dogs as their core temperature fell due to the anesthetic agent pentobarbital. The MTS was maintained at normal rates if the humidification system was adjusted to deliver gas at close to body temperature and 100% RH. Similarly, if the dog's body temperature was maintained at 37°C by use of a hot water blanket then inspired gas conditioned to 37°C and 100% RH maintained or optimized the MTS.

Another approach to investigate optimal humidity is to consider the thermodynamics of the gas being delivered to the patient via the

ETT. Ryan et al[9] found that when the inspired gas was conditioned to less than BTPS the gas warmed as it passed through the ETT with no additional moisture being added by the ETT. This results in low RH gas being delivered to the base of the ETT. Miyao et al[10] demonstrated that the risk of ETT obstruction or partial occlusion is greatly increased if the RH of the inspired gas is less than 100%. Not only is the patency of the ETT at risk, but any mucus which has collected at the base of the ETT (due the action of the MTS) is at risk of dehydration as it awaits removal via suctioning.

In a practical setting, delivering low levels of humidity can have serious consequences. Many authors report an increased risk of ETT occlusion in mechanically ventilated patients as a result of low humidity delivery[3)11)~14]. Low humidity is also associated with increased secretion viscosity[3], atelectasis[13] and reduced ETT patency[15]. Conditioning inhaled gas to close to BTPS can avoid these complications[16)17].

● Other Factors Affecting the MTS

Injury of the MTS can result from inhalation of gases and aerosols. Tobacco smoke has been shown to impair mucociliary clearance by a number of authors[18)~20]. Goodman et al[19] measured mucus velocity in young and old, smokers and non-smokers. Age, and a history of smoking, were both associated with significantly slower mucus velocities (**table** 2). Several authors have shown that anesthetic agents, such as atropine[21)22], pentobarbital[23] and halothane[24], impair the performance of the MTS. Greater than normal F_{IO_2}[25], and dehydration[26] have also been demonstrated to slow the MTS.

The presence of underlying lung disease or injury also influences the performance of the MTS. Intubation in its own right results in impaired mucociliary clearance through injury of the epithelium and reduction in the extent of ciliation of the bronchial epithelium. Impaired mucociliary function was also correlated with longer ventilation times[27]. Asthma exacerbation, viral and bacterial acute bronchitis, and chronic bronchitis can have a negative effect on mucociliary clearance[25]. Respiratory tract infection can also impair mucociliary clearance through cytotoxic effects on the epithelium or production of substances that directly affect the MTS[28].

Table 2 Mean tracheal mucus velocity (mm/min) in various groups of people. (From Goodman et al., 1978)

	Young (19～28 years)	Old (40～70 years)
Non-Smokers	10.1±3.5	5.8±2.6
Smokers	3.4±4.0	0.8±1.6*

*Members of this group also had smoking-induced chronic bronchitis.

The combination of poor humidity delivery and the presence of any other factors that impair mucosal function, such as those mentioned above, will have a cumulative adverse effect on the MTS, in a fashion that is consistent with the model proposed by[6]. That is, mucosal dysfunction is likely to occur faster following exposure to a humidity level that might otherwise be considered adequate in a lung-healthy patient. Hence, people with impaired lung function should always receive ventilator gases conditioned to BTPS-the only level of humidity shown to not adversely affect the MTS.

In summary, low inspired humidity can compromise the MTS of a healthy individual, or further complicate a diseased lung, while at the same time make the airway toilet of the patient difficult due to thickened secretions at the base of the ETT. To reduce the risk of ETT occlu-

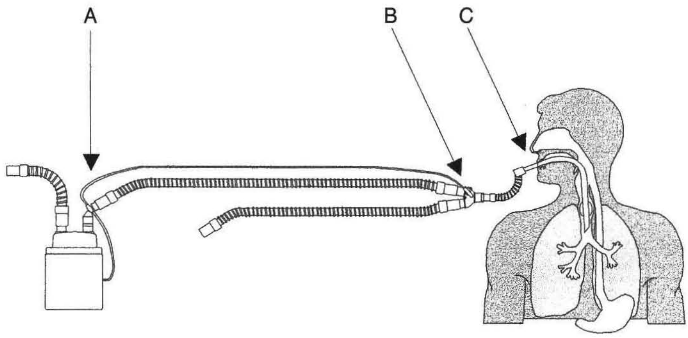


Fig. 3 Humidification system
To deliver optimal humidity (BTPS) to an intubated patient, the gas must leave the water reservoir at 37°C and 100% RH (A). The gas is then heated as it passes through the breathing circuit to reduce condensate and arrive at the Y-piece at 40°C and 85% RH (B). Then the gas will cool over the unheated deadspace to reach 37°C and 100% RH (C) before the gas enters the patient.
(Reprinted with permission from Peterson, 1998)

sion, thickened secretions, and poor MTS function, inspired gases must be conditioned as close as possible to BTPS (37°C, 100% RH, 44 mg/l).

Choice of Humidification System

The clinical and physiological evidence demonstrates that humidification devices should provide gases to intubated patients as close as possible to BTPS so that mucosal dysfunction and related clinical complications are prevented. The conditioning of inhaled gas is influenced by the humidifier settings, the need to control condensate generation, infection control issues, and the need for aerosols or water vapor. Only a heated humidifier is capable to conditioning gases to BTPS. Heated humidifiers should be set to heat the water in the humidifier chamber so that the gas exiting the chamber is conditioned to 37°C and 100% RH. The breathing circuit should deliver as much of this as possible to the patient, minimizing condensate formation and temperature loss. However, since the catheter mount, which connects the Y-piece of the circuit to the ETT, is unheated it is not uncommon to see a temperature drop of 2～3°C over this region. Therefore, delivering gas to the Y-piece at 2～3°C warmer than the optimal gas condition can compensate for this cooling. Hence, the humidifier should condition gas close to 37°C and 100% RH at the water reservoir and the heated breathing circuit should warm the gas a further 3°C to arrive at the Y-piece at 40°C (**figure** 3).

A range of devices are used to produce humidity : the method of humidity generation can be active (such as heated humidifiers) or passive (the heat and moisture exchangers or artificial nose) ; producing aerosols (such as nebulizers or bubble-through humidifiers) or water vapor (heated passover or wick humidifiers)[29]. However, it is generally accepted that humidification devices should generate water vapor only since there is a high risk that aerosol generators such as nebulizers[30] and bubble-through humidifiers[31] can transport bacteria to the patient increasing the risk of nosocomial pneumonia. Delivering aerosols to the airway has also been shown to increase the pulmonary arterial wall thickness, decrease alveolar space and increase interstitial and intra-alveolar edema in rabbits[32]. In addition, any liquid water delivered to the airway will ultimately be evaporated by the body, increasing the workload of an already stressed organ.

Nosocomial pneumonia is a serious problem in the intensive care unit and is thought to result from aspiration of contaminated nasal, oropharyngeal, and/or gastric fluid from around the outside of the ETT cuff into the patient's lungs. The ETT and breathing circuit quickly become contaminated as a result of patient coughing and the insertion and withdrawal of the suction catheter down the artificial airway. The risk of contaminated condensate being accidentally lavaged into the airway is reduced by the use of heated-wire circuits which can reduce buildup of mobile condensate in the circuit. Several studies have shown that nosocomial pneumonia rates are not influenced by increasing circuit change out times from 2 days to 7 days and beyond (despite the presence of condensate or not)[33][34]. Many studies have also shown that the choice of humidification device (heated humidifier or HME) does not affect the incidence of nosocomial pneumonia[4][35]. However, it should be noted that in none of these studies were patients given gas conditioned to BTPS. If this were the case, the possibility exists that an optimized MTS would have removed contaminants from the lungs more efficiently. Data published by Whiteside et al[21] on the time taken to clear contaminants from the airway of sheep inoculated with bacteria lends support to this hypothesis. Animals with induced mucosal dysfunction failed to clear contaminants as quickly from the airway as those with a fully functional MTS. One study published recently has reported a reduction in the rate of nosocomial pneumonia when using HMEs compared to heated humidifiers[36]. However, the heated humidifier was set to deliver humidity below BTPS, while the "per-protocol" analysis resulted in patients with thickened secretions and pneumonia being transferred from an HME to a heated humidifier and then included in the heated humidifier group for statistical analysis biasing the results in favor of the HME group. All other randomized controlled trials have shown no influence of the humidification device on nosocomial pneumonia rates, but future studies delivering gas to patients at BTPS may show a difference[37].

Summary

Humidification of inspired gases is essential for intubated patients. Currently published international standards and institution guidelines are in disagreement as to the appropriate level of humidity that should be delivered to mechanically ventilated patients. However, a recent meta analysis by Williams et al[6] offers the possibility of consensus, showing that only BTPS gases optimize mucociliary function, and that the lower the delivered humidity (less than BTPS) the faster mucosal dysfunction occurs. In addition, many lung diseases, a history of smoking, hydration status, or interventions such as anesthesia or supplemental oxygen, can easily disrupt the mucociliary transport system, putting these patients at greater risk of complications if low humidity is delivered. Therefore, to ensure the best mucosal function for the patient and to reduce the risk of mucus thickening or ETT occlusion inspired gases should be conditioned to BTPS (37°C, 100% RH, 44 mgH_2O/l).

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