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Effect of heated humidified ventilation on bronchial mucus transport velocity in general anaesthesia: A randomized trial

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Abstract

Objective: To evaluate the effects of heated humidified ventilation on mucociliary function during general anaesthesia.

Methods: Male patients (ASA physical status 1 or 2), scheduled for elective radical retropubic prostatectomy, were allocated to receive sevoflurane general anaesthesia with conventional or heated humidified ventilation. Bronchial mucus transport velocity was assessed via fibreoptic bronchoscope and methylene blue dye at 3h after induction of anaesthesia.

Results: Median (SE) bronchial mucus transport velocity was significantly higher in the heated humidified group ($n = 26$) than the conventional ventilation group ($n = 24$) (1.7 [0.3] mm/min vs 0.9 [0.1] mm/min).

Conclusion: Heated humidified ventilation effectively maintains mucociliary clearance of patients during sevoflurane general anaesthesia.

Keywords

Mucociliary clearance, bronchoscopy, humidity, temperature, heated humidifier, mucus transport, general anaesthesia, mechanical ventilation

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Introduction

Maintenance of the appropriate temperature and humidity of the respiratory tract is essential for the continued function of cilia in patients undergoing mechanical ventilation.[1] In ventilated patients, heated humidifiers moisturize and heat inspiratory gas

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drawn from a temperature-regulated water reservoir and can prevent dryness of the tracheobronchial mucous membrane. It has been reported that heated humidifiers can improve gas conditioning in critically ill patients receiving prolonged mechanical ventilation[2] and in neonates.[3] Heated humidifier studies have been generally performed in intensive care unit settings; few studies have investigated patients under general anaesthesia in surgical situations.[4–8]

Bronchial mucus transport velocity (BTV) is simply and directly assessed via fibreoptic bronchoscope (FOB), and offers a visual assessment of mucociliary clearance in the lower respiratory tract.[9,10] The aim of this prospective randomized study was to evaluate the effects of heated humidified ventilation on BTV, in patients undergoing general anaesthesia.

Patients and methods

Study population

This randomized controlled clinical trial was conducted between June 2011 and January 2012 at the Department of Urology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, and was registered at an international clinical trials registry platform (http://cris.nih.go.kr, KCT0000172). Male patients (ASA physical status 1 or 2),[11] scheduled for elective radical retropubic prostatectomy under general anaesthesia, were enrolled. Exclusion criteria were: any history of respiratory disease; abnormal pulmonary function discerned during preoperative testing; obesity (body mass index [BMI] $\geq$30 kg/m^2); any smoking within the previous year before surgery; current use of drugs known to influence BTV.

The Institutional Review Board of Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, approved the study design. Written informed consent was obtained from all patients.

Study design and anaesthesia

Patients were allocated to one of the following two groups, using computer-generated random-number tables: conventional ventilator circuit; heated humidified ventilation. None of the patients received premedication. Intraoperative monitoring included electrocardiography, systolic and diastolic blood pressure, oesophageal temperature and peripheral oxygen saturation; all were undertaken using standard methods. General anaesthesia was induced with 5 mg/kg thiopental sodium and 1–2 µg/kg fentanyl, administered intravenously (i.v.). Tracheal intubation (Hi-Lo oral/nasal tracheal tube, Covidien, Mansfield, MA, USA) was facilitated using 0.6 mg/kg rocuronium, i.v. A swivel connector (Intersurgical, Wokingham, UK) was placed between the tracheal tube and the breathing circuit. Anaesthesia was maintained by administration of 1–3 vol% sevoflurane and 2 l/min of 50% oxygen in medical air, with positive pressure ventilation in a circle system. The depth of anaesthesia was adjusted to be equal in all patients during surgery, as assessed using the bispectral index (BIS; BIS A-1050 Monitor, Aspect Medical Systems, Newton, MA, USA). BIS was held between 40 and 60. Body temperature was measured via an oesophageal stethoscope with temperature sensor (DeRoyal, Powell, TN, USA). Patients were ventilated with a tidal volume of 8–10 ml/kg, and the respiratory rate was adjusted to maintain end-tidal carbon dioxide pressure of 30–35 mmHg.

Ventilation

The heated humidifier was a heated pass-over system comprising a heated wire in the inspiratory limb (Heated Wire Breathing Circuit, Flexicare, Mountain Ash, UK) and humidification chamber (MR850, Fisher & Paykel Healthcare,

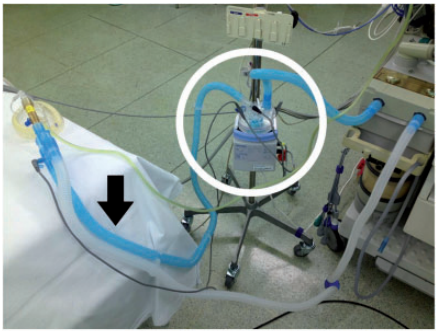

Figure 1. Heated humidifier mounted in an anaesthesia workstation. The inspiratory limb delivers inspiratory gas flow to the auto-filled humidification chamber (white circle). Humidified inspiratory gas is delivered to the patient via an electrically heated limb (black arrow). The expiratory limb from the patient is directly connected to the anaesthesia machine. Not shown: distilled water bottle for automatic filling of the humidification chamber. The colour version of this figure is available at: http://imr.sagepub.com

Auckland, New Zealand) (Figure 1). The temperature of the electrically heated wire was set to 38°C by a servo-controlled regulator and the humidifying chamber was automatically filled with distilled water. A closed type anaesthetic breathing system (Aestiva/5, GE Healthcare, Buckinghamshire, UK) was used for all patients during surgery. To ensure double blinding, all heated humidifiers were taped with an opaque piece of cloth and the power button was screened. A member of the nursing staff (who did not participate in the study) then either did or did not switch on the power to the heated humidifier, according to the group allocation of the patient. The ambient operating room temperature was maintained at 25–26°C during surgery. Intraoperative fluids were administered at room temperature and warming blankets were not used.

Study outcomes

Demographic data including age, sex and BMI were collected. Preoperative pulmonary function tests (including forced expiratory volume in 1s [FEV_1], forced vital capacity [FVC], and FEV_1/FVC ratio were performed in all patients. Duration of anaesthesia, volume of administered fluid and estimated blood loss were recorded.

The primary outcome measure was BTV after 3 h intubation. BTV was assessed using a modified method as described.[9,10] In brief, the FOB (Olympus LF-DP, Olympus Optical, Tokyo, Japan) was passed through the swivel connector and placed at the right main bronchus. A 20 G epidural catheter (BD Perisafe™, BD Medical, Franklin Lakes, NJ, USA) with the tip cut off was inserted into the working channel of the scope (Figure 2A) until it was seen through the lens; it was positioned close to the posterior mucosal surface of the right main bronchus. A single drop of 1% methylene blue dye was applied onto the mucosal surface through the epidural catheter; the catheter was flushed with an air-filled 1-ml syringe, with care taken to avoid touching other mucosal surfaces (Figure 2B). After dye application, the FOB was marked at the point of entry of the swivel connector, and was removed. The position of the proximal dye margin was assessed at 5 and 10 min after application. FOB was marked again at the entry point of the swivel connector. The mean of two measurements was calculated and divided by five to generate BTV values expressed as mm/min. The overall duration of each measurement was <2 min. No patient showed evidence of desaturation (indicated by peripheral oxygen saturation <90%) during the procedure.

Temperature and relative humidity (RH) in the tracheal tube ($Temp_{TT}$ and $Humid_{TT}$, respectively) were evaluated using a capacitive-type thermohygrometer (TH200, Kimo, Montpon, France) with a specially designed

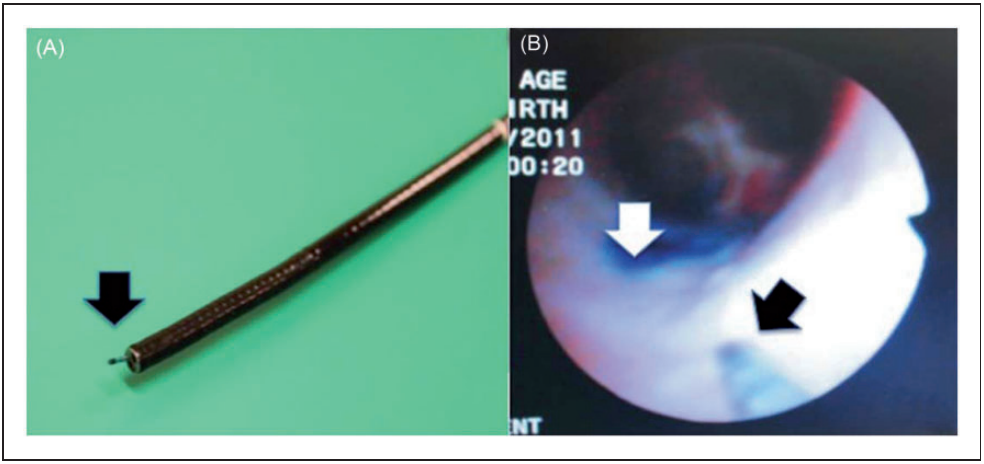

Figure 2. Equipment for assessment of bronchial mucus transport velocity during general anaesthesia. (A) Epidural catheter (black arrow) with single end-standing hole was inserted into the working channel of a fibreoptic bronchoscope. (B) Bronchoscopy view showing the site of application of methylene blue dye on the surface of the bronchial mucosa (white arrow) and the tip of the epidural catheter (black arrow). The colour version of this figure is available at: http://imr.sagepub.com

probe (Figure 3). The available range of the thermohygrometer was 0–100%RH and -40 – 180°C. The temperature dependence of %RH was $\pm 0.04 \times$ (temperature $-$ 20) at <15°C or >25°C. The thermohygrometer probe was placed between the Y-piece of the breathing circuit and the tracheal tube connector. $Temp_{TT}$, and $Humid_{TT}$ were recorded at 10 min after intubation (baseline) and again at 3 h after intubation. $Temp_{TT}$ and $Humid_{TT}$ were measured three times, and mean values were calculated. Absolute humidity (AH) was calculated as: $Humid_{TT} \times$ (saturated vapour pressure at measured temperature) $\times$ 0.01.

Fever (body temperature >37.5°C) and dyspnoea were recorded until the third postoperative day.

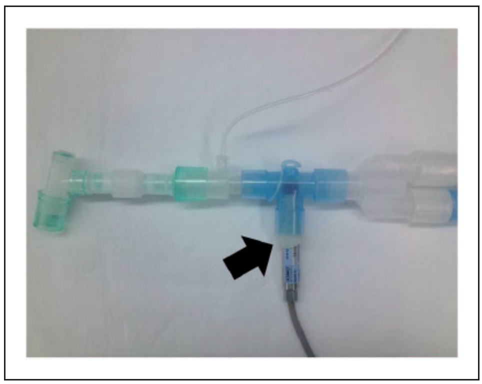

Figure 3. Thermohygrometer probe (black arrow) for assessment of tracheal tube humidity and temperature during general anaesthesia. The probe was located between the Y-piece of the breathing circuit and the swivel connector. The colour version of this figure is available at: http://imr.sagepub.com

Statistical analyses

Sample size was calculated as described[12] and the mean ± SD BTV in the reference was 1.5 ± 0.7 mm/min. A total of 50 patients in two groups permitted an α-value of 0.05 and β-value of 0.1 for a 50% between-group difference in the reference value. Data were presented as mean ± SD, *n* (%) or median (SE). The Shapiro–Wilk test for normality was performed. Intergroup differences in

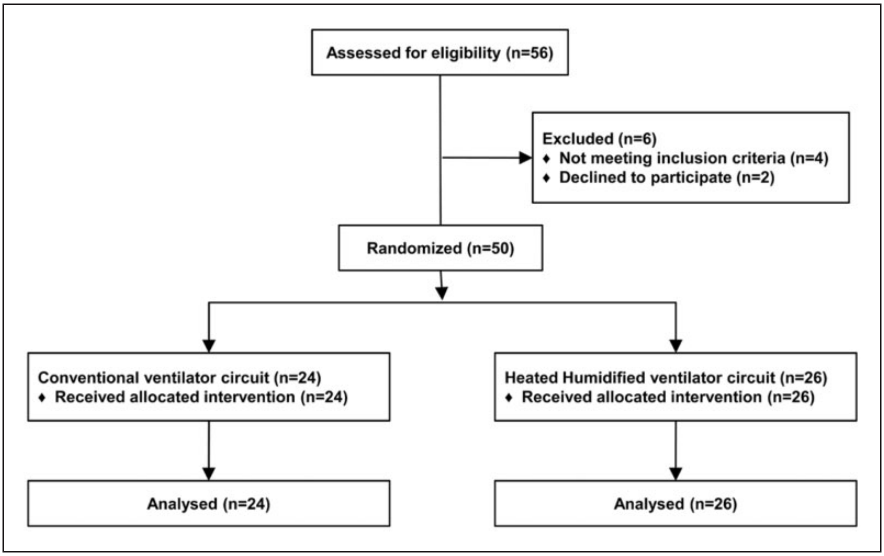

Figure 4. CONSORT chart (http://www.consort-statement.org/), indicating flow of patients through a study to evaluate the effects of heated humidified ventilation on BTV, in patients undergoing general anaesthesia.

demographics, preoperative pulmonary function test, intraoperative data and BTV were analysed using Mann–Whitney Rank Sum test or Student's *t*-test. Between-group and between-timepoint comparisons of $Temp_{TT}$, $Humid_{TT}$ and AH were made using two-way repeated-measure analysis of variance. Fisher's exact test was used to compare the incidence of postoperative fever and dyspnoea between groups. Statistical analyses were performed using SPSS® version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows®. P values < 0.05 were considered statistically significant.

Results

The study included 50 patients. Patient flow through the study is shown in (Figure 4). Patient characteristics and intraoperative and postoperative data are shown in Table 1. There were no statistically significant between-group differences in any parameter.

Median BTV was significantly higher in the heated humidified group than in the conventional group (1.7 mm/min vs 0.9 mm/min; $P < 0.001$). Median dye transport distances were also significantly higher in the heated humidified group than in the conventional group at 5 min after application (12.8 ± 2.2 mm versus 7.0 ± 0.6 mm; $P = 0.001$) and at 10 min after application (16.8 ± 2.9 mm vs 9.0 ± 0.9 mm; $P = 0.001$).

Data regarding $Temp_{TT}$, $Humid_{TT}$ and AH are given in Table 2. There were no between-group differences in any parameter at baseline. At 3 h after intubation, $Temp_{TT}$, $Humid_{TT}$ and AH were significantly higher in the heated humidified group than the conventional group ($P < 0.05$ for each comparison, Table 2). In addition, at 3 h after intubation all parameters were significantly higher than baseline in the heated humidified group ($P < 0.05$ for each comparison, Table 2), but were unchanged in the conventional group.

Table 1. Demographic and pre-, intra- and postoperative data for patients undergoing elective radical retropubic prostatectomy under general anaesthesia, included in a study to compare the effects of conventional and heated humidified ventilation on bronchial mucus transport ($n = 50$).

Characteristic	Conventional group $n = 24$	Heated humidified group $n = 26$
Age, years	65.8 ± 7.0	67.8 ± 6.6
Weight, kg	66.7 ± 9.6	66.6 ± 7.9
Height, cm	167.1 ± 7.5	166.3 ± 6.6
BMI, kg/m^2	23.9 ± 2.9	24.1 ± 2.5
Preoperative pulmonary function		
FEV_1, l	2.6 ± 0.6	2.7 ± 0.5
FVC, l	3.9 ± 0.7	3.7 ± 0.5
FEV_1/FVC ratio	66.8 ± 11.6	71.2 ± 7.8
Intraoperative data		
Duration of anaesthesia, min	227 ± 94	232 ± 102
Total administered crystalloid, ml	2160 ± 714	2302 ± 1393
Total administered colloid, ml	463 ± 255	515 ± 296
Estimated blood loss, ml	1011 ± 533	1010 ± 611
Postoperative data		
Fever ≥37.5°C	8 (33.3)	7 (26.9)
Dyspnoea	1 (4.2)	3 (11.5)

Data presented as mean ± SD or n (%).
No statistically significant between-group differences ($P \geq 0.05$; Mann–Whitney Rank Sum test, Fisher's exact test or Student's t-test).
BMI, body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Discussion

This randomized controlled trial demonstrated that heated humidified ventilation leads to significantly less depression of BTV than conventional ventilation during general anaesthesia, and can effectively maintain mucociliary function. It has been shown that the use of a heat moisture exchanger (HME) results in better hygrometric measurements than low-flow anaesthesia.[13] This suggests that the preservation of mucociliary function is a result of hygrometric conditions, and is consistent with the present finding that small changes in AH can affect mucociliary function (BTV).

Impairment of mucociliary function can result in a predisposition to retain secretions and an inability to maintain a patent airway, leading to complications of the lower respiratory tract. Chemical and physical factors in the external environment can affect mucociliary function. These include drugs (such as catecholamine, theophylline, cortisone, atropine, and β-adrenergic receptor antagonists), oxygen concentration, trauma resulting from suction procedures and the presence of a cuffed tracheal tube.[9,14] Decreased BTV is associated with an increased rate of pulmonary complications in ventilated critically ill patients.[15] In addition, anaesthetic agents are reported to influence BTV.[12,16,17] Maintenance of anaesthesia with sevoflurane has been shown to reduce BTV significantly, compared with propofol in patients undergoing general surgery.[16] Although the mechanism of reduction in mucus transport during

Table 2. Tracheal tube temperature and relative and absolute humidity in patients undergoing elective radical retropubic prostatectomy, under general anaesthesia with conventional or heated humidified ventilation, stratified according ventilation type.

Parameter	Conventional group $n = 24$	Heated humidified group $n = 26$
Baseline		
$Temp_{TT}$, °C	25.2 (0.5)	26.2 (0.4)
$Humid_{TT}$, %	99.0 (1.31)	99.0 (0.5)
AH, mg H_2O/l	23.4.(0.6)	24.7 (0.5)
After 3 h anaesthesia		
$Temp_{TT}$, °C	25.7 (0.5)	28.1 (0.4)[a,b]
$Humid_{TT}$, %	98.7 (1.2)	99.6 (0.3)[a,b]
AH, mg H_2O/l	23.7 (0.5)	28.2 (0.7)[a,b]

Data presented as median (SE).
$Temp_{TT}$: temperature in tracheal tube; $Humid_{TT}$: relative humidity in tracheal tube; AH: absolute humidity.
[a]$P < 0.05$ versus control group; [b]$P < 0.05$ versus baseline; two-way repeated-measure analysis of variance.

inhalational anaesthesia has not been entirely elucidated, the frequency of ciliary beating is decreased by volatile anaesthetics.[18,19]

Although heated humidified ventilation is widely used in various medical and surgical conditions, its direct effect on mucociliary clearance has not previously been evaluated in patients undergoing anaesthesia. In addition, its clinical efficacy in critically ill patients remains unclear. The use of a heated humidifier was found to be efficient and have a good safety profile for control of hypercapnic acidosis in acute respiratory distress syndrome,[20] and improved lung compliance and reduced plateau airway pressure in patients with acute lung injury.[21]

The use of heated humidified ventilation effectively prevented BTV depression during sevoflurane general anaesthesia in the present study. This finding may be related to optimization of the tracheal environment and the maintenance of mucociliary function by heat and humidification. Ciliated epithelial cells are damaged by dry inspired gases,[22] and the maintenance of tracheal temperature and humidity within their optimal range contributes to the preservation of mucus flow rate.[23–25] Tracheal mucus velocity has been reported to be depressed at 30 min after general anaesthesia,[18] therefore appropriate conditioning of inspired gas can be required even during short-term mechanical ventilation.

The assessment of postoperative pulmonary complications in the present study was limited and did not include many variables. As mentioned above, impaired mucociliary function can promote the retention of secretions, resulting in atelectasis or respiratory difficulty after surgery. There were no significant differences in the incidence of fever or dyspnoea in the early postoperative period in the present study, possibly due to the small sample size. Although the present study did not demonstrate important clinical implications, small changes in AH were shown to affect mucociliary function during general anaesthesia. Further studies (with larger populations or objective modalities such as radiography and arterial blood gas analyses) are required, to evaluate the effects of heated humidified ventilation on post-operative pulmonary variables.

A potential limitation of the present study relates to the accuracy with which the distance of methylene blue transport can be measured. This method can evaluate mucociliary function directly via FOB, but inaccuracies arise from the fact that mucus transport is nonlinear,[10] and the method of dye application and distance measurement are observer-dependent. For this reason, we measured dye transport distance twice and used the mean value. Despite the many possible sources of variation, the modified method of Sackner et al[10] has been used in many studies and is proven to be effective for evaluating mucociliary function under general anaesthesia.[9,12,16,26,27] A further limitation of our study is that we did not compare the heated humidifier with a passive conditioning device such as an HME. Despite several limitations,[28–31] the HME is a simple to use and cost-effective device that is widely employed in general anaesthesia. It would be therefore be of interest to compare mucociliary function and pulmonary complications following use of a heated humidifier or HME. Interestingly, although our findings were statistically significant, the changes in $Temp_{TT}$ and $Humid_{TT}$ were small, and the AH value was low compared with physiological values. This may be due to the location of thermohygrometer probe being too far from the tracheal tube and close to the Y-piece of the ventilator circuit, allowing mixing of inspiratory and expiratory airflow and resulting in measurement errors. Humidity output has been found to be related to inlet gas temperature.[32] Appropriate positioning of the thermohygrometer probe would be required for accurate evaluation of heated humidified ventilation.

In conclusion, BTV is significantly higher in patients using heated humidified ventilation than conventional ventilation after 3h of sevoflurane anaesthesia. It is vital to keep the AH and temperature of inspiratory gas within the physiological range, during general anaesthesia. The use of a heated humidifier can provide physiological gas conditioning and is useful for maintaining mucociliary clearance of patients during general anaesthesia.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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