# An Artificial Cough Maneuver to Remove Secretions From Below the Endotracheal Tube Cuff

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**BACKGROUND: Endotracheal suctioning is mandatory to prevent complications caused by the retention of tracheal secretions. Endotracheal suctioning is often performed late, when patients show signs of respiratory and hemodynamic alterations. We conceived a prototype device that, when synchronized with the ventilator, automatically removes secretions collected below the endotracheal tube (ETT) cuff, thus avoiding endotracheal suctioning. The aim of our investigation was to assess the performance of this novel prototype in vitro. METHODS: Three studies were performed to examine the characteristics of the prototype. We tested device's ability to generate an effective artificial cough flow (artificial cough maneuver) > 1 L/s by rapidly deflating the ETT cuff within the time of a sustained inflation (at 30 and at 40 cm $H_2O$) (cough flow study). We also tested the prototype's ability to remove the fluid positioned below the ETT cuff using saline dye (fluid removal study), and to prevent the aspiration of saline dye from above the ETT cuff during the deflation phase of the ETT cuff (aspiration study). The trachea model was positioned at 45° in the aspiration study, and horizontally in the other two studies. RESULTS: In the cough flow study, the prototype provided an effective artificial cough maneuver, with a mean ± SD of 1.78 ± 0.19 L/s (range, 1.42–2.14 L/s). The tracheal pressure after ETT cuff deflation never decreased below the PEEP level. In the fluid removal study, the prototype cleared the fluid from below the ETT cuff and the experimental trachea. No fluid was aspirated from the area above the ETT cuff toward the lower airways. CONCLUSIONS: We conceived an system capable of automatically expelling fluid from below the ETT cuff outside an experimental trachea by generating an artificial cough maneuver. This system may decrease the use of endotracheal suctioning and its complications. Future in vivo studies are needed to confirm this first in vitro evaluation.** *Key words: cough; ventilator-associated pneumonia; mechanical ventilation; intubation; in vitro.* [Respir Care 2019;64(4):372–383. 

## Introduction

Healthy human lungs are extremely resistant to environmental harms, despite continuous exposure to pathogens, particles, and toxic chemicals in the atmosphere. Humidification and filtration of the upper airways, mucociliary clearance, and cough reflex protect lower airways and guarantee resistance to potential exogenous insults.[1]

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Drs Zanelli, Scaravilli, and Pesenti are inventors of a patent owned by the University of Milano-Bicocca. The other authors have disclosed no conflicts of interest.

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In healthy humans, mucus is continuously removed from distal to proximal airways by mucociliary clearance. Mucus is first driven cephalad from the trachea, and it then passes through the vocal cords and is swallowed. Endotracheal intubation and mechanical ventilation considerably impair airway defenses, increasing the risk of bacterial colonization and ventilator-associated pneumonia.[2,3] The endotracheal tube (ETT) cuff, which allows positive-pressure ventilation and prevents aspiration, compromises mucociliary clearance by mechanically preventing the flow of mucus toward the oropharynx.[4,5] Therefore, secretions accumulated in the trachea must be removed by endotracheal suctioning. This is essential to prevent airway obstruction, which may lead to increased work of breathing, deterioration of gas exchange, pulmonary infections, and hemodynamic instability. However, premature endotracheal suctioning is associated with patient distress and pain, as well as severe respiratory and hemodynamic complications.[6]

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We conceived a prototype system that, when synchronized with a mechanical ventilator, removes secretions collected below the ETT cuff of intubated patients, thus avoiding the need for endotracheal suctioning. The prototype produces an artificial cough maneuver by briefly deflating and re-inflating the ETT cuff during the time of a sustained inflation delivered by the mechanical ventilator. During the ETT cuff deflation, the gas coming from the inflated artificial lungs and from the ventilator rapidly flows out of the artificial trachea around the deflated cuff, exploiting the difference of pressure between the airways and the atmosphere. This air flow allows expulsion of the secretions accumulated near the ETT tip around the ETT cuff. The aim of this study was to evaluate the efficacy of this new prototype in vitro.

**QUICK LOOK**

**Current knowledge**

Intubated patients require endotracheal suctioning to remove secretions from the trachea, which can eventually lead to ventilator-associated pneumonia. Endotracheal suctioning is a procedure with several complications, and it is often performed late due to the absence of early indicators. Thus, patients are also exposed to complications due to secretion retention.

**What this paper contributes to our knowledge**

We conceived a prototype to automatically remove secretions from below the endotracheal tube cuff and the trachea by rapidly deflating the cuff within the time of a sustained inflation (artificial cough maneuver). The artificial cough maneuver produces an effective expiratory flow that cleared tracheal secretions and prevented aspiration. Our invention might prevent the need for endotracheal suctioning and its complications in patients who are intubated and mechanically ventilated.

## Methods

### Prototype Device

We designed and developed a prototype system (Fig. 1) capable of timely and quickly deflating and re-inflating the cuff of an ETT within the duration of a sustained inspiration delivered by a mechanical ventilator. The prototype consisted of an Arduino board with a pressure sensor connected to the Y-piece of a breathing circuit and a mechanical device able to quickly move the plunger of a 20-mL syringe connected to the cuff lumen of an ETT.

When the pressure in the breathing circuit reaches a threshold value (eg, 29 cm $H_2O$ or 39 cm $H_2O$) during the sustained inflation (30 and 40 cm $H_2O$, respectively), a pressure sensor activates a predetermined first-hold phase (delay time). At the end of the delay time, a second predetermined hold phase (deflation time) is activated. Upon activation of the deflation time, the device immediately pulls back the plunger of the syringe to completely deflate the ETT cuff. During the ETT cuff deflation, the gas flow exits the trachea around the deflated cuff and is defined as artificial cough flow. At the end of the deflation time, the plunger is fully pushed back into the syringe within the time of a sustained inflation maneuver (eg, 4 s).

### Study Design

We performed three different studies to evaluate three major aspects of the prototype. First was the cough flow study, which evaluated the device's efficacy in generating an artificial cough flow > 1 L/s, a value deemed effective to mobilize even the thickest secretions.[7] The pressure of the ETT cuff was also recorded. We then performed the fluid removal study, in which we evaluated the prototype's

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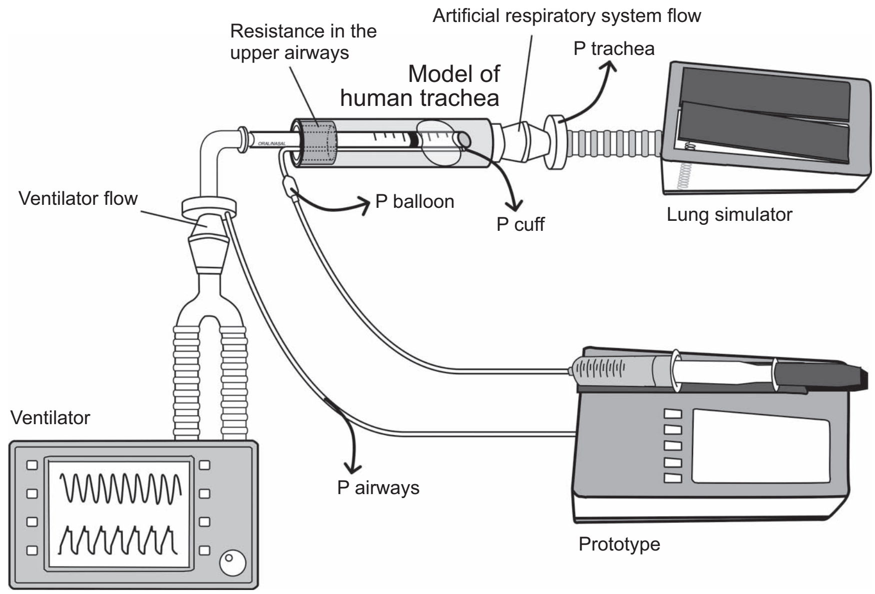


Fig. 1. Design of the prototype and of the study setup. P = pressure.

ability to move all of the secretions and fluids positioned close to the tip of the ETT (thus below the ETT cuff) to above the ETT cuff. We then performed an aspiration study evaluate the device's efficacy in preventing aspiration of secretions accumulated above the ETT cuff during the deflation phase of the ETT cuff.

## Cough Flow Study

An ETT (Mallinckrodt Hi-Lo; internal diameter 7.5 mm, polyvinyl chloride cuff; Mallinckrodt, Staines-upon-Thames, United Kingdom) was inserted into a horizontal, transparent, rigid cylinder (25 cm long, 20 mm internal diameter) used as a model of the human trachea. The ETT was connected to the breathing circuit of a mechanical ventilator (Hamilton-S1, Hamilton Medical AG, Bonaduz, Switzerland). Between the ETT and the Y-piece of the breathing circuit, we positioned a pneumotachograph to measure ventilator flow and an airway pressure ($P_{aw}$) measuring port. The distal portion of the model trachea was connected through 2 side connectors to a second pneumotachograph to measure artificial respiratory system flow and to a mechanical lung simulator (Dual Adult Test Lung Simulator, Michigan Instruments, Grand Rapids, Michigan) (Fig. 1). The first side door allowed measurement of the pressure in the trachea (tracheal pressure, $P_{trach}$) and the second door allowed insertion of a pressure line into the trachea in a sealed manner. This pressure line was connected a 20G needle previously inserted through the ETT tip up to the ETT cuff to allow direct measurement of the pressure inside the ETT cuff (cuff pressure, $P_{cuff}$). The ETT cuff seal was tested for each modified ETT. A silicon ring (3 cm long, 18 mm external diameter) was inserted into the proximal side of the model trachea and wrapped around the ETT to create a resistance to gas flow of approximately 4 cm $H_2O$/L/s measured at 1 L/s of gas flow. The cuff lumen of the ETT cuff was connected through a 3-way stopcock to a pressure transducer (balloon pressure, $P_{ball}$) and to the 20-mL syringe of the prototype. At the start of each experiment, $P_{ball}$ measured at the end of expiration was checked using a manual manometer and maintained at a pressure of 30 ± 1 cm $H_2O$.

The ventilator was set as follows: pressure controlled ventilation with PEEP = 5 cm $H_2O$, respiratory rate = 7 respiratory cycles/min, and an inspiratory time of 4 s. Two sustained inflation pressures were studied: 30 cm $H_2O$ and 40 cm $H_2O$ (inspiratory pressure of 25 and 35 cm $H_2O$ + PEEP 5 cm $H_2O$, respectively). Four delay times were tested: 400, 800, 1,200, and 1,600 ms. Two deflation times were tested: 400 and 800 ms.

Three different lung simulator setups were tested: a normal pattern entailed compliance of 50 mL/cm $H_2O$ and an airway resistance of 5 cm $H_2O$/L/s; a high-resistance pattern entailed compliance of 50 mL/cm $H_2O$ and airway resistance 20 cm $H_2O$/L/s; and a low-compliance pattern entailed compliance of 30 mL/cm $H_2O$ and airway resistance 5 cm $H_2O$/L/s.

Pressure and flow waveforms of 5 consecutive respiratory cycles for each combination of variables (2 inspiratory pressures, 4 delay times, 2 deflation times, and 3 lung simulator setups) were recorded with LabChart Pro v.8.1.5 (AD Instruments, Sydney, Australia). The 3 central respiratory cycles were considered for statistical analysis. We also recorded pressure and flow waveforms of 5 consecutive respiratory cycles (2 inspiratory pressures and 3 lung simulator setups), during which the prototype was not activated (control breaths). Artificial cough flow was calculated as the sum of ventilator flow and lung simulator expiratory flow. Volumes were calculated as the integral of the flow waveforms.

### Fluid Removal Study

The setup used for the cough flow study was used without the $P_{cuff}$ measurement. Two mL saline solution mixed with methylene blue were placed at the tip level of the ETT. Three artificial cough maneuvers were performed for each combination of variables (ie, 2 inspiratory pressures, 4 delay times, 2 deflation times, and 3 lung simulator setups). At the end of each cough maneuver, the model trachea was evaluated for the presence of saline dye below the ETT cuff. The model trachea was then cleaned before the start of a new artificial cough maneuver. We further evaluated the efficacy of the artificial cough maneuver in removing a known synthetic solution (0.5 mL) with standardized viscoelastic properties similar to human mucus,[7] which was placed just below the ETT cuff. The synthetic secretions were mixed with methylene blue and the contrast medium iobitridol (Xenetix 350, Guerbet, Villepinte, France) in a ratio 20:1 and 4:1, respectively. We used the most efficient setup (delay time = 1,600 ms, deflation time = 800 ms, and $P_{aw}$ = 40 cm $H_2O$), which produced the highest artificial cough flow and volume as shown in the cough flow study. We performed 5 artificial cough maneuvers for each of the 3 studied patterns of lung simulator setups (normal, high resistance, and low compliance). We used computed tomography to scan the model trachea and the ETT before and after the 5 artificial cough maneuvers for each respiratory pattern. We then quantified and compared the percentage of removal of the artificial secretions versus baseline using dedicated software (Maluna v.3.17, University of Mannheim, Göttingen, Germany). Furthermore, we tested our prototype in a swine model of cerebral death. The animal was ventilated in prone position and placed on a horizontal plane. We insufflated 5 radiopaque tantalum disks into the lower trachea below the ETT cuff and studied their transit along the airways through radiographic tracking as previously reported.[4] To test our prototype in the pilot animal experiment, we performed a single artificial cough maneuver at $P_{aw}$ = 40 cm $H_2O$, with a delay of 1,600 ms and a deflation time of 800 ms. The pilot animal had healthy lungs. Approval to perform the pilot animal test was waived due to the use of a model of cerebral death.

### Aspiration Study

The same setup used for the cough flow study was used, with several exceptions: an ETT with a polyurethane cuff (internal diameter 7.5 mm; Halyard Health, Alpharetta, Georgia) was tested, the model trachea was positioned at 45°, and 2 mL saline dye were positioned above the ETT cuff (and not below the ETT cuff, as in the fluid removal study). Three artificial cough maneuvers were performed for each combination of variables (ie, 2 inspiratory pressures, 4 delay times, 2 deflation times, 3 lung simulator setups). The artificial trachea was evaluated for the presence of saline dye either below or above the ETT cuff, during and at the end of each cough maneuver. The model trachea was then cleaned before the start of a new artificial cough maneuver.

### Statistical Analysis

Continuous variables were described as mean ± SD and range. Multivariate ordinary least squares analysis was used to examine the effect of the change of independent variables (ie, delay time, deflation time, inspiratory pressure, and lung simulator setups) on the change of the artificial cough flow and volume, which were dependent variables. A post hoc analysis with the Tukey's range test was used to test the difference of artificial cough flow and volume over the different delay times (400, 800, 1,200, and 1,600 ms) and the lung simulator setups (healthy, low compliance, and high resistance). A post hoc analysis with the unpaired Student *t* test was used to assess the differences in artificial cough flow and volume over different deflation times (400 and 800 ms) and inspiratory pressures (30 and 40 cm $H_2O$). The correlation among the artificial cough flow and the tracheal pressure measured immediately before the cuff deflation was tested using Pearson's correlation coefficient (r). Fluid volume change of the artificial secretions at the computed tomography assessment after artificial cough maneuvers versus baseline in the 3 respiratory patterns was tested using a 1-way analysis of variance for independent measures. Statistical significance was set at $P < .05$ (2-tailed). Statistical analyses were performed using Microsoft Excel for Mac 2017, version 15.32 (Redmond, Washington), and JMP Pro 12 (SAS, Cary, North Carolina).

## Results

### Cough Flow Study

**Artificial Cough Flow.** Figure 2 shows an exemplary image of pressure and flow recorded waveforms with the prototype on (Fig. 2A, 2B) and off (Fig. 2C, 2D). The artificial cough flow was > 1 L/s throughout the entire in vitro experiment. The overall artificial cough flow was 1.78 ± 0.19 L/s (range, 1.42–2.14 L/s). All of the independent analyzed variables significantly affected the artificial cough flow.

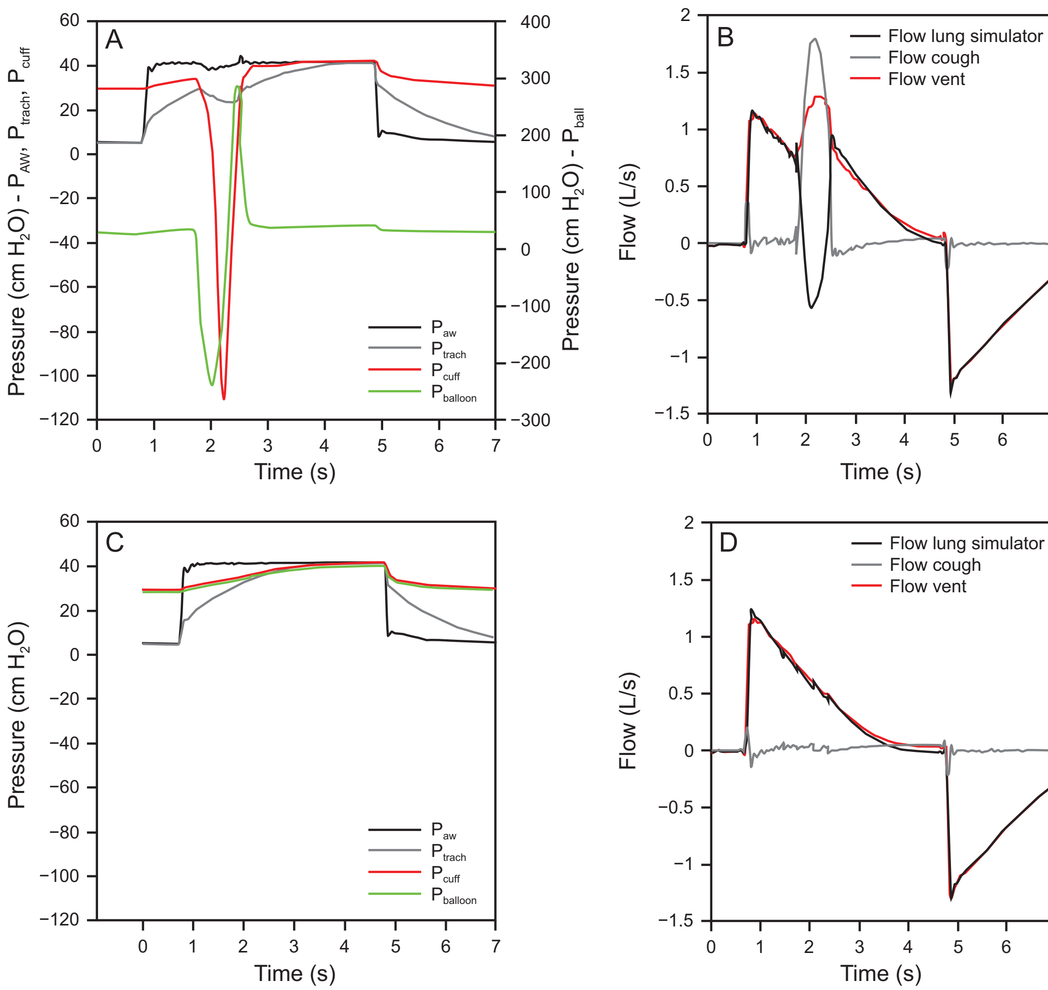


Fig. 2. Pressure and flow waveforms of a respiratory cycle with the prototype on (A, B) and with the prototype off (C, D). The setup used to record the waveforms was a high resistance pattern; delay time = 800 ms; deflation time = 800 ms; $P_{aw}$ = 40 cm $H_2O$. Lung simulator, cough, and ventilator flows ae depicted in B and D. $P_{aw}$ = airway pressure; $P_{trach}$ = tracheal pressure; $P_{cuff}$ = cuff pressure; $P_{ball}$ = balloon pressure.

The artificial cough flow was 1.66 ± 0.12 L/s at $P_{aw}$ 30 cm $H_2O$ and significantly increased up to 1.90 ± 0.18 L/s at $P_{aw}$ 40 cm $H_2O$ ($P < .001$). The artificial cough flow was 1.63 ± 0.16 L/s with 400 ms of delay time, and this increased significantly to 1.77 ± 0.17, 1.84 ± 0.17, and 1.89 ± 0.17 L/s with 800, 1,200, and 1,600 ms of delay time, respectively ($P < .001$). The artificial cough flow was 1.77 ± 0.20 L/s with 400 ms of deflation time, and this increased significantly to 1.80 ± 0.18 L/s with 800 ms of deflation time ($P < .001$).

The artificial cough flow was 1.66 ± 0.14 L/s with the high-resistance pattern and increased up to 1.78 ± 0.18 and 1.91 ± 0.16 L/s with the healthy pattern and the low-compliance pattern, respectively ($P < .001$) (Fig. 3). The component of the artificial cough flow due to the lung simulator expiratory flow was 23.1 ± 7.4% with the high-resistance pattern and 33.8 ± 9.9% and 41.9 ± 5.0% with the healthy pattern and the low-compliance pattern, respectively ($P < .001$).

The cough flow was highly correlated to the $P_{trach}$ measured immediately before the cuff deflation (r = 0.85, $P < .001$) (Fig. 4). Such correlation was positive by analyzing each of the 3 patterns separately: r = 0.95, 0.89, and 0.95 in healthy, low-compliance, and high-resistance patterns, respectively. During the cuff deflation, the $P_{trach}$ decreased to an average minimum value of 19.1 ± 3.5 cm $H_2O$ (range, 12.9–27.2 cm $H_2O$). The minimum value of $P_{trach}$ during cuff deflation (12.9 cm $H_2O$) was measured with a sustained inflation pressure of 30 cm $H_2O$, delay time 400 ms, deflation time 800 ms, and high-resistance pattern.

**Artificial Cough Volume.** The overall artificial cough volume was 1.26 ± 0.35 L (range, 0.70–1.88 L). All of

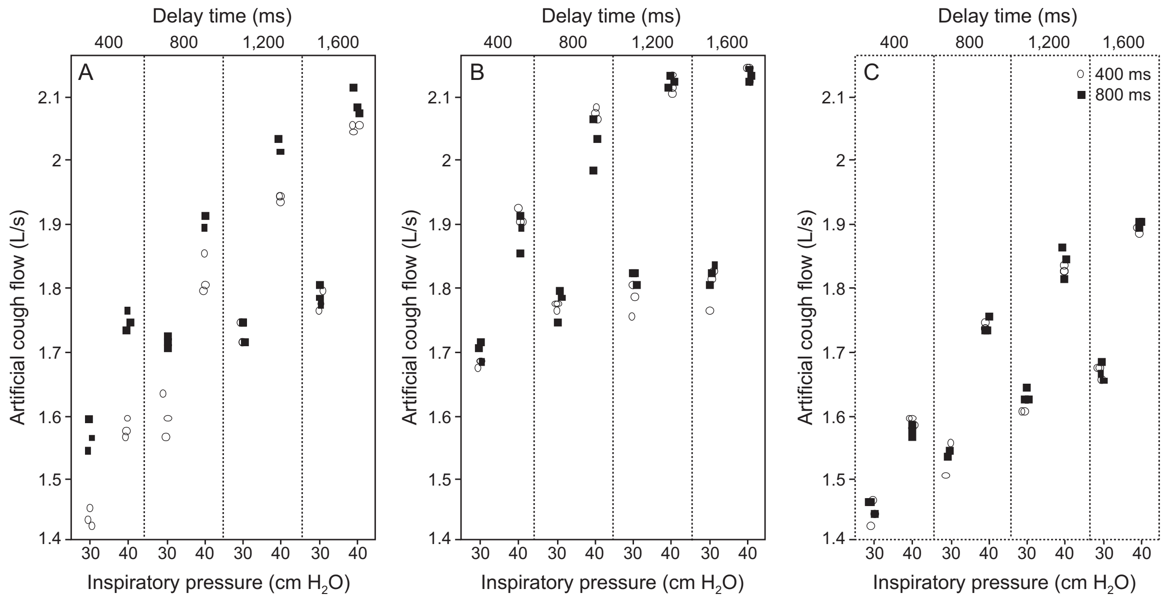


Fig. 3. Changes of artificial cough flow at different delay times, deflation times (400 and 800 ms), and inspiratory pressures during the 3 lung simulator setups. A: Normal pattern, 50 mL/cm $H_2O$ compliance and 5 cm $H_2O$ airway resistance; B: low compliance pattern, 30 mL/cm $H_2O$ compliance and 5 cm $H_2O$ airway resistance; and C: high resistance pattern, 50 mL/cm $H_2O$ compliance and 20 cm $H_2O$ airway resistance.

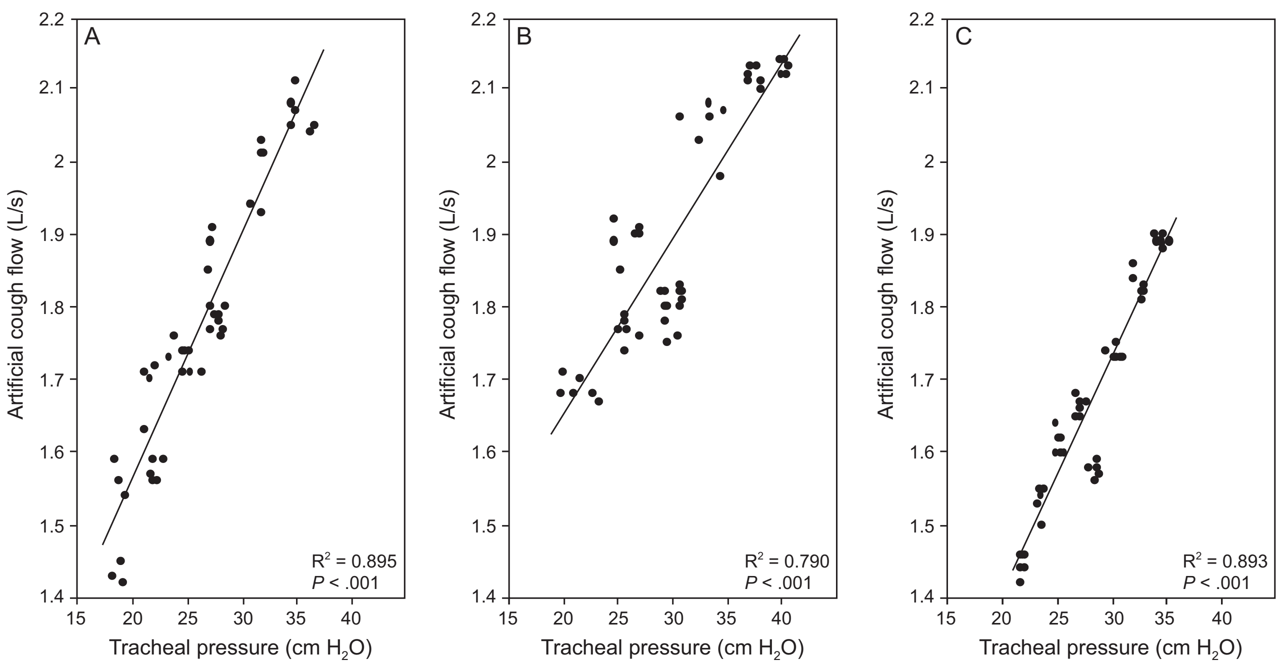


Fig. 4. Correlation of artificial cough flow and tracheal pressure measured immediately before the endotracheal tube cuff deflation during the 3 lung simulator setups: normal pattern, 50 mL/cm $H_2O$ compliance and 5 cm $H_2O$ airway resistance, B: low compliance pattern, 30 mL/cm $H_2O$ compliance and 5 cm $H_2O$ airway resistance, and C: high resistance pattern, 50 mL/cm $H_2O$ compliance and 20 cm $H_2O$ airway resistance. Linear regression with equation of the best-fit line, R2, and 2-sided $P$ value.

the independent variables significantly affected the artificial cough volume. The artificial cough volume was 1.18 ± 0.31 L at $P_{aw}$ 30 cm $H_2O$, and this increased significantly to 1.35 ± 0.37 at $P_{aw}$ 40 cm $H_2O$ ($P < .001$). The artificial cough volume was 1.14 ± 0.32 L with 400 ms of delay time, and this increased significantly to 1.25 ± 0.35, 1.31 ± 0.35, and 1.36 ± 0.35 L/s with 800, 1,200, and 1,600 ms of delay time, respective-

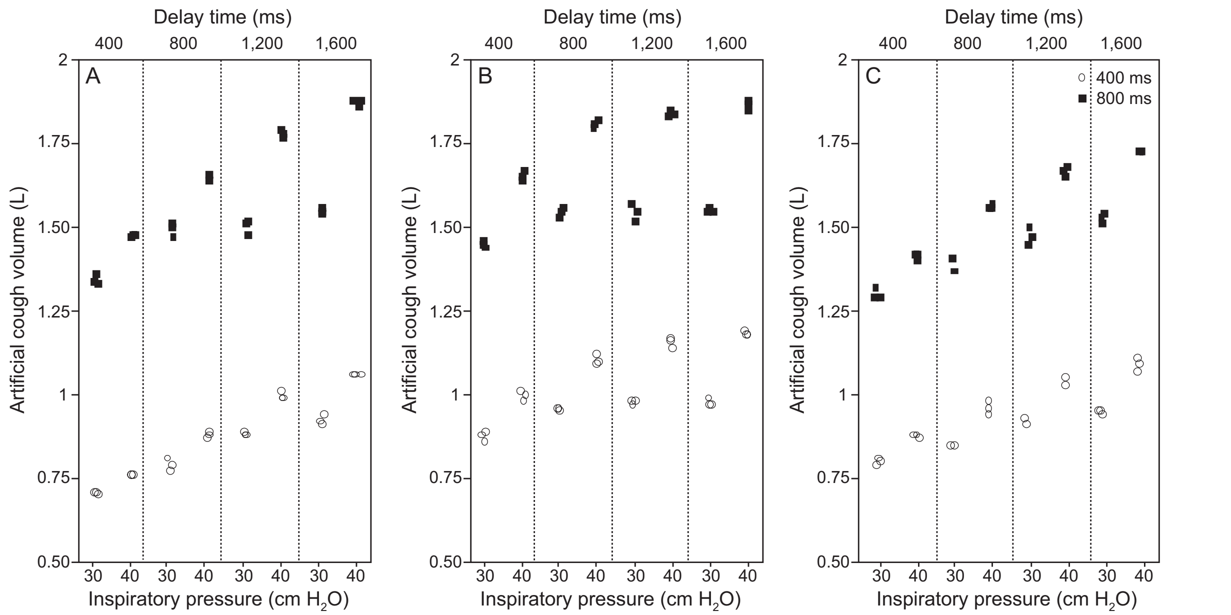


Fig. 5. Changes of artificial cough volume at different delay time, deflation times (400 and 800 ms), and inspiratory pressures during the 3 lung simulator setups: normal pattern, 50 mL/cm $H_2O$ compliance and 5 cm $H_2O$ airway resistance; B: low compliance pattern, 30 mL/cm $H_2O$ compliance and 5 cm $H_2O$ airway resistance; and C: high resistance pattern, 50 mL/cm $H_2O$ compliance and 20 cm $H_2O$ airway resistance. Key shows deflation times.

ly ($P < .001$). The artificial cough volume was 0.95 ± 0.12 L with 400 ms of deflation time, and this increased significantly to 1.58 ± 0.16 with 800 ms of deflation time ($P < .001$). The artificial cough volume was 1.22 ± 0.31 and 1.23 ± 0.38 L with the high-resistance and the healthy patterns, respectively, and this increased significantly to 1.34 ± 0.34 with the low-compliance pattern ($P < .001$) (Fig. 5).

The $P_{cuff}$ at end expiration was 30.9 ± 1.1 and 30.8 ± 1.7 cm $H_2O$ with the prototype active and non-active, respectively ($P = .69$). The $P_{cuff}$ at end inspiration was 38.7 ± 2.2 and 37.5 ± 2.9 cm $H_2O$ with the prototype active and non-active, respectively ($P < .001$).

With the prototype active, the $P_{ball}$ at end expiration and end inspiration were 29.8 ± 0.9 and 37.7 ± 2.2 cm $H_2O$, respectively. During the cuff deflation, the minimum $P_{ball}$ values were −228.2 ± 8 cm $H_2O$, while during cuff inflation the maximum $P_{ball}$ values were 285.3 ± 17.1 cm $H_2O$.

## Fluid Removal Study

All of the artificial cough maneuvers completely removed the saline dye from below the ETT cuff (Fig. 6, Supplemental Video 1; see the supplementary materials at http://www.rcjournal.com). After performing a series of 5 artificial cuff maneuvers, synthetic secretions below the ETT cuff where effectively cleared from below the ETT cuff (Fig. 7). The volume of synthetic secretions removed by 5 artificial cuff maneuvers was 80 ± 5%, 70 ± 10%, and 63 ± 5% in the low compliance, normal, and high resistance patterns, respectively ($P < .001$). The fluid volume change was determined with computed tomography assessment after artificial cough maneuvers vs baseline in all 3 respiratory patterns. In the swine model, all of the insufflated tantalum disks reached the ETT cuff within 7 min of performing the artificial cough maneuver. After performing 1 artificial cough maneuver, all of the tantalum disks were ejected from the lower trachea and were visible above the ETT cuff. We could assess the gradual movement of the tantalum disks from the lower airways across the deflated ETT cuff up to the upper airways (Fig. 8, Supplemental Video 2; see the supplementary materials at http://www.rcjournal.com).

## Aspiration Study

No leakage of saline dye or synthetic secretions was observed during any of the tested artificial cough maneuvers (Fig. 9, Supplemental Video 3; see the supplementary materials at http://www.rcjournal.com).

## Discussion

We designed and tested in vitro a prototype system to perform an automated artificial cough maneuver in a respiratory system setup that simulated intubated and mechanically ventilated patients. This goal of this technology

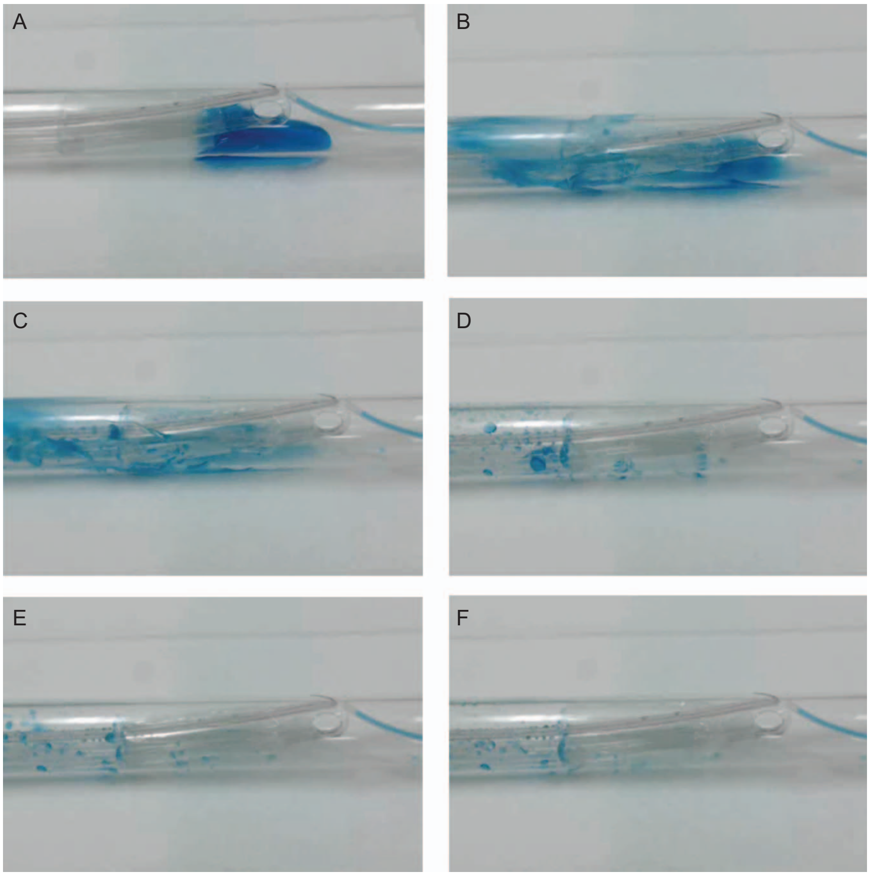


Fig. 6. Fluid-removal study with saline dye. (A) Setup preparation with placement of 2 mL saline dye with methylene blue below the inflated ETT cuff. (B) Prototype on: at the end of the delay time, the ETT cuff was rapidly deflated. A tracheal gas flow was generated from the lower airways outside the trachea, simultaneously dragging the saline dye. (C, D). The artificial cough flow effectively removes the tracheal fluid during the deflation time. (E) The ETT cuff was then inflated again. (F) After the artificial cough maneuver, with the ETT cuff inflated, no saline dye was present below the ETT cuff. ETT = endotracheal tube.

is to remove accumulated secretions below the ETT cuff without manual endotracheal suctioning.

Our experimental in vitro investigation suggests that the prototype was able to timely deflate and re-inflate the ETT cuff within the time of a sustained inflation delivered by the mechanical ventilator (ie, an artificial cough maneuver); that the gas flowing around the deflated cuff toward the glottis removed all of the saline dye below the ETT cuff from the trachea during deflation of the ETT cuff within the time of an artificial cough maneuver, and most of the synthetic secretions after a series of 5 artificial cough maneuvers; and that the prototype prevented aspiration across the ETT cuff during the deflation time of the artificial cough maneuver.

Our prototype, applied with a currently used ventilator, was able to effectively provide adequate expiratory flow within the time of a sustained inflation maneuver. This gas flow, intended to mimic the expiratory flow generated during the human cough reflex, was generated by the flow coming from the ventilator plus the expiratory flow coming from the lung simulator.

Li Bassi et al[8] found that different inspiratory and expiratory flows in intubated pigs could play a role in mucus transport via 2-phase, gas-liquid flow mucus clearance. They showed that an expiratory flow of 0.72 L/s coupled with an inspiratory flow of 0.17 L/s, resulting in a net difference of approximately 0.5 L/s, significantly improved the mucus clearance. In an in vitro study, Volpe and colleagues[7] showed that a flow of 0.5 L/s could move fluid secretions, and a flow of 1 L/s was required to move thicker secretions positioned in an in vitro model of an experimental trachea. Therefore, because the expiratory flow produced by our prototype ranged between 1.42–2.14 L/s, our artificial cough maneuver may clear even the thickest secretions accumulated below the ETT cuff.

In our experimental study, the simulation of different patients with high resistance and low compliance showed the lowest and the highest artificial cough flow, respectively. As expected, the use of sustained inflation at a higher pressure (40 cm $H_2O$) delivered a higher cough flow compared to the sustained inflation at a lower pressure (30 cm $H_2O$). We also observed that a prolonged

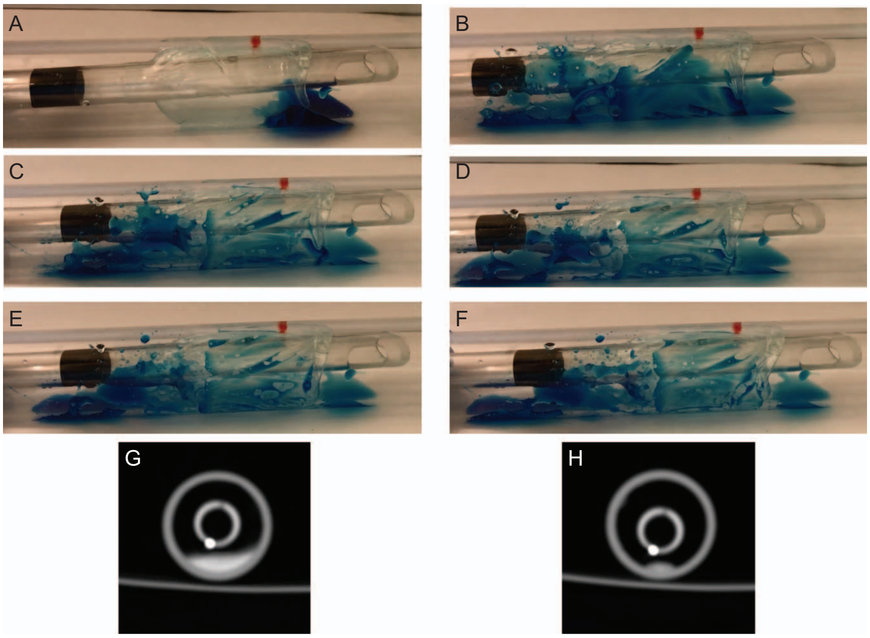


Fig. 7. Fluid removal study with artificial secretions. (A) Setup preparation with placement of 0.5 mL synthetic solution with standardized viscoelastic properties similar to human mucus. (B) Effect on fluid removal after the first, (C) second, (D) third, (E) fourth, (F) fifth, and last artificial cough maneuver. (G) Axial section view of the secretions below the ETT cuff by the computer tomography evaluation at baseline and (H) at the end of the series of 5 artificial cough maneuvers.

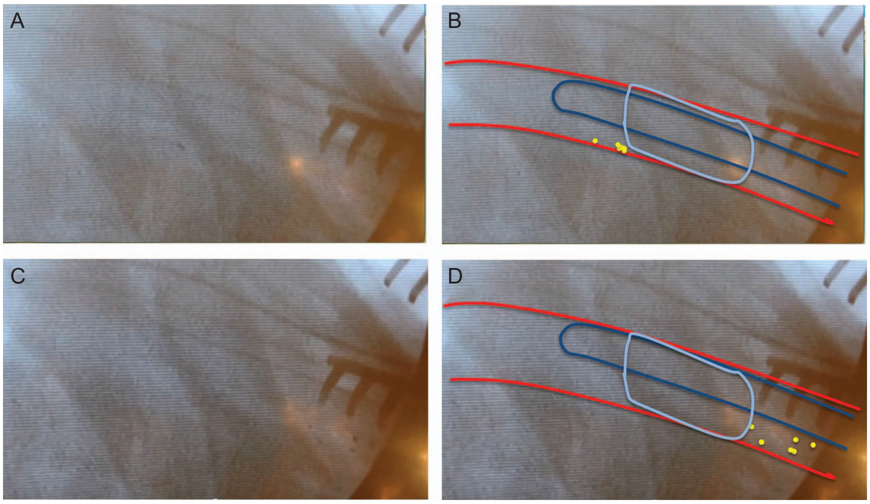


Fig. 8. Fluid removal study in a pig, which was the first in-vivo animal experiment. Fluoroscopic images were taken immediately after placing 6 tantalum disks below the ETT cuff (A) and 7 min after performing the artificial cough maneuver (C). (B, D) The ETT tube (blue line), ETT cuff (light blue line), trachea (red line), and tantalum disks (yellow dots) were superimposed on panels A and B, respectively. ETT = endotracheal tube.

delay time up to 1,600 ms is an effective strategy to guarantee a higher expiratory flow compared to shorter delay times. This finding can be explained by the longer inflation time of the lung simulator, which results in a higher peak expiratory flow. On the other hand, the increase of the deflation time did not lead to a clinically relevant higher cough flow because, during the artificial cough maneuver, the peak expiratory flow occurs within the first 400 ms of the deflation time. Furthermore, our study showed that the difference of the pressure in the ETT cuff was clinically irrelevant when measured with the prototype on and off, at the end of inspiration. This finding suggests that no leakage of volume from the ETT cuff was present during the artificial cough maneuver.

For more than than 20 years, a number of studies have tried to address the urgent need to effectively remove se-

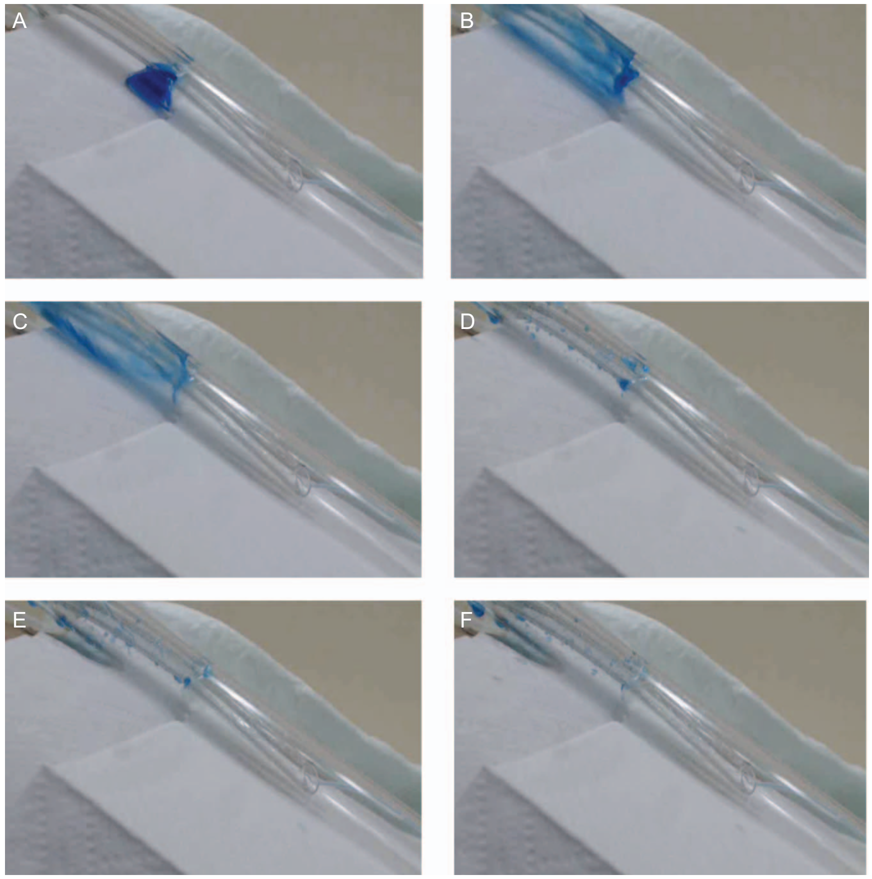


Fig. 9. Aspiration study. (A) Setup preparation with placement of 2 mL saline dye with methylene blue above the inflated ETT cuff. (B) Prototype on: at the end of the delay time, the ETT cuff was rapidly deflated. A tracheal gas flow was generated from the lower airways outside the trachea, simultaneously dragging the saline dye. (C, D) No leakage was visible throughout the entire deflation time; the artificial cough removed the tracheal fluid from below the ETT cuff outside the experimental trachea. (E) The ETT cuff was then inflated again. (F) After the artificial cough maneuver, with the ETT cuff inflated, no saline dye was present either above or below the ETT cuff. ETT = endotracheal tube.

cretions from the lower airways in mechanically ventilated patients. Among various strategies, continuous subglottic aspiration,[9] Mucus Shaver,[10] and Mucus Slurper[11] have proven effective in removing secretions from the trachea or from within the inner surface of the ETT. Despite this progress, clinical practice has not changed substantially, and suctioning of endotracheal secretions still remains the standard of care.[12] A sawtooth pattern on the flow-volume loop and auscultation of respiratory crackles can help the health care provider determine the need for endotracheal suctioning. However, indications for endotracheal suctioning are based mostly on signs of clinical deterioration due to secretion retention, such as hypoxemia, ineffective spontaneous cough, or acute respiratory distress.[6] As a result, endotracheal suctioning is performed in mechanically ventilated patients mainly after they have experience the potentially severe consequences of ineffective mucus clearance. This suggests that clinical indicators for secretion removal are late signs. Furthermore, endotracheal suctioning is not without its complications. These include hypoxemia, bronchospasm, increased intracranial pressure, and hemodynamic alterations.[6] Endotracheal suction has been described as the most stressful experience at 6 months in a post-ICU recollections study.[13]

We previously showed the advantage of using an airway sounds analyzer (TBA Care) to detect the presence of tracheal secretions in intubated and mechanically ventilated patients.[14] The integration of such a device with our prototype could be useful in determining the right timing and frequency of these artificial cough maneuvers.

Our prototype system performs artificial cough maneuvers that effectively removed synthetic secretions accumulated in the model trachea below the ETT cuff. This prototype appears to be clinically promising on the basis of the confirmation of its in vitro effectiveness and the in vivo experiment that analyzed the progression of the tantalum disks across the ETT cuff. Its action is timely and might allow automatic and frequent removal of secretions, thus avoiding the need to rely on late clinical indicators to determine the need for endotracheal suctioning. This technology may substitute for the use of endotracheal suctioning and may prevent the hazards of endotracheal suctioning and secretion retention.

Endotracheal suctioning is a manual technique and can lead to injuries of the bronchial epithelium. Different preclinical[15,16] and clinical studies[17] have associated endotracheal suctioning with necrosis and inflammation of the tracheobronchial wall, loss of cilia, increased production of mucus, transient bacteremia, and lower airway contamination. Our findings suggest that an automatic system able to produce an artificial cough maneuver could prevent external sources of colonization and inflammation, such as the use of suction catheters and their direct damage to the bronchial epithelium. Moreover, the prompt and constant removal of secretions from the trachea, achieved by mimicking normal mucociliary clearance of the bronchial epithelium, could prevent the back flow of secretions toward the lungs, thus preventing ventilator-associated pneumonia[4] and reducing the dispersion of cytokines.[18-20] Although standard ETT cuffs are not designed for repeated inflations and deflations, which is necessary in the artificial cough maneuver, no damage was evident during the experiments. Although this was not a safety study, we hypothesize that the artificial cough maneuver should not lead to tracheal injury for 2 reasons: during the decrease of tracheal pressure, the capillary flow should increase, which might help mucosal perfusion; and the prototype system has been conceived to keep the maximum pressure within the cuff always equal to the pressure that would be reached during normal breaths. However, the effects of repeated inflation and deflation on the tracheal epithelium will have to be addressed in future in vivo studies.

The idea of using lung hyperinflation to mobilize bronchial secretions dates back almost 50 years.[21] At that time, the technique was manual and did not involve the deflation of the ETT cuff, and the expiratory flow was centered within the inner diameter of the ETT and could only be guaranteed by the passive elastic recoil of the respiratory system (ie, the mechanically ventilated patient) or active patient expiration (in spontaneous breathing) with the addition, in some cases, of manual chest compressions.[22]

Li et al.[23] recently conceived a strategy of subglottic secretion drainage above the ETT cuff to address the issue of ventilator-associated pneumonia caused by the leakage of colonized subglottic secretions across the ETT cuff to the lower airways. The authors developed a manual technique that effectively removed subglottic secretions above the ETT cuff and prevented aspiration by deflating the ETT cuff and producing a high peak expiratory flow around the ETT cuff by a resuscitation bag.[23]

Our prototype provides 2 further advancements compared to the technique proposed by Li et al.,[23] which was aimed at removing subglottic secretions above the ETT cuff. Primarily, our technology is automated. Thanks to pressure and time sensors, the prototype can be used as a stand-alone device and synchronized with the respiratory cycle, or it can be inserted into a commercially available ventilator and be activated according to clinical indications determined by a physician or respiratory therapist. This development may be cost-effective and may contribute to a significant reduction of the work load of both respiratory therapists and nurses in the ICU. Second, our prototype is aimed at reducing the secretions on both sides of the ETT cuff. Specifically, our research assessed the prototype's performance in the removal of fluid below the ETT cuff, proving its efficacy in the timely clearance of secretions that neither continuous subglottic suctioning nor endotracheal suctioning clear.

This experimental in vitro investigation has some limitations that should be considered. First, the prototype system did not work properly with an abnormal cuff-leak test[24] in the presence of significant edema of the tracheobronchial mucosa. Second, the time of cuff deflation may be a potential risk for patient extubation; for this reason, careful preventive measures should be considered to avoid the risk of ETT dislocation. Third, where there is a risk that the patient may contaminate the health care provider, a closed system of endotracheal suctioning should be considered.

## Conclusions

We conceived a prototype system capable of effectively removing secretions from below the ETT cuff by generating an artificial cough maneuver in an in vitro model and in the first in vivo animal experiment. This system could decrease the use of endotracheal suctioning and its complications, and it may reduce clinician work load if proven safe and effective in vivo. Future studies are needed to assess the role of the artificial cough maneuver in humans and to compare this new prototype with endotracheal suctioning in terms of outcomes and cost-effectiveness.

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### REFERENCES

1. Fahy JV, Dickey BF. Airway mucus function and dysfunction. N Engl J Med 2010;363(23):2233-2247.
2. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med 2011;39(12):2612-2618.
3. Rezoagli E, Zanella A, Cressoni M, De Marchi L, Kolobow T, Berra L. Pathogenic link between postextubation pneumonia and ventilator-associated pneumonia: an experimental study. Anesth Analg 2017; 124(4):1339-1346.
4. Li Bassi GL, Zanella A, Cressoni M, Stylianou M, Kolobow T. Following tracheal intubation, mucus flow is reversed in the semi-

recumbent position: possible role in the pathogenesis of ventilator-associated pneumonia. Crit Care Med 2008;36(2):518-525.
5. Sackner MA, Hirsch J, Epstein S. Effect of cuffed endotracheal tubes on tracheal mucous velocity. Chest 1975;68(6):774-777.
6. American Association for Respiratory Care. Clinical practice guideline: endotracheal suctioning of mechanically ventilated patients with artificial airways: 2010. Respir Care 2010;55(6):758-764.
7. Volpe MS, Adams AB, Amato MB, Marini JJ. Ventilation patterns influence airway secretion movement. Respir Care 2008;53(10):1287-1294.
8. Li Bassi G, Saucedo L, Marti JD, Rigol M, Esperatti M, Luque N, et al. Effects of duty cycle and positive end-expiratory pressure on mucus clearance during mechanical ventilation. Crit Care Med 2012;40(3):895-902.
9. Berra L, De Marchi L, Panigada M, Yu ZX, Baccarelli A, Kolobow T. Evaluation of continuous aspiration of subglottic secretion in an in vivo study. Crit Care Med 2004;32(10):2071-2078.
10. Kolobow T, Berra L, Li Bassi G, Curto F. Novel system for complete removal of secretions within the endotracheal tube: the Mucus Shaver. Anesthesiology 2005;102(5):1063-1065.
11. Li Bassi G, Curto F, Zanella A, Stylianou M, Kolobow T. A 72-hour study to test the efficacy and safety of the "Mucus Slurper" in mechanically ventilated sheep. Crit Care Med 2007;35(3):906-911.
12. Branson RD. Secretion management in the mechanically ventilated patient. Resp Care 2007;52(10):1328-1342.
13. Granja C, Lopes A, Moreira S, Dias C, Costa-Pereira A, Carneiro A; JMIP Study Group. Patients' recollections of experiences in the intensive care unit may affect their quality of life. Crit Care 2005;9(2):R96-R109.
14. Lucchini A, Zanella A, Bellani G, Gariboldi R, Foti G, Pesenti A, Fumagalli R. Tracheal secretion management in the mechanically ventilated patient: comparison of standard assessment and an acoustic secretion detector. Respir Care 2011;56(5):596-603.
15. Kamiyama J, Jesmin S, Sakuramoto H, Shimojo N, Islam MM, Khatun T, et al. Assessment of circulatory and pulmonary endothelin-1 levels in a lavage-induced surfactant-depleted lung injury rabbit model with repeated open endotracheal suctioning and hyperinflation. Life Sci 2014;118(2):370-378.
16. Bailey C, Kattwinkel J, Teja K, Buckley T. Shallow versus deep endotracheal suctioning in young rabbits: pathologic effects on the tracheobronchial wall. Pediatrics 1988;82(5):746-751.
17. Hagler DA, Traver GA. Endotracheal saline and suction catheters: sources of lower airway contamination. Am J Crit Care 1994;3(6):444-447.
18. Graf J, Marini JJ. Do airway secretions play an underappreciated role in acute respiratory distress syndrome? Curr Opin Crit Care 2008;14(1):44-49.
19. Graf J, Mentzelopoulos SD, Adams AB, Zhang J, Tashjian JH, Marini JJ. Semi-quantitative tracking of intra-airway fluids by computed tomography. Clin Physiol Funct Imaging 2009;29(6):406-413.
20. Marini JJ, Gattinoni L. Propagation prevention: a complementary mechanism for "lung protective" ventilation in acute respiratory distress syndrome. Crit Care Med 2008;36(12):3252-3258.
21. Clement A, Hubsch S. Chest physiotherapy by the "bag squeezing" method. Physiotherapy 1968;54:355-359.
22. Denehy L. The use of manual hyperinflation in airway clearance. Eur Respir J 1999;14:958-965.
23. Li J, Zong Y, Zhou Q, Dai H, Wang C. Evaluation of the safety and effectiveness of the rapid flow expulsion maneuver to clear subglottic secretions in vitro and in vivo. Respir Care 2017;62(8):1007-1013.
24. Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truwit JD, et al.; ATS/CHEST Ad Hoc Committee on Liberation from Mechanical Ventilation in Adults. An official American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med 2017;195(1):120-133.