Optimization of Endotracheal Tube Cuff Pressure by Monitoring CO_2 Levels in the Subglottic Space in Mechanically Ventilated Patients: A Randomized Controlled Trial

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BACKGROUND: Many of the complications of mechanical ventilation are related to inappropriate endotracheal tube (ETT) cuff pressure. The aim of the current study was to evaluate the effectiveness of automatic cuff pressure closed-loop control in patients under prolonged intubation, where presence of carbon dioxide (CO_2) in the subglottic space is used as an indicator for leaks. The primary outcome of the study is leakage around the cuff quantified using the area under the curve (AUC) of CO_2 leakage over time.

METHODS: This was a multicenter, prospective, randomized controlled, noninferiority trial including intensive care unit patients. All patients were intubated with the AnapnoGuard ETT, which has an extra lumen used to monitor CO_2 levels in the subglottic space.

The study group was connected to the AnapnoGuard system operating with cuff control adjusted automatically based on subglottic CO_2 (automatic group). The control group was connected to the AnapnoGuard system, while cuff pressure was managed manually using a manometer 3 times/d (manual group). The system recorded around cuff CO_2 leakage in both groups.

RESULTS: Seventy-two patients were recruited and 64 included in the final analysis. The mean hourly around cuff CO_2 leak (mm Hg AUC/h) was 0.22 ± 0.32 in the manual group and 0.09 ± 0.04 in the automatic group ($P = .01$) where the lower bound of the 1-sided 95% confidence interval was 0.05, demonstrating noninferiority (>−0.033). Additionally, the 2-sided 95% confidence interval was 0.010 to 0.196, showing superiority (>0.0) as well. Significant CO_2 leakage (CO_2 >2 mm Hg) was 0.027 ± 0.057 (mm Hg AUC/h) in the automatic group versus 0.296 ± 0.784 (mm Hg AUC/h) in the manual group ($P = .025$). In addition, cuff pressures were in the predefined safety range 97.6% of the time in the automatic group compared to 48.2% in the automatic group ($P < .001$).

CONCLUSIONS: This study shows that the automatic cuff pressure group is not only noninferior but also superior compared to the manual cuff pressure group. Thus, the use of automatic cuff pressure control based on subglottic measurements of CO_2 levels is an effective method for ETT cuff pressure optimization. The method is safe and can be easily utilized with any intubated patient. (Anesth Analg 2017;XXX:00–00)

Appropriate endotracheal tube (ETT) cuff inflation is an important part of the management of any intubated patients.[1,2] An appropriately inflated ETT cuff should achieve isolation of the lower airways, allowing positive pressure ventilation without gas leak, while reducing the risk of secretion aspiration around the cuff, thereby decreasing the risk of ventilator-associated pneumonia (VAP).[1–4] An overinflated cuff may cause mechanical complications: mucosal ischemia, ulcerations, tracheal stenosis, and ultimately tracheoesophageal fistulae.[2] Consequently, the optimal cuff pressure for the specific patient can be defined as the minimal cuff pressure needed to prevent leakage around the cuff.

Several methods/technologies for continuous control of the ETT cuff pressure (Pcuff) are currently used.[1,5,6] While the optimal cuff pressure is a "moving target" based on the specific anatomy, cuff location and peak inspiratory pressure, the current available methods maintain a constant pressure irrespective of individual patient needs.[1] Even in elective surgical patients, new leakage around the ETT cuff

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Conflicts of Interest: See Disclosures at the end of the article.

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develops in 27% of patients due to variety of causes such as increased peak inspiratory pressure, increased muscle tone, inadequate anesthesia, changes of head and neck position, and ETT movement.[7] In the intensive care unit (ICU), patients are expected to be more prone to develop leakages due to prolonged intubations, frequent changes in ventilation parameters, changes in patient position, changes in intra-abdominal pressure, and different degrees of sedation.

Carbon dioxide pressure (Pco_2) proximal to the ETT cuff, in the subglottic space, can be used as an objective biomarker to detect and quantify leakage around the cuff.[7–9] When appropriate sealing is achieved, CO_2 leakage is not expected. A CO_2 level above 2 mm Hg is considered clinically significant since it correlates with leakage of fluid and indicates a higher risk for aspiration of subglottic secretions into the lungs.[7] The AnapnoGuard 100 (AG 100) system (Hospitech Respiration Ltd, Petach-Tikva, Israel) is an innovative ETT cuff management system that continuously monitors and controls cuff pressure (Pcuff) based on CO_2 levels in the subglottic space. When the system operates in its full function, the Pcuff is maintained using automatic feedback loop technology to achieve adequate tracheal sealing with minimum ETT cuff pressures.

The aim of the current study was to evaluate the effectiveness of automatic ETT-cuff pressure control in ventilated ICU patients. This was done by assessing leakage reduction around the cuff in ventilated ICU patients, where subglottic, above the cuff, CO_2 is used as a leak detector. The closed-loop cuff pressure control was performed using the AG system and was compared to the current recommended standard of care, using a manometer to measure Pcuff at least 3 times/d. CO_2 leakage was quantified and compared between study and control groups, using area under the curve (AUC) of valid CO_2 readings recorded over time, normalized by the total time for which patient has valid recordings.

METHODS

This was a multicenter, prospective, double-arm (allocation ratio 1:1), randomized controlled clinical trial at 4 ICUs in Israel: neurosurgery ICU and cardiac surgery ICU at Rambam Medical Center; general ICU at Wolfson Medical Center; and general ICU at Mayanei Hayeshua Medical Center. The study protocol was approved by each center's ethics committee (The study was registered on May 16, 2013, to ClinicalTrials.gov with Identifier: NCT01857986.)

Study Population

Inclusion criteria: ICU patients aged 18 years or older, within 12 hours of tracheal intubation and expected to be intubated for more than 12 hours post-AG 100 system initiation.

Exclusion criteria: facial, oropharyngeal, or neck trauma; body mass index >40; pregnant women; ventilation in prone position; difficult intubation (defined as more than 3 intubation attempts).

A subject was excluded from the study if the subject's legal representatives withdrew consent, a significant protocol deviation occurred or a significant adverse event developed that in the investigator's opinion may have been related to the AG system.

Study Procedures

Subjects were block randomized to automatic or manual groups within center following intubation and before being connected to the AG 100 system. Randomization allocation sequence and block size were automatically generated by software by a company unaffiliated with Hospitech, which was also responsible for data management and statistical analysis. Following informed consent, patients were enrolled and assigned to intervention by medical staff according to the following process: patients in both groups were intubated with the AG ETT, which has an extra lumen used for monitoring CO_2 levels in the subglottic space and an additional suction line (Figure 1). Patients allocated to the study group were connected to the AG 100 system, using all functional modalities: active cuff pressure control, using subglottic CO_2 readings as an indicator for leaks, and automatic, periodic rinsing and suction of subglottic secretions (automatic group). Patients allocated to the control group were connected to the AG 100 system, with automatic, periodical rinsing and suction of subglottic secretions, with cuff pressure control not activated (turned OFF). In the control group (manual group), the system recorded the CO_2 levels in the subglottic space, but cuff pressure was managed manually using a manometer at least 3 times per day, according to standard guidelines (Figure 1). Principal and subinvestigators enrolled the patients to the study. All care providers were blinded to the CO_2 levels detected above the cuff by the AG system.

Patients' demographic and medical information was documented and a chest x-ray was performed daily.

The main functions of the AG 100 system are as follows:

- Automatic continuous closed-loop control of intracuff pressure (Pcuff) using CO_2 measured in the subglottic space as an indicator for leaks.
- Automatic evacuation of subglottic secretions, by synchronized, simultaneous rinsing and suction.

The system operates as a unit when the AG 100 control unit and AG ETT, a multilumen ETT with dual-suction line and an additional CO_2/Vent line (Figure 1), are used together.

The AG 100 system is used for continuous control of cuff pressure via a feedback loop control, using CO_2 levels in the subglottic space as a leak detector (Figure 1). In addition, the system automatically performs programmable subglottic suction of secretions through dual intraluminal embedded suction lumens. Unlike other subglottic suctioning methods (eg, the Continuous Aspiration of Subglottic Secretions [CASS] system),[10,11] where vacuum created in the subglottic space leads to adherence of the suction orifice to the tracheal mucosa, the AG system uses a specially designed ETT that has an extra lumen, minimizing the creation of a vacuum (Figure 1). In addition to the dual-suction lumens, the lumen used for CO_2 readings serves as venting/rinsing line during the suction period. When the subglottic suction is activated, air is forced synchronously through the CO_2 lumen preventing the occurrence of a vacuum. Additionally, the AG 100 system irrigates saline into the subglottic space via the CO_2/vent lumen synchronized with the subglottic suctioning, facilitating secretion removal.

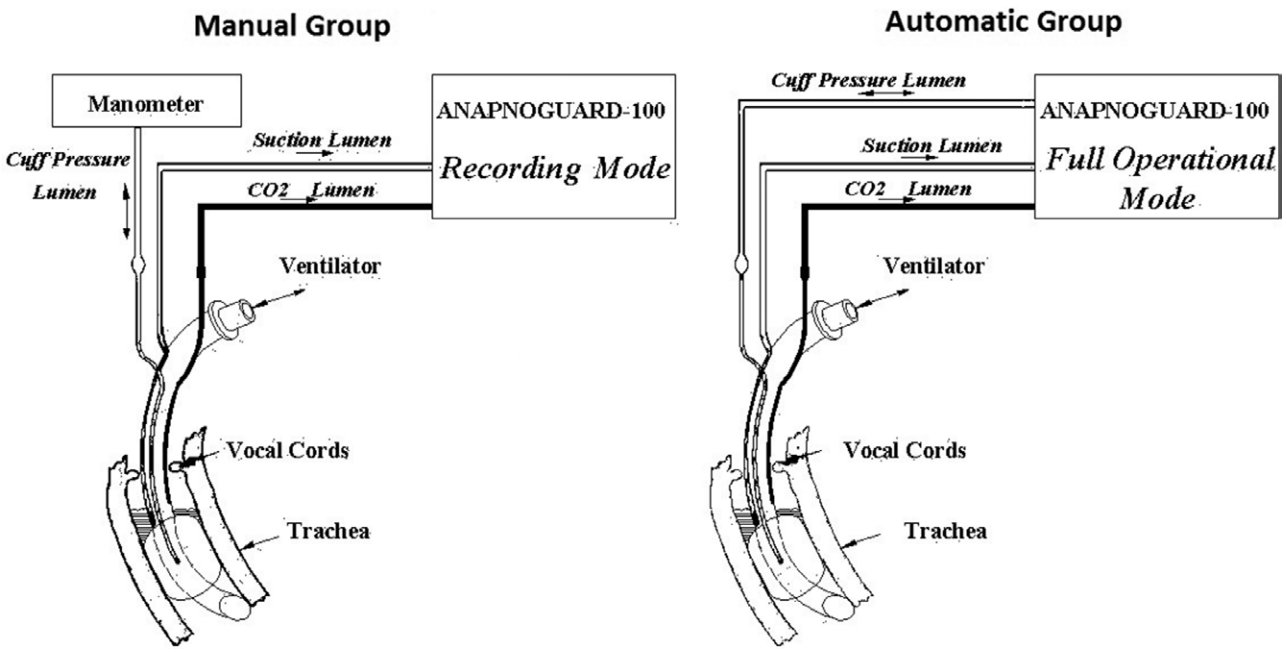

Figure 1. Endotracheal tube cuff pressure control and CO_2 monitoring in the automatic and manual groups. The images are schematic and do not consist real-world scale (ie, the distance between the cuff and vocal cords).

Study End Points

The primary effectiveness end point in this study was AUC of CO_2 leakage measured above the cuff in the subglottic space over time (while patient was connected to the AG system), normalized by total time of valid recordings for each patient; that is, AUC was computed from points on the X-Y coordinates, where X = time and Y = CO_2 leakage.

Secondary end points were (1) number of cuff pressure measurements within the predefined safety range of 24 to 40 cm H_2O; and (2) number of CO_2 leakage readings at or above 2 mm Hg (significant leakages).

Statistical Considerations and Analysis

Numerical variables were tabulated using mean, standard deviation, minimum, median, maximum, and number of observations. Categorical variables were tabulated using number of observations and percentages.

Primary End Point Analysis

AUC of CO_2 leakage over time was computed using the trapezoid rule and standardized by hour; that is, the AUC end point was the total AUC divided by the number of hours recorded. AUC was computed from the curve created by connecting adjacent CO_2 readings by straight line, with the first CO_2 reading reported serving as the first time point.

While the trial was planned and powered for noninferiority of the automatic cuff pressure and group to the manual cuff pressure group (statistical hypotheses specified below), superiority was also assessed after satisfying noninferiority. The automatic cuff pressure group was to be considered superior to the manual cuff pressure group if the 2-sided 95% confidence interval (CI) for the difference of means lies wholly above zero.

Study groups were compared on the primary end points using a 2-sided independent sample *t* test CI with T3 correction proposed by Zhou and Dinh[12] to correct for the skewed AUC distribution. The T3 methodology proposed by Zhou and Dinh[12] improves coverage of CIs of the difference between means, when the original distribution is skewed, and even highly so. The methodology modifies the conventional *t* statistic to remove the effect of skewness, the greater the skewness the greater the adjustment.

In this trial, the noninferiority margin was 0.033 so that noninferiority of the automatic cuff pressure group to the manual cuff group is concluded when the lower confidence bound of the 1-sided 95% CI of the difference (manual-automatic cuff) is greater than −0.033.

Secondary End Point Analysis

The number of cuff pressure measurements within the safety range was normalized per subject using the subject's total number of valid cuff pressure measurements, and the number of CO_2 leakage events at or above 2 mm Hg was normalized per subject using the total time of active intubation (excluding intermediate breaks).

Normalized number of cuff pressure measurements within the safety range was analyzed using Poisson regression. Normalized number of CO_2 leakage events at or above 2 mm Hg was analyzed using zero-inflated negative binomial regression. The rate of events per hour and the ratio between the 2 groups' rates (automatic/manual) were estimated by Poisson regression for cuff pressure measurements within the safety range and zero-inflated negative binomial regression for CO_2 leakage. Automatic group was considered superior to manual group if the 2-sided 95% CI for the ratio was wholly above one.

Sample Size Considerations

Based on predefined US Food and Drug Administration requirements, the study aimed to show that the standardized

AUC of CO_2 leakage of the automatic group was noninferior to that of the manual group using a noninferiority delta of 0.033.

Based on historical data, we assumed that population standardized AUC in treatment is 0.09 (SD = 0.07) and in control, 0.33 (SD = 0.52). Given these assumptions, a sample of N = 30 per group would provide at least 80% power (81.8%) for demonstrating noninferiority of study to control with a noninferiority delta of 0.033 using an 2-sample, independent *t* test with 1-sided alpha = 0.05 on log-transformed AUCs. Data were generated by simulation using historical records. To account for 15% dropouts, the total sample specified was at least 35 patients per group or 70 overall.

This article adheres to the applicable Equator guidelines.

RESULTS

A total of 76 patients were found eligible (Figure 2) and enrolled in the study between September 2013 and March 2015. Trial was terminated when the planned sample size was reached. Three patients were not intubated with the AG tube and therefore not connected to the system, and 1 patient self-extubated before connection to the system. In addition, 3 patients who had less than 1 hour of valid CO_2 recording were excluded, yielding 69 subjects. Five of these patients were excluded from the final analysis due to major protocol violations. Thus, 64 patients were included in the final analysis, 34 in the automatic group and 30 in the manual group (Figure 2).

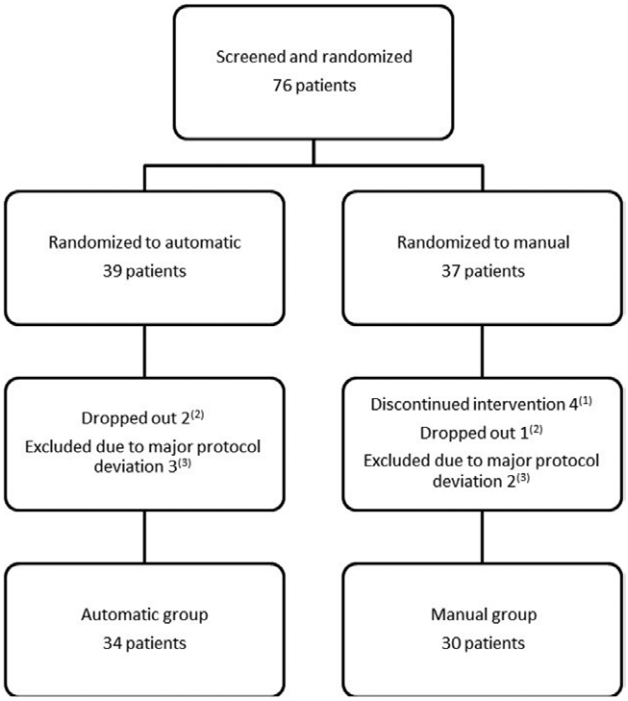

Figure 2. Study flow chart. (1) Discontinued intervention: Three elective intubation patients were not intubated with AnapnoGuard (AG) tube and were therefore not connected to the AG system; one elective intubation patient self-extubated before being connected to the AG system. (2) Excluded: The final analysis included all subjects for whom there was at least 1 hour of valid CO_2 leakage recording and for whom there were no major protocol violations likely to affect the outcome. Majority of protocol violations were determined by review prior to data lock.

Patient Baseline Characteristics

Baseline patient characteristics, total connection time to the AG system, and total connection time in clinical mode (CO_2 readings) are detailed in Table 1. The difference between the groups on peak inspiratory pressure, 23.6 ± 3.4 cm H_2O and 20.7 ± 4.6 cm H_2O in automatic and manual groups, respectively, was not expected to impact study outcome.

Primary and Secondary Outcome Results

Cuff leakage was defined in 2 ways: (a) any time-standardized leakage AUC (ie, of any CO_2 level) and (b) significant leakage—time-standardized AUC when CO_2 leakage exceeded 2 mm Hg

(a) CO_2 leakage in the automatic group was 0.09 ± 0.04 (mm Hg AUC/h) vs 0.22 ± 0.32 (mm Hg AUC/h) in the manual group (P = .01; Table 2, Figure 3), where the lower bound of the 1-sided 95% CI is 0.05. This result demonstrates the noninferiority of the automatic group to the manual group, since the lower confidence bound is greater than the noninferiority limit of −0.033. The 2-sided 95% CI is 0.010 to 0.196, the lower bound of which is above zero, indicating superiority as well.

(b) Significant CO_2 leakage was 0.027 ± 0.057 (mm Hg AUC/h) in the automatic group versus 0.296 ± 0.784 (mm Hg AUC/h) in the manual group (P = .025).

The normalized number of cuff pressure measurements within the safety range, estimated by the regression was 0.977 for the automatic group and 0.482 for the manual

Table 1. Baseline Patient Characteristics

Parameter	Automatic Group (n = 34)	Manual Group (n = 30)
General parameters (±SD)		
Sex, % (M/F)	67.4/32.4	60/40
Age, y	65.0 (±18.8)	66.7 (±11.2)
Weight, kg	78.6 (±12.6)	77.5 (±17.7)
Height, cm	167.3 (±10.4)	165.3 (±9.3)
BMI, kg/m^2	28.0 (±4.1)	28.5 (±6.6)
Reasons for admission, n (%)		
Postsurgery	21 (61.7)	21 (70)
Pneumonia	5 (14.7)	4 (13.3)
Head injury	2 (5.8)	1 (3.3)
Septic shock	3 (8.8)	2 (6.6)
Other	3 (8.8)	2 (6.6)
Ventilation, mean (±SD)		
Peak inspiratory pressure, cm H_2O	23.6 (±3.4)	20.7 (±4.6)
Mean peak end-expiratory pressure (PEEP), cm H_2O	5.7 (±3.3)	5.3 (±2.5)
Mean respiratory rate, breaths/min	10.5 (±4.0)	10.0 (±3.9)
Spo_2, %	97.1 (±3.7)	96.2 (±9.3)
Mean Pao_2, mm Hg	146.8 (±95.3)	167.6 (±98.8)
Fraction of inspired oxygen (Fio_2), mm Hg	62.2 (±30.3)	73.9 (±23.4)
End-tidal ($Etco_2$), mm Hg	35.1 (±4.8)	36.7 (±4.8)
Total connection time to the AnapnoGuard system (±SD)		
Total connection time, h	3199.95	3018.30
Per patient mean, h	94.1 (±152.8)	100.6 (±191.8)
Total connection time, h	2725.4	2782.7
Per patient mean, h	80.2 (±138.3)	92.8 (±190.3)

Abbreviations: BMI, body mass index; F, female; M, male; SD, standard deviation.

Table 2. Efficacy End Points

Parameter	Automatic Group (n = 34)	Manual Group (n = 30)	*P* Value
Any CO_2 leak			
Mean AUC (AUC/h) ± SD	0.09 (±0.04)	0.22 (±0.32)	.01[a]
Significant leakages (CO_2 ≥ 2 mm Hg)			
Mean AUC (AUC/h) ± SD	0.003 (±0.01)	0.072 (±0.22)	.025
Mean duration of significant leakage (minutes/leakage event)	4.61 (±3.53)	34.53 (±83.27)	.005
Cuff pressure measurements within the predefined safety range			
Cuff pressure measurements within the safety range	97.6%	48.2%	<.001
Cuff pressure measurement <24 cm H_2O	0.7%	38.8%	<.001
Cuff pressure measurement >40 cm H_2O	1.7%	13%	<.001
Subglottic evacuation of secretions			
Net evacuated secretions (mL/d)	149.7±197	132.9±351	.029

Abbreviations: AUC, area under the curve; SD, standard deviation.
[a]Lower bound of confidence interval of the difference is 0.05, which is above the noninferiority criterion (−0.033) and meets superiority as well (0).

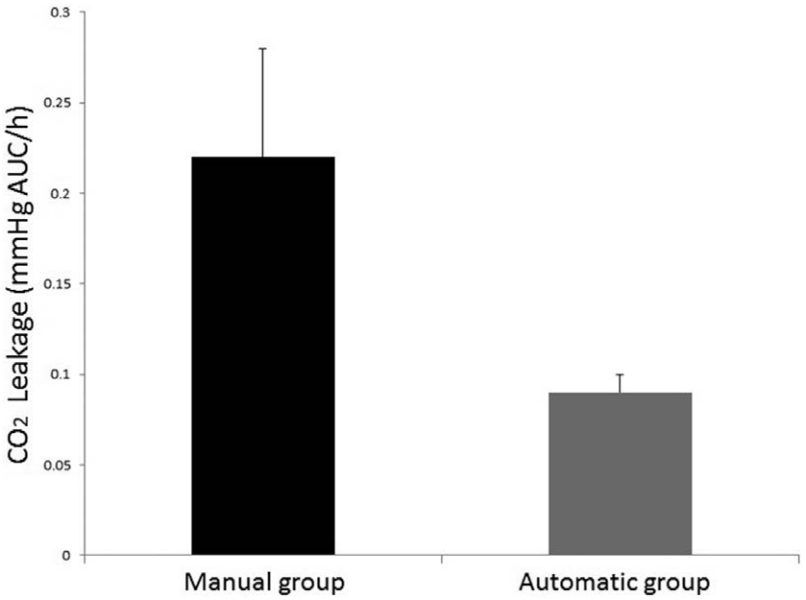

Figure 3. Leakage around the endotracheal tube cuff. Leakage around the endotracheal tube cuff-normalized per hour general area under the curve (AUC) of any CO_2 level. Data are presented as mean ± standard error of mean.

group. The estimated ratio between the 2 rates was 2.03 (95% CI, 1.67–2.46), which estimates the rate of cuff pressure measurements within the safety range in the automatic group was around 2 times greater than in the manual group ($P < .001$).

Time to identification and resolution of significant leak was longer in the manual group compared to the automatic group (Figure 4). Once a significant leak was detected, the mean time until sealing was 4.6 ± 3.5 minutes in the automatic group versus 34.5 ± 83.2 minutes in the manual group ($P = .005$).

The normalized number of CO_2 leakage events at or above 2 mm Hg was 0.056 in the automatic group and 0.628 in the manual group. The estimated ratio between the 2 rates was 0.09 with CI of 0.03–0.25, showing that the AG 100, while operating in full clinical mode, significantly reduced the rate of CO_2 leakage events ($P < .001$).

Other Analyses

Evacuation of Subglottic Secretions. The AG 100 system, when connected to multilumen ETT with dual-suction lumens line and an additional CO_2/vent line lumen, performed effective evacuation of subglottic secretions in both groups (Table 2). The amount of evacuated secretions was statistically significantly higher in the automatic group, but this may not have been clinically significant (140 ± 191 mL/d vs 137.3 ± 344 mL/d; $P = .029$).

Cuff Pressure. The Pcuff measurements were in the predefined safety range 97.6% of the time in the automatic group compared to 48.2% of the time in the manual group, $P < .001$ (Table 2; Supplemental Digital Content, Appendix, http://links.lww.com/AA/B945). In the manual group, Pcuff dropped below 24 cm H_2O 38.8% of the time and went above 40 cm H_2O 13% of the time.

Safety. No significant device (AG system) related adverse events were detected or reported, in either group, throughout the study.

DISCUSSION

Many of the complications related to tracheal intubation and mechanical ventilation are related to ETT cuff management. Multiple factors influence the pressure needed to achieve airway isolation, rendering cuff pressure and its appropriate management a dynamic activity.[1] This study

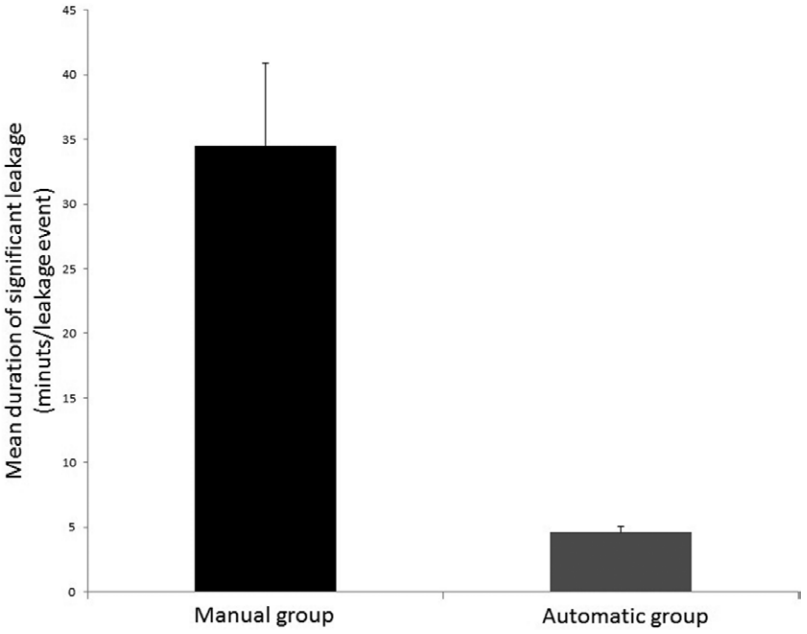

Figure 4. Time to identification of significant leakage and reoptimization of the endotracheal tube (ETT) cuff. Significant leakage—CO_2 leakage exceeded 2 mm Hg. Data are presented as mean ± standard error of mean.

used CO_2 levels, in the subglottic space, as an objective indicator to detect leaks around the cuff. The study clearly demonstrated that the standard, nonobjective cuff pressure measurement 3 times per day, using a manometer (manual group) is not adequate. Continuous, automatic closed-loop cuff pressure control driven by CO_2 monitoring in the subglottic space can be used safely and effectively to optimize ETT cuff pressure.

The provision of mechanical ventilation can be divided into 2 parts: ventilator to ETT tube and the ETT, including ETT cuff interaction with the patient. While the newest ventilators include state of the art electronics, mechanics, and software for appropriate control, the ETT has lagged behind with some improvement in cuff design and some ability to evacuate secretions with no objective automatic adjusted control of cuff pressure. The detection of leak around ETT cuff is relatively rudimentary: auscultation over the larynx or volumetric calculations via a difference in inspired and expired volumes. The current recommendations are that cuff pressure will be kept within recommended limits according to these parameters by measuring Pcuff and adjusting it 3 times/d, while attempting to use the 2 techniques above. The current study clearly proves that using an objective indicator with an automatic closed-loop control can significantly reduce the occurrence of leak by 59% and the risk for significant leak (correlated with secretion leakages) by 96%. While the incidence and occurrence of VAP and its sequelae were beyond the scope of the current study, prevention of subglottic secretion aspiration is a major part of any VAP prevention strategy.[4,13,14]

A Pcuff above 24 cm H_2O (18 mm Hg) is recommended to prevent leakage around the ETT cuff and to decrease the rate of VAP.[15] However, a cuff pressure higher than 40 cm H_2O (30 mm Hg) may increase the risk of pressure necrosis.[1] Additionally, hemodynamically unstable patients may have tissue perfusion pressures that are significantly reduced secondary to the disease process and/or the use of vasoconstrictors resulting in mucosal ischemia at lower Pcuff (<30 cm H_2O).[1,16] Adequate tracheal sealing should therefore be achieved at the lowest possible Pcuff. Most ETTs used today have high-volume low-pressure cuffs, which during prolonged intubation, may lead to over- or underinflation depending on different individual ventilation parameters.[1,17–19] This permeability effect was clearly demonstrated in the current ICUs study cohort. In the manual group, even though the cuff pressure was set by manometer within a predefined safety range at least 3 times per day, overinflation was indicated in 13% of the measurements and underinflation was indicated in 38.8% of the measurements.

Evacuation of subglottic secretions is an additional important element of the treatment of an intubated patient. Moreover, to achieve appropriate CO_2 readings, the distal opening of the CO_2 line, located just above the cuff in the subglottic space, should be free from secretions. It is known that CASS and Intermittent CASS (ICASS) methods that suction from the subglottic space may cause trauma and negative squeal to the tracheal mucosa.[10,11] To overcome the hazards related to vacuum in the subglottic space, in the current study a specially designed ETT that has an additional 2 lumens was used (Figure 1). When the subglottic suction is activated, the other lumen, used for CO_2 reading, is opened and air is pumped inside. Hazardous subglottic vacuum is prevented and tracheal mucosa adherence is avoided, minimizing punctuated suction lesions. The AG system also irrigates the subglottic space, via this extra lumen, synchronized with the evacuation process. This dilution of the secretions facilitates suction evacuation and dilutes the bioburden of any fluid left in the subglottic space.

The study has several limitations, the first relates to study end points. Specifically, while inappropriate sealing and around cuff aspiration of bacteria is well recognized as the leading cause of VAP, estimation of VAP rates was beyond the scope of this study. Future clinical studies, using larger samples and different inclusion criteria (eg, normal chest x-ray at intubation), are needed to evaluate the effect of the AG on VAP occurrence. In addition, there

are a variety of automatic cuff pressure controllers, based on other technologies, available on the market, and further clinical studies are needed to compare the efficacy of those technologies/devices with the AG system, which utilizes the above cuff CO_2 as a biomarker for inappropriate cuff sealing.

In conclusion, the use of automatic cuff pressure control based on subglottic measurements of CO_2 levels is an effective method for continuous monitoring and optimization of the ETT cuff pressure. The method is safe, and it can be easily utilized with any intubated patient.

DISCLOSURES

Name: Shai Efrati, MD.
Contribution: This author is responsible for the study design and study protocol, per the requirements of the US Food and Drug Administration agency, helped interpret the study results and write the first and final drafts of the manuscript.
Conflicts of Interest: Shai Efrati is a shareholder at Hospitech Respiration Ltd, the company which manufactures the AnapnoGuard 100 system and ETTs used in this study.
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Conflicts of Interest: None.
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Contribution: This author is responsible for patient enrollment and follow-up at the Department of Neurosurgery, Rambam Medical Center, and helped review the manuscript.
Conflicts of Interest: None.
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Name: Ludmila Guralnik, MD.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
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Conflicts of Interest: None.
Name: William T. Denman, MD, PhD.
Contribution: This author is a major contributor to the study design and helped interpret the study results and actively participate in writing the manuscript.
Conflicts of Interest: None.
Name: Gabriel M. Gurman, MD.
Contribution: This author is a major contributor to the study design and helped interpret the study results and actively participate in writing the final version of the manuscript.
Conflicts of Interest: None.
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