ANESTHESIOLOGY

Airway Closure during Surgical Pneumoperitoneum in Obese Patients

Domenico Luca Grieco, M.D., Gian Marco Anzellotti, M.D., Andrea Russo, M.D., Filippo Bongiovanni, M.D., Barbara Costantini, M.D., Marco D'Indinosante, M.D., Francesco Varone, M.D., Fabio Cavallaro, M.D., Lucia Tortorella, M.D., Lorenzo Polidori, M.D., Bruno Romanò, M.D., Valerio Gallotta, M.D., Antonio Maria Dell'Anna, M.D., Liliana Sollazzi, M.D., Giovanni Scambia, M.D., Giorgio Conti, M.D., Massimo Antonelli, M.D.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Airway closure has been described in chronic obstructive pulmonary disease, acute respiratory distress syndrome, and cardiac arrest patients
- This phenomenon makes tidal inflation start only after a critical airway opening pressure is overcome
- Although previously reported during general anesthesia, airway closure was partially misinterpreted

What This Article Tells Us That Is New

- Airway closure affects a relevant proportion of obese patients undergoing general anesthesia in supine position, with a variable degree of airway opening pressure
- With Trendelenburg pneumoperitoneum, airway opening pressure increases consistently with esophageal pressure and pneumoperitoneum insufflation pressure: consequently, transalveolar pressure, lung volumes, and alveolar recruitment do not vary
- Airway closure yields bedside misinterpretation of respiratory mechanics and underestimation of actual alveolar pressure in the intraoperative setting
- It is an occult phenomenon that generates an airway pressure threshold, whereby inspiratory gas does not inflate the lung unless the airway opening pressure is exceeded

ABSTRACT

Background: Airway closure causes lack of communication between proximal airways and alveoli, making tidal inflation start only after a critical airway opening pressure is overcome. The authors conducted a matched cohort study to report the existence of this phenomenon among obese patients undergoing general anesthesia.

Methods: Within the procedures of a clinical trial during gynecological surgery, obese patients underwent respiratory/lung mechanics and lung volume assessment both before and after pneumoperitoneum, in the supine and Trendelenburg positions, respectively. Among patients included in this study, those exhibiting airway closure were compared to a control group of subjects enrolled in the same trial and matched in 1:1 ratio according to body mass index.

Results: Eleven of 50 patients (22%) showed airway closure after intubation, with a median (interquartile range) airway opening pressure of 9 cm H_2O (6 to 12). With pneumoperitoneum, airway opening pressure increased up to 21 cm H_2O (19 to 28) and end-expiratory lung volume remained unchanged (1,294 ml [1,154 to 1,363] *vs.* 1,160 ml [1,118 to 1,256], $P = 0.155$), because end-expiratory alveolar pressure increased consistently with airway opening pressure and counterbalanced pneumoperitoneum-induced increases in end-expiratory esophageal pressure (16 cm H_2O [15 to 19] *vs.* 27 cm H_2O [23 to 30], $P = 0.005$). Conversely, matched control subjects experienced a statistically significant greater reduction in end-expiratory lung volume due to pneumoperitoneum (1,113 ml [1,040 to 1,577] *vs.* 1,000 ml [821 to 1,061], $P = 0.006$). With airway closure, static/dynamic mechanics failed to measure actual lung/respiratory mechanics. When patients with airway closure underwent pressure-controlled ventilation, no tidal volume was inflated until inspiratory pressure overcame airway opening pressure.

Conclusions: In obese patients, complete airway closure is frequent during anesthesia and is worsened by Trendelenburg pneumoperitoneum, which increases airway opening pressure and alveolar pressure: besides preventing alveolar derecruitment, this yields misinterpretation of respiratory mechanics and generates a pressure threshold to inflate the lung that can reach high values, spreading concerns on the safety of pressure-controlled modes in this setting.

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Airway closure is a lack of communication between proximal airways and alveoli due to airway collapse. When this phenomenon is present, tidal inflation starts only after a critical airway opening pressure is overcome and airway pressure at end expiration does not reflect alveolar pressure, with some alveoli still inflated with higher pressure not transmitted to airway opening.[1]

Airway closure has been suggested as a mechanism driving expiratory flow limitation in mechanically ventilated patients with asthma and chronic obstructive pulmonary disease.[2,3] Recently, it has been systematically defined and its occurrence described in up to 20% of patients with acute respiratory distress syndrome.[1,4] These patients show a pronounced inflection point in the inspiratory limb of the respiratory system pressure–volume curve obtained during low-flow inflation. Below this pressure, the compliance of

the system equals compliance of an occluded respiratory circuit, and the increase in airway pressure does not yield any change in esophageal pressure (P_{ES}), suggesting that no changes in lung volume are occurring. This allows the hypothesis that below this "critical point" (*i.e.*, the airway opening pressure), no gas is inflated in the lung because of an obstacle distal to the respiratory circuit but proximal to alveoli, which was hence defined airway closure.[1] A case report recently confirmed that this mechanical pattern may be dependent on airway collapse, as electrical impedance tomography showed that, effectively, any increase in airway pressure below airway opening pressure is not accompanied by lung inflation.[5] During general anesthesia, a similar phenomenon has been reported in obese patients undergoing abdominal surgery but was interpreted as an airway pressure threshold to generate positive transpulmonary pressure.[6,7]

Among the procedures of a clinical trial in obese patients undergoing robot-assisted laparoscopic surgery in the Trendelenburg position, we measured end-expiratory lung volume, respiratory, and lung mechanics before and after surgical pneumoperitoneum induction. During this study, we noticed that some patients exhibited a pressure-volume curve profile compatible with airway closure, with some of them having an airway opening pressure that reached high values after pneumoperitoneum was instituted in Trendelenburg position.

We hypothesized that these patients could have a peculiar physiologic behavior during general anesthesia, paralysis, and mechanical ventilation. We therefore conducted a study to report the occurrence of airway closure in obese patients undergoing robotic gynecological surgery, comparing their respiratory mechanics with those of matched control subjects who were enrolled in the same trial but did not show any airway closure phenomenon.

Materials and Methods

This analysis was conducted on patients enrolled in the ongoing randomized study "Intraoperative protective ventilation for obese patients undergoing gynecological laparoscopic surgery," which is aimed at assessing the effects of a composite strategy providing low tidal volumes (V_T), higher positive end-expiratory pressure (PEEP), and scheduled recruitment maneuvers on postoperative oxygenation. The study was approved by the local ethics committee and is conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in the trial and data analysis; the study protocol was registered at clinicaltrials.gov (NCT03157479).

Patients

All adult morbidly obese patients (body mass index greater than 35 kg/m^2) scheduled for gynecological laparoscopic and/or robot-assisted surgery in the Trendelenburg position were considered eligible for inclusion in this trial. Main exclusion criteria were clinical history or signs of chronic heart failure, history of neuromuscular disease, history of thoracic surgery, pregnancy, and chronic respiratory failure requiring any kind of domiciliary respiratory support.

Among patients enrolled in the trial, we identified those who showed airway closure during respiratory mechanics assessment after intubation in the supine position. Airway closure was diagnosed on the low-flow inflation pressure-volume curve of the respiratory system conducted after prolonged exhalation, according to the criteria proposed by Chen *et al.*1 Airway closure was diagnosed when the pressure-volume curve exhibited a pronounced lower inflection point and the compliance (ratio of inflated volume to pressure change) of its initial flat part equaled the one of an occluded respiratory circuit, which was measured by the ventilator during the pre-use self-test and always ranged between 1.5 and 2.5 ml/cm H_2O (figs. 1 and 2). In the current study, we compared affected subjects with a control group of patients who had been enrolled in the same study, who did not show any airway closure phenomenon and were matched to affected subjects in a 1:1 ratio, according to the body mass index (±2 kg/m^2). If in the control group more than one patient met this criterion, the one with body mass index closest to the case subject was included.

Procedures

All patients enrolled in the trial underwent pulmonary function testing at hospital admission. During surgery, patients received total intravenous anesthesia with full paralysis according to a standard protocol that included the following: propofol 2 mg/kg for induction of anesthesia and 6 to 8 mg · kg^{-1} · h^{-1} for maintenance, titrated to keep a bispectral index value between 35 and 45%; fentanyl 8 mcg/kg in divided doses; rocuronium bromide 0.6 to 0.8 mg/kg for induction and then administered to ensure a profound neuromuscular block, as assessed by train-of-four monitoring and absence of inspiratory swings on esophageal pressure tracing; and 3 to 5 ml · kg^{-1} · h^{-1} of intravenous balanced crystalloids administered throughout the whole surgical procedure. Fluid boluses or amine (*i.e.*, norepinephrine, ephedrine, dobutamine) administration were allowed if deemed necessary by the attending anesthesiologist to maintain cardiac output and hemodynamic parameters within the physiologic range.

All patients were intubated and connected to a gas-compressed–based mechanical ventilator equipped with a tool for

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Submitted for publication August 10, 2018. Accepted for publication January 29, 2019. From the Department of Anesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart (D.L.G., G.M.A., A.R., F.B., F.C., L.P., B.R., A.M.D., L.S., G.C., M.A.); Anesthesia, Emergency and Intensive Care Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS (D.L.G., G.M.A., A.R., F.B., F.C., L.P., B.R., A.M.D., L.S., G.C., M.A.); Department of Obstetrics and Gynecology, Catholic University of The Sacred Heart (B.C., M.D., L.T., V.G., G.S.); Gynecologic Oncology, Fondazione Policlinico Universitario A. Gemelli IRCCS (B.C., M.D., L.T., V.G., G.S.); Department of Internal Medicine, Catholic University of The Sacred Heart (F.V.); and Respiratory Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS (F.V.), Rome, Italy.

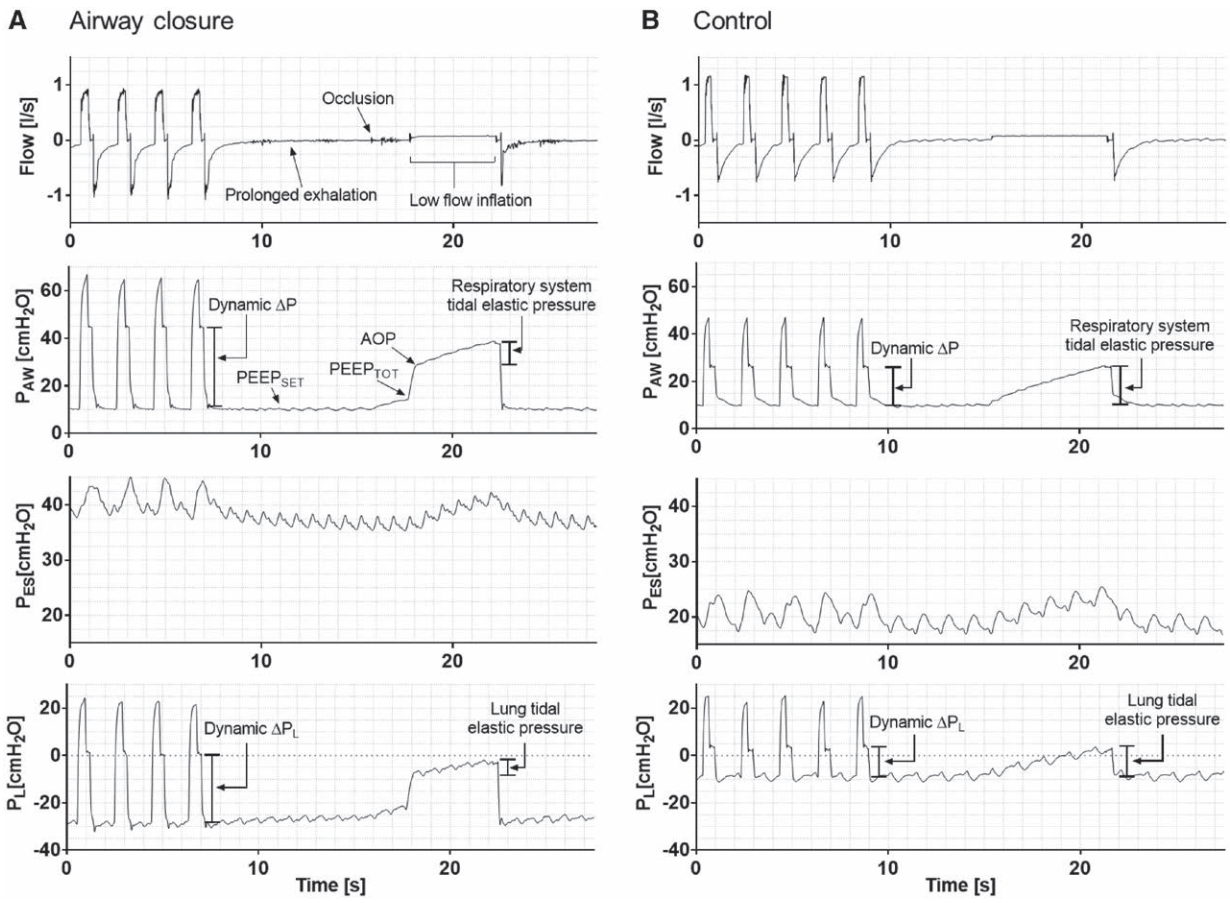

Fig. 1. Flow, airway pressures (P_{AW}), esophageal pressures (P_{ES}), and transpulmunary pressures (P_L) during low-flow inflation from one patient with (*A*) and without (*B*) airway closure after pneumoperitoneum institution. Airway closure/opening can be detected during a low-flow inflation after prolonged exhalation and end-expiratory occlusion. Airway opening is evident on the P_{AW} tracing as a brisk change in steepness of the pressure-time curve during low-flow inflation. Note that the airway opening pressure (AOP) is higher than set and total positive end-expiratory pressure ($PEEP_{SET}$ and $PEEP_{TOT}$, respectively), suggesting that AOP and intrinsic PEEP are different phenomena, although commonly coexisting. As P_{AW} overcomes AOP, gas is delivered to the alveoli and pressure starts to rise according to respiratory system compliance (fig. 2). Because lung inflation starts only after AOP is overcome, also P_{ES} increases only after this critical opening pressure is overcome. This phenomenon is absent in control patients, who show a linear increase in P_{AW}, P_{ES}, and P_L immediately after inflation starts. During tidal ventilation, patients with airway closure are hardly identifiable.

lung volume measurement (Carescape R860, General Electrics HealthCare, USA) and received volume-controlled ventilation with V_T and PEEP set according to the assigned protocol. In the protective ventilation arm, V_T was set at 6 ml/kg of predicted body weight (calculated as $45.5 + 0.91 \cdot [\text{height} - 152.4]$), PEEP 10 cm H_2O and scheduled recruitment maneuvers were performed; in the standard ventilation arm V_T was set at 10 ml/kg predicted body weight and PEEP 5 cm H_2O. In both groups, inspiratory flow was set at 1 l/s, and inspiratory pause at 0.3 s. Fraction of inspired oxygen (FIO_2) was titrated to obtain an oxygen saturation measured by pulse oximetry greater than or equal to 94%. Respiratory rate was set to maintain end-tidal carbon dioxide was between 30 and 40 mmHg for the whole duration of the study.

After intubation, a polyfunctional nasogastric tube provided with an esophageal balloon (Nutrivent, Sidam, Italy) was placed and secured in all patients to measure esophageal pressure and estimate transpulmonary pressure. The signal was validated according to the most recent recommendations both before and after pneumoperitoneum induction and Trendelenburg position.[8–10]

At the end of surgery, all patients were extubated and received oxygen therapy with a 40% FIO_2 VenturiMask (FIAB, Florence, Italy) in the semirecumbent position. After 1 h and on day 1 after surgery, patients were reassessed with arterial blood gas analysis and clinical evaluation. All patients underwent postoperative pulmonary function testing on day 2 after surgery.

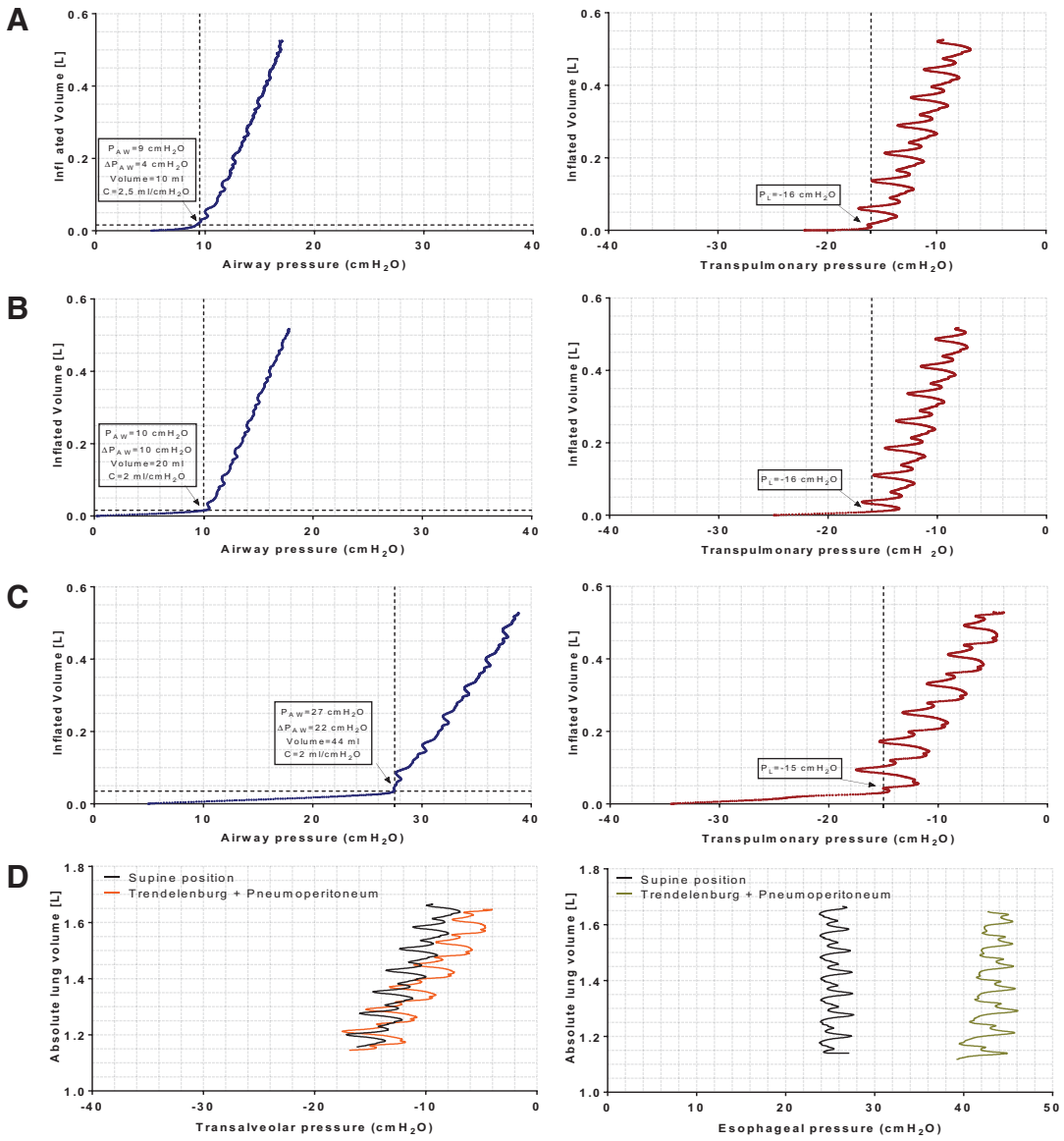

Fig. 2. (*A–C; left*) Airway pressure-volume curves during low-flow inflation before pneumoperitoneum in the supine position (starting from zero end-expiratory pressure [*B*] and positive end-expiratory pressure [PEEP] = 5 cm H_2O [*A*]) and after pneumoperitoneum in the Trendelenburg position (starting from PEEP = 5 cm H_2O [*C*]). In the box, we report the pressure (ΔP_{AW}) and volume changes along with the corresponding compliance (C) between start of inflation and airway opening pressure (AOP). Note that this compliance suggests gas compression in an occluded circuit and, hence, complete airway closure.[1] Note that, as described in the main text, pneumoperitoneum increases the AOP (and hence the inflation volume needed to overcome it). (*A–C*; *right*) Transpulmonary pressure-volume curves during low-flow inflation before pneumoperitoneum in the supine position (starting from zero end-expiratory pressure [*B*] and PEEP = 5 cm H_2O [*A*]) and after pneumoperitoneum in the Trendelenburg position (starting from PEEP = 5 cm H_2O [*C*]). Transpulmonary pressure (P_L) at which AOP is overcome (reported in the *box*) remains constant after pneumoperitoneum induction, as AOP increases consistently with the rise in esophageal pressures (P_{ES}). In other words, the pneumoperitoneum inflation pressure is transmitted to the pleural space, thus increasing P_{ES} and AOP in a consistent manner. (*D*) Multiple pressure-volume curves of the transalveolar pressure (*i.e.*, transpulmonary pressure with patent airways, *left*) and P_{ES} (*right*) recorded during low-flow inflation and plotted starting from measured end-expiratory lung volume, before pneumoperitoneum in the supine position and after pneumoperitoneum in the Trendelenburg position, respectively. The absence of change in the transalveolar pressure-volume curve indicates that lung recruitment is unmodified, while the esophageal pressure-volume curves show a shift that describes the change in the conditions of the chest wall after pneumoperitoneum: end-expiratory P_{ES} is raised by 18 cm H_2O, and chest wall compliance is reduced.

Measurements

End-expiratory lung volume, static respiratory mechanics, and pressure-volume curves during low-flow inflation (5 l/min) after 6 to 8 s of prolonged exhalation were recorded after intubation in the supine position and 15 min after pneumoperitoneum in the Trendelenburg position. End-expiratory lung volume was measured through a modified technique during nitrogen wash-out (20% F_{IO_2} increase) and wash-in (20% F_{IO_2} decrease), as previously described.[11,12] Wash-out and wash-in data were averaged automatically and considered valid if the difference between the two was less than 20% (cut-off determined by the manufacturer).

A Fleisch-type pneumotacograph (n.2, Metabo, Switzerland) and a pressure transducer measured (sample rate = 200 Hz) flow and airway pressure, which were transmitted to an analog-digital converter together with esophageal pressure. Tidal volume was calculated by digital integration of the expiratory flow signal. All the signals were recorded and reviewed offline through a dedicated software (ICU Lab, Kleistek, Italy). Airway plateau pressure (P_{PLAT}) and end-inspiratory esophageal pressure ($P_{ESend\text{-}insp}$) were measured during 0.5-s end-inspiratory occlusion, total PEEP ($PEEP_{TOT}$) and end-expiratory esophageal pressure ($P_{ESend\text{-}exp}$) during end-expiratory hold.

End-inspiratory and end-expiratory transpulmonary pressures were computed as airway pressure minus esophageal pressure ($P_{Lend\text{-}insp}$ and $P_{Lend\text{-}exp}$, respectively). Airway driving pressure (ΔP) was calculated as P_{PLAT}–$PEEP_{TOT}$ and transpulmonary driving pressure (ΔP_L) as $P_{Lend\text{-}insp}$–$P_{Lend\text{-}exp}$. Respiratory system and lung static compliance (C_{RS} and C_L, respectively) were defined as $V_T/\Delta P$ and $V_T/\Delta P_L$, respectively, while static chest wall compliance (C_{CW}) was computed as $V_T/(P_{ESend\text{-}insp}\text{–}P_{ESend\text{-}exp})$.[13] End-inspiratory transpulmonary pressure was also calculated with the elastance-derived method ($P_{Lel\text{-}der}$) as $P_{PLAT}\cdot(\Delta P_L/\Delta P)$.[14] Dynamic ΔP and C_{RS} were calculated from set PEEP and P_{PLAT} measured after the 0.3-s inspiratory pause. These are commonly displayed by ventilators during ventilation and were used as surrogates for respiratory mechanics assessment or clinical interventions in several studies on this topic.[15–20]

As shown in figure 1, respiratory system tidal elastic pressure was defined as the total increase in alveolar pressure due to tidal volume and was calculated on the respiratory system pressure-volume curve as end-inspiratory pressure minus $PEEP_{TOT}$ or, in case of airway closure, airway opening pressure (no patient exhibited a drop in the airway pressure after airway opening pressure was overcome during low-flow inflation). Lung tidal elastic pressure (*i.e.*, the increase in transalveolar pressure due to V_T) was measured in a similar fashion on the transpulmonary pressure-volume curve. Respiratory system and lung linear compliances (linear C_{RS}, C_L) were calculated as the slope of the steeper segment of the respiratory system and transpulmonary pressure-volume curve, respectively.[21,22]

Statistical Analysis

No statistical power calculation was conducted before the study, and the sample size was based on the available data from patients enrolled in the trial. Continuous data are expressed as median (interquartile range), and qualitative data as number of events (%).

Comparisons between patients with and without airway closure (before and after pneumoperitoneum) were performed with the Mann–Whitney test or the Fisher exact test, as appropriate. Intragroup comparisons between measurement in the supine and Trendelenburg position, before and after pneumoperitoneum, respectively, were conducted with the Wilcoxon rank sum test. Mean differences (95% CI) are displayed for most clinically significant results. Correlation between continuous variables was assessed with Spearman correlation: rho and the *P* value are reported. No correction was made for multiple comparisons.

Results with a two-tail *P* value less than 0.05 are considered statistically significant. Statistical analysis was performed with SPSS v. 20.0 (IBM Corp. Released 2011. IBMSPSS Statistics for Windows, Version 20.0, IBM Corp., USA). Manuscript figures were prepared with GraphPad Prism (GraphPad Software, USA).

Results

Between May 2017 and June 2018, 50 patients were enrolled in the clinical trial. Airway closure with a variable degree of airway opening pressure after intubation in the supine position was diagnosed in 11 patients (22%), who were matched with 11 unaffected patients with similar body mass index who represent the control group. There were no missing data regarding the analyzed variables.

All patients received laparoscopic/robotic surgery in the Trendelenburg position (25 to 30°): surgical pneumoperitoneum was obtained by insufflation of carbon dioxide at constant pressure of 12 mmHg, which approximately corresponds to 16 cm H_2O.

Baseline Characteristics

Demographics and most relevant clinical characteristics are displayed in table 1 and were not different between patients with and without airway closure. Neither preoperative nor postoperative respiratory function was different between patients with and without airway closures, being within the physiologic range for most of them. No differences were found regarding preoperative or postoperative gas exchange. Intraoperative ventilator settings and hemodynamic parameters are displayed in table 2. Main results of the study are reported in table 3.

Airway Opening Pressure

In patients with airway closure, after intubation in the supine position, pressure-volume curve of the airway pressure exhibited various degree of airway opening pressure (median value, 9 [interquartile range, 6 to 12] cm H_2O), with complete airway closure when airway pressure was below this threshold (representative ventilator tracings in

Table 1. Demographics and Clinical Characteristics of Enrolled Patients

	Airway Closure (n = 11)	Control (n = 11)	*P*
Age, yr	62 [56–69]	62 [52–67]	0.339
Female sex, n (%)*	11 (100)	11 (100)	n/a
Height, cm	160 [157–165]	159 [157–164]	0.425
Weight, kg	110 [95–130]	106 [102–120]	0.974
Body mass index, kg/m^2	41 [39–49]	41 [39–47]	0.895
Predicted body weight, kg	52 [50–57]	52 [50–56]	0.425
Comorbidities, n (%)			
Hypertension	9 (82)	6 (55)	0.361
Tobacco use	1 (9)	1 (9)	> 0.999
Diabetes	3 (27)	3 (27)	> 0.999
Preoperative respiratory function†			
Forced vital capacity, % of predicted value	106 [104–114]	100 [94–112]	0.119
FEV_1, % of predicted value	105 [92–112]	96 [83–109]	0.238
Tiffeneau–Pinelli index, %	80 [76–84]	81 [77–85]	0.653
Preoperative gas exchange‡			
Pao_2/Fio_2, mmHg	419 [400–438]	390 [338–467]	0.742
$Paco_2$, mmHg	37 [36–39]	36 [34–41]	0.409
HCO_3^-, mEq/l	29 [26–30]	28 [26–30]	0.765
Type of surgery, n (%)			0.783
Hysterectomy	11 (100)	11 (100)	
Annessiectomy	9 (82)	10 (91)	
Lymphadenectomy	4 (36)	6 (55)	
Randomization arm, n (%)			0.670
Standard ventilation	7 (64)	5 (45)	
Protective ventilation	4 (36)	6 (55)	
Length of surgery, min	180 [150–220]	180 [150–180]	0.456
Length of intraoperative mechanical ventilation, min	220 [180–255]	230 [180–240]	0.974
Pao_2/Fio_2 1 h after extubation, mmHg§	280 [248–393]	272 [231–330]	0.577
$Paco_2$ 1 h after extubation, mmHg§	40 [37–45]	41 [40–43]	0.766
Borg dyspnea 1 h after extubation§	0 [0–1]	0 [0–1]	0.661
Respiratory rate 1 h after extubation, breaths/min§	18 [16–20]	16 [15–18]	0.274
Postoperative respiratory function‖			
Forced vital capacity, % of predicted value	100 [85–107]	93 [80–104]	0.534
FEV_1, % of predicted value	96 [78–106]	87 [81–98]	0.374
Tiffeneau–Pinelli index, %	83 [74–84]	80 [80–97]	0.810

Data are expressed as median [first quartile–third quartile], if not otherwise specified.

*Due to morbid obesity, all subjects were classified as American Society of Anesthesiologists Physical Status III. †Preoperative pulmonary function was assessed on the day before surgery. ‡Preoperative gas exchange was assessed before anesthesia in the supine position, while patients were breathing ambient air. §Postoperative gas exchange and respiratory rate were assessed while patients were receiving 40% oxygen with VenturiMask (FIAB, Florence, Italy) in the semiseated position. ‖Postoperative pulmonary function testing was performed on day 2 after surgery.

FEV_1, forced expiratory volume in 1 s; Fio_2, fraction of inspired oxygen.

fig. 1). Airway closure was confirmed on the pressure-volume curve by measured compliance between end-expiratory pressure and airway opening pressure, which corresponded to compliance of occluded respiratory circuit (2 ml/cm H_2O automatically measured by the ventilator during pre-use self-test; fig. 2, A, B, and C).

No patient in the control group developed airway closure after pneumoperitoneum induction. Conversely, in all patients with diagnosis of airway closure after intubation in the supine position, pneumoperitoneum in Trendelenburg position (25 to 30° head-down) yielded a rise in the airway opening pressure that reached a median value of 21 (interquartile range, 19 to 28) cm H_2O (representative patient in fig. 2C, left). The mean pneumoperitoneum-induced increase in airway opening pressure was 15 (95% CI, 11 to 18) cm H_2O ($P < 0.001$) and was consistent with pneumoperitoneum insufflation pressure (12 mmHg = 16 cm H_2O), and the mean increase in end-expiratory esophageal pressure that this generated, which was 9 (95% CI, 5 to 14) cm H_2O ($P = 0.001$).

Respiratory Mechanics after Intubation in the Supine Position

Respiratory mechanics after intubation in the supine position were similar in the two groups, except for respiratory system linear compliance, which was slightly higher in patients with airway closure (table 3).

Pneumoperitoneum Effects

In both groups, surgical pneumoperitoneum yielded increases in inspiratory and expiratory esophageal pressure, airway

Table 2. Ventilatory Settings and Hemodynamics, before Pneumoperitoneum in the Supine Position and with Pneumoperitoneum in the Trendelenburg Position

	Airway Closure (n = 11)			Control Group (n = 11)		
	Without Pneumoperitoneum	With Pneumoperitoneum	*P**	Without Pneumoperitoneum	With Pneumoperitoneum	*P**
Respiratory						
Tidal volume, ml	440 [330–550]	500 [375–550]	0.102	380 [350–525]	375 [330–525]	0.416
Tidal volume/PBW, ml/kg	9.4 [6.3–9.8]	9.7 [6.7–10]	0.323	7.2 [6.7–10.2]	7.2 [6.7–10.2]	0.534
Set PEEP, cm H_2O	5 [5–10]	5 [5–10]	>0.999	10 [5–10]	10 [5–10]	>0.999
Respiratory rate, breaths/minute	15 [14–20]	18 [15–21]	0.049	19 [13–25]	20 [15–26]	0.028
End-tidal CO_2, mmHg	33 [33–38]	36 [33–39]	0.570	37 [33–42]	34 [32–39]	0.067
Hemodynamics						
Heart rate, beats/min	75 [66–82]	65 [57–75]	0.229	69 [60–78]	60 [54–62]	0.007
Systolic arterial pressure, mmHg	118 [84–130]	155 [133–170]	0.014	128 [112–135]	150 [137–161]	0.018
Diastolic arterial pressure, mmHg	65 [49–80]	88 [78–97]	0.008	73 [61–77]	90 [80–93]	0.003
Mean arterial pressure, mmHg	83 [61–97]	107 [101–123]	0.010	90 [85–95]	110 [100–117]	0.006

Results are expressed as medians [first quartile–third quartile].

*Two-tail *P* values are related to the intragroup comparison between measurements before and after pneumoperitoneum. No differences were found between patients with and without airway closure.

PBW, predicted body weight; PEEP, positive end-expiratory pressure.

plateau pressure, dynamic driving pressure of the respiratory system, respiratory system and lung static driving pressure, and tidal elastic pressure. These were caused by drops in static respiratory system, lung and chest wall compliance, and reduction in the respiratory system linear compliance (table 3).

In the control group, surgical pneumoperitoneum caused reduction in the linear compliance of the lung, which was accompanied by higher tidal lung elastic pressure. Conversely, in patients with airway closure, neither tidal lung elastic pressure nor lung linear compliance was modified by pneumoperitoneum (table 3; representative patient in fig. 2D).

Lung Volume

In the supine position, end-expiratory lung volume was not different between groups ($P = 0.511$); differently, after institution of surgical pneumoperitoneum, patients with airway closure showed higher end-expiratory lung volume ($P = 0.017$). This occurred because in patients in the control group, but not in those with airway closure, gas insufflation for pneumoperitoneum reduced end-expiratory lung volume ($P = 0.006$ and $P = 0.155$, respectively; $P = 0.045$ for intergroup difference, fig. 3), with a mean decrease of 312 (95% CI, 118 to 505) ml.

As patients with airway closure experienced decreases neither in lung linear compliance nor in end-expiratory lung volume due to pneumoperitoneum, the pressure-volume curves of the transpulmonary pressure with patent airways (*i.e.*, the transalveolar pressure) showed no changes in alveolar recruitment due to this procedure (representative patient in fig. 2D, left).

Misinterpretation of Respiratory Mechanics by Static Measurements

In the airway closure group, but not in the control group, static and dynamic respiratory system driving pressure overestimated respiratory system tidal elastic pressure (intergroup difference, both $P = 0.007$; fig. 4). Similarly, lung driving pressure was higher than lung tidal elastic pressure ($P = 0.01$). Correspondingly, lung dynamic, respiratory system static, and dynamic compliances were lower than the corresponding linear ones ($P \leq 0.05$ for all). The entity of elastic pressure overestimation and compliance underestimation by dynamic measurements was proportional to the airway opening pressure (fig. 5).

Effects of the Pressure-controlled Ventilation

Four patients with airway closure and six in the control group received scheduled recruitment maneuvers over the course of the trial. According to study protocol, these were performed after intubation, after pneumoperitoneum induction, and then on an hourly basis by switching to pressure-controlled ventilation (inspiratory pressure 10 cm H_2O, unchanged respiratory rate) and increasing PEEP by 5 to 10 cm H_2O every 4 to 6 breaths up to PEEP equals 30 cm H_2O. During recruitment maneuvers after pneumoperitoneum in patients with airway closure, pressure-controlled

Table 3. Respiratory Mechanics in the Study Groups, before Pneumoperitoneum in the Supine Position and with Pneumoperitoneum in the Trendelenburg Position

	Airway Closure (n = 11)			Control Group (n = 11)		
	Without Pneumoperitoneum	With Pneumoperitoneum	*P**	Without Pneumoperitoneum	With Pneumoperitoneum	*P**
Airway opening pressure, cm H_2O	9 [6 to 11]	21 [19 to 28]	0.003	n/a	n/a	
EELV, ml	1,294 [1,154 to 1,363]	1,160 [1,118 to 1,256]†	0.155	1,113 [1,040 to 1,577]	1,000 [821 to 1,061]†	0.006
End-expiratory measurements						
$PEEP_{TOT}$, cm H_2O	7 [5 to 11]	13 [10 to 21]†	0.004	10 [5 to 10]	10 [5 to 10]†	0.496
$P_{ESend-exp}$, cm H_2O	16 [15 to 19]	27 [23 to 30]	0.005	16 [13 to 18]	24 [17 to 28]	0.029
$P_{Lend-exp}$, cm H_2O	–9 [–11 to –7]	–10 [–16 to –7]	0.286	–9 [–10 to –6]	–17 [–19 to –8]	0.026
End-inspiratory measurements						
P_{PLAT}, cm H_2O	18 [17 to 19]	36 [30 to 40]†	0.003	19 [18 to 22]	31 [26 to 33]†	0.003
$P_{ESend-insp}$, cm H_2O	19 [17 to 21]	33 [30 to 36]	0.003	18 [16 to 22]	31 [27 to 37]	0.005
$P_{Lend-insp}$, cm H_2O	–1 [–3 to 2]	2 [0 to 3]	0.075	1 [–2 to 3]	-2 [–4 to 3]	0.326
$P_{L\ el-der}$, cm H_2O	14 [14 to 16]	20 [18 to 28]	0.004	13 [11 to 16]	18 [12 to 24]	0.050
Driving pressure						
ΔP, cm H_2O	11 [8 to 12]	21 [14 to 25]	0.004	11 [9 to 15]	22 [15 to 26]	0.003
Dynamic ΔP, cm H_2O	11 [9 to 13]	31 [22 to 34]†	0.003	11 [9 to 15]	22 [16 to 26]†	0.003
Respiratory system tidal elastic pressure, cm H_2O	8 [7 to 10]	12 [10 to 16]†	0.019	10 [9 to 15]	22 [15 to 26]†	0.003
ΔP_L, cm H_2O	8 [6 to 10]	14 [8 to 18]	0.016	8 [5 to 12]	10 [9 to 20]	0.021
Lung tidal elastic pressure, cm H_2O	6 [4 to 9]	7 [6 to 8]†	0.859	7 [5 to 11]	10 [9 to 20]†	0.013
Compliances						
Static C_{RS}, ml/cm H_2O	44 [40 to 53]	25 [16 to 26]	0.006	40 [31 to 44]	20 [18 to 24]	0.003
Dynamic C_{RS}, ml/cm H_2O	39 [35 to 48]	17 [13 to 19]†	0.003	39 [29 to 43]	19 [18 to 22]†	0.003
Linear C_{RS}, ml/cm H_2O	57 [41 to 72]	38 [27 to 51]†	0.041	39 [33 to 44]	20 [18 to 24]†	0.003
Static C_L, ml/cm H_2O	56 [50 to 69]	35 [29 to 49]	0.075	60 [42 to 74]	32 [24 to 50]	0.016
Linear C_L, ml/cm H_2O	66 [46 to 91]	71 [58 to 102]†	0.508	57 [45 to 80]	33 [24 to 47]†	0.010
Static C_{CW}, ml/cm H_2O	226 [140 to 360]	70 [49 to 103]	0.004	123 [108 to 204]	64 [38 to 80]	0.003

Results are expressed as medians [first quartile to third quartile]. No differences were found between patients with and without airway closure in the measurements before pneumoperitoneum in the supine position. With pneumoperitoneum, as compared to the control group, patients with airway closure had significantly higher end-expiratory lung volume (EELV), total positive end-expiratory pressure ($PEEP_{TOT}$), airway plateau pressure (P_{PLAT}), and dynamic ΔP, and lower dynamic respiratory system compliance (C_{RS}). Also, respiratory system and lung tidal elastic pressures were lower, and corresponding linear compliances were higher, in the airway closure group.

*Two-tail *P* values are related to the intragroup comparison between measurements before and after pneumoperitoneum. †$P<0.05$ for intergroup comparisons with pneumoperitoneum in the Trendelenburg position.

C_{CW}, chest wall compliance; C_L, lung compliance; n/a, not applicable; $P_{ESend-exp}$, end-expiratory esophageal pressure; $P_{ESend-insp}$, end-inspiratory esophageal pressure; PL_{el-der}, elastance-derived end-inspiratory transpulmonary pressure; $P_{Lend-exp}$, end-expiratory transpulmonary pressure; $P_{Lend-insp}$, end-inspiratory transpulmonary pressure; ΔP, respiratory system driving pressure; ΔPL, transpulmonary driving pressure.

ventilation did not generate any tidal inflation until total inspiratory pressure overcame airway opening pressure, resulting in complete apnea. Conversely, in the control group, pressure-controlled ventilation always produced some tidal ventilation, irrespective of the applied pressure (fig. 6).

Discussion

The results of the current study can be summarized as follows:

1. A relevant proportion of obese patients undergoing general anesthesia exhibit airway closure after intubation, with a variable degree of airway opening pressure. When pneumoperitoneum is combined with Trendelenburg position, airway opening pressure increases consistently with the rise in end-expiratory esophageal pressure and pneumoperitoneum insufflation pressure.
2. Airway closure can be suspected in the presence of total PEEP greater than set PEEP and particularly high plateau/driving pressure after pneumoperitoneum institution.
3. When pneumoperitoneum is instituted in the head-down position, airway closure increases end-expiratory alveolar pressure, maintaining transalveolar pressure at end expiration unchanged. This hampers any pneumoperitoneum-induced change in end-expiratory lung volume and lung compliance, finally preventing alveolar derecruitment.
4. With airway closure, static respiratory mechanics and dynamic measures performed by ventilators lead overestimation of lung and respiratory system driving pressures with underestimation of corresponding compliances. This effect, being proportional to the airway opening pressure, is already present after intubation in the supine position but is more pronounced as pneumoperitoneum is instituted.

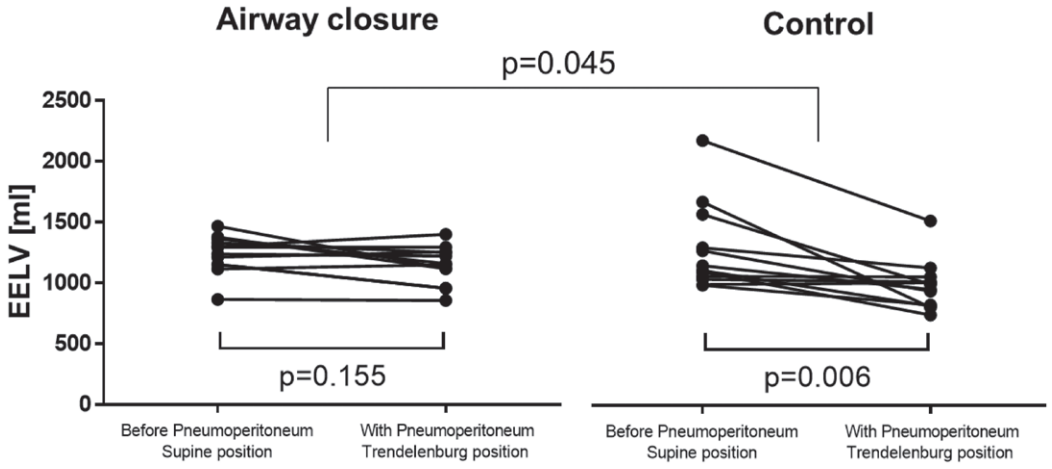

Fig. 3. End-expiratory lung volumes (EELVs) before and after induction of pneumoperitoneum in airway closure and control group. In patients in the control group, but not in those with airway closure, gas insufflation for pneumoperitoneum reduced EELV. In the supine position, EELV was not different between groups ($P = 0.511$), while after pneumoperitoneum, patients with airway closure showed higher EELV ($P = 0.017$). Accordingly, pneumoperitoneum-induced change in EELV was significantly higher in control than in airway closure group ($P = 0.045$).

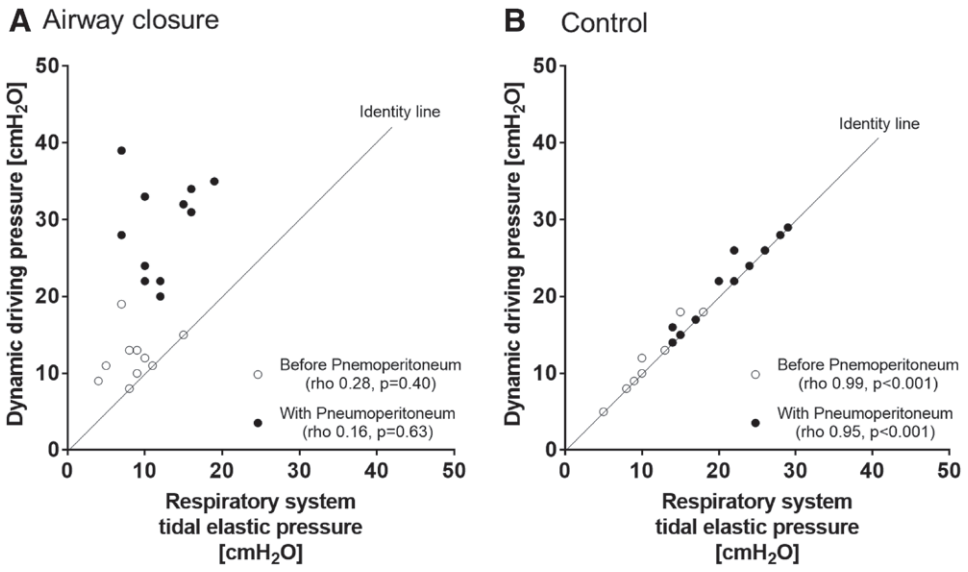

Fig. 4. Relationship between dynamic driving pressure and tidal elastic pressure in airway closure patients versus control patients (see definitions for dynamic driving pressure and tidal elastic pressure in the Methods section). In patients with airway closure, dynamic driving pressure grossly overestimates actual tidal elastic pressure, especially with pneumoperitoneum in the Trendelenburg position (A). Conversely, dynamic driving pressure closely estimates tidal elastic pressure in patients without airway closure (B).

5. When patients with airway closure receive pressure-controlled ventilation, no tidal volume is delivered if inspiratory pressure does not overcome airway opening pressure.

Airway closure with a variable degree of opening pressure has been documented in patients with acute respiratory distress syndrome, in human cadavers, and in cardiac arrest patients undergoing cardiopulmonary resuscitation.[1,4,23,24]

Different from what initially suggested during general anesthesia,[6,7] the opening pressure is not an airway pressure threshold to overcome pleural pressure and generate positive transpulmonary pressure. Indeed, this phenomenon has been reported in the excised lung, where transpulmonary pressure is necessarily positive,[25,26] and in our study, airway opening often occurred at a transpulmonary pressure lower

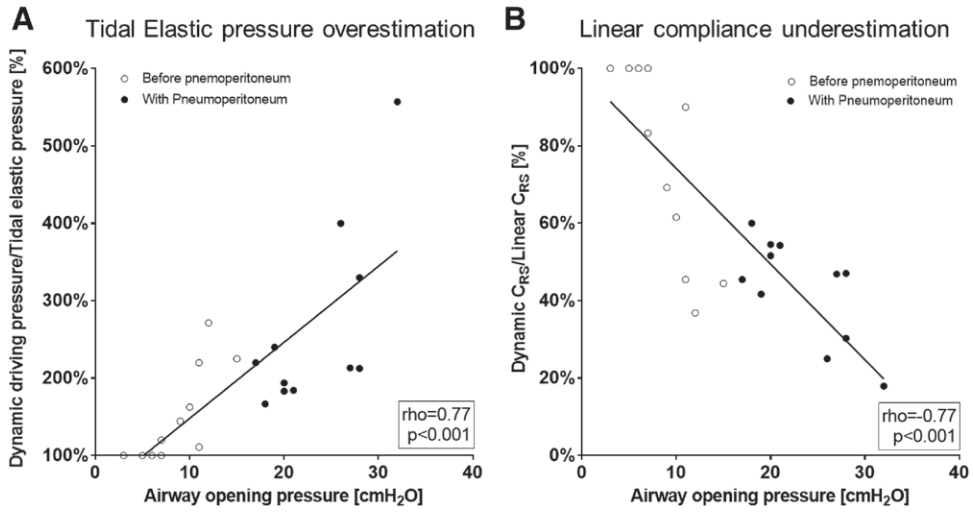

Fig. 5. Tidal elastic pressure overestimation and linear compliance underestimation in patients with airway closure (see definitions for dynamic respiratory system compliance [C_{RS}] and linear respiratory system compliance in the Methods section). As shown in figure 4, in patients who display airway closure, dynamic driving pressure overestimates tidal elastic pressure because the actual end-expiratory alveolar pressure is higher than set positive end-expiratory pressure (PEEP). For the same reason, dynamic respiratory system compliance, calculated as tidal volume/dynamic respiratory system driving pressure, underestimates linear respiratory system compliance, calculated as the slope of the steeper segment of the respiratory system pressure-volume curve. This figure shows that entity of elastic pressure overestimation (*A*) and compliance underestimation (*B*) by the ventilator's dynamic measurements is proportional to the airway opening pressure (AOP). This likely happens because the higher the AOP, the higher the difference between the actual end-expiratory alveolar pressure and PEEP used in dynamic measurements. Since after pneumoperitoneum induction, AOP tends to be higher, respiratory mechanics misinterpretation with pneumoperitoneum (*black dots*) is greater than without (*white dots*).

than 0 cm H_2O (figs. 1, 2, and 6). Moreover, transpulmonary pressure is variable across the lung, both in patients with lung injury and (to a lesser extent) in those with healthy lungs, depending on the ventral-to-dorsal gradient in pleural pressure,[14] while the airway opening we are reporting is an all-or-nothing phenomenon.

In the current study, we show that airway closure affects a relevant proportion of obese patients with no impairment in preoperative respiratory function who undergo general anesthesia. Because no patient without airway closure after intubation developed it as a consequence of pneumoperitoneum, its occurrence possibly depends on some anatomo-functional individual characteristic of patients' airways, such as the surface tension in the liquid–gas interface, as already suggested.[1,25,27] In patients with airway closure, conversely, airway opening pressure was systematically increased by pneumoperitoneum in the head-down position: it is likely that the increase in pleural pressure caused by abdominal gas insufflation generates a drop in the transmural pressure of the airways, which finally yields airway closure. This is consistent with the hypothesized cause for airway collapse in spontaneously breathing patients with active expiration, highlighting the close relationship between this condition and the wider concept of expiratory flow limitation.[3,28] Importantly, in our patients with airway closure, the increase in the expiratory driving pressure (*i.e.*, plateau pressure minus set PEEP) produced by pneumoperitoneum did not result in reduction in end-expiratory lung volume, which is itself a diagnostic criterion for certifying limited expiratory flow.[3]

Other authors reported respiratory mechanics compatible with airway closure during laparoscopic surgery in obese patients, showing that neither the "critical pressure" (*i.e.*, the airway opening pressure) nor end-expiratory esophageal pressure was modified by surgical pneumoperitoneum and suggesting that this procedure could not act as a compression force for lungs and airways at end expiration.[6,7] Differently, our findings indicate that pneumoperitoneum increases esophageal pressure and airway opening pressure: in previous case series,[6,7] patients were studied in the supine or reverse Trendelenburg position, while our study shows pneumoperitoneum effects in head-down position. Thus, the Trendelenburg position plays a crucial role in enhancing the transmission of intraabdominal force to the pressure that is superimposed on the lungs (estimated by esophageal pressure[14]), which also squeezes airways contributing to determine the pressure required to maintain airway patency. It appears reasonable to suggest that any increase in the lung superimposed pressure (*i.e.*, obesity, Trendelenburg position, alveolar flooding in acute respiratory distress syndrome, lung edema with chest compressions during cardiopulmonary resuscitation[1,24,29]) can enhance airway closure by determining a decrease in the functional residual capacity

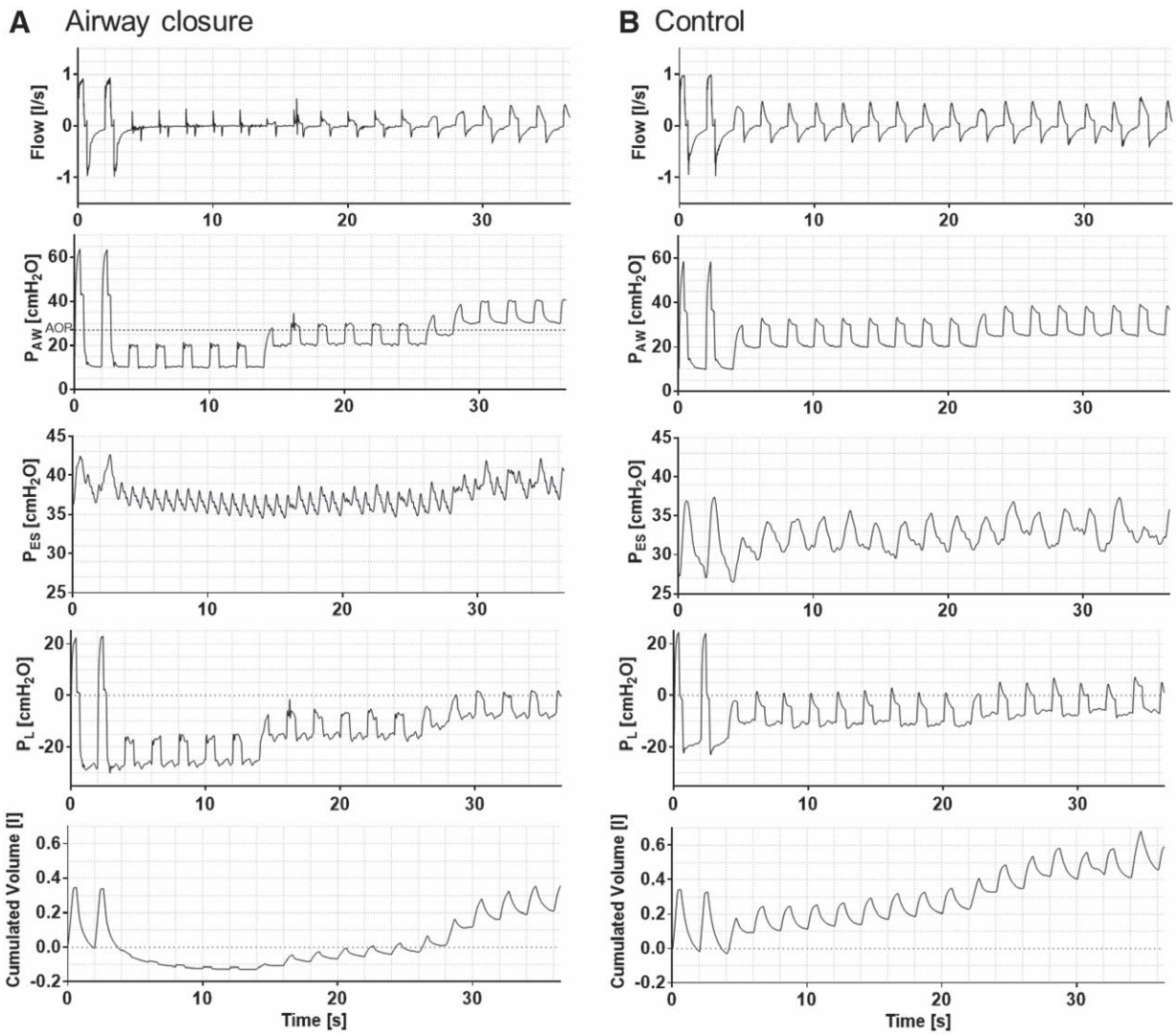

Fig. 6. Effects of pressure-controlled ventilation. Flow, airway pressures (P_{AW}), esophageal pressures (P_{ES}), transpulmonary pressures (P_L), and cumulated inflated/deflated volume (digital integration of the flow signal over time), during recruitment maneuvers in a representative patient with (*A*) and without (*B*) airway closure after pneumoperitoneum institution. Recruitment maneuvers were conducted in the pressure-controlled mode by progressive increasing positive end-expiratory pressure (PEEP) increase up to 30 cm H_2O, with inspiratory pressure set at 10 cm H_2O. In the presence of airway closure, there is no tidal ventilation (nor increases in P_{ES} and P_L, as discussed in fig. 1) until airway opening pressure (AOP) is overcome (*i.e.*, until the sum of PEEP and inspiratory pressure becomes higher than the AOP), as shown by the first five pressure-controlled breaths in (*A*). This shows how pressure-controlled ventilation in a patient with airway closure can produce complete apnea or hypoventilation.

below the closing capacity (*i.e.*, sum of residual and closing volume) of the airways.[30]

Our results on end-expiratory lung volume demonstrate that, in the case of airway closure, pneumoperitoneum does not cause alveolar derecruitment. This confirms that the airway opening pressure does not reflect alveolar kinetics and alveolar collapse, as the "lower inflection point" concept would suggest.[25] In our patients, the increase in airway opening pressure caused by pneumoperitoneum, being itself proportional to pneumoperitoneum pressure, prevented alveolar collapse when this external load was applied. Essentially, the rise in airway opening pressure induced by pneumoperitoneum generated consistent changes in alveolar pressure at end expiration, which kept the transalveolar pressure unmodified and prevented any lung volume loss. Accordingly, while in control patients pneumoperitoneum yielded decreases in end-expiratory lung volume and lung linear compliance, the pneumoperitoneum-induced decrease in respiratory system linear compliance detected in patients with airway closure was due to a more rigid chest wall, with unchanged lung linear compliance and lung tidal elastic pressure.[31,32] Unrecognized increases in airway opening pressure and end-expiratory

alveolar pressure may explain why obese patients are less prone to experience reduction in functional residual capacity due to pneumoperitoneum in Trendelenburg position.[33]

Our results carry relevant clinical consequences. First, under this condition, driving pressure, measured both with occlusions and dynamically by the ventilator, relevantly overestimates tidal elastic pressure. Similarly, dynamic compliance does not accurately reflect actual respiratory system compliance.[1,13] These aspects appear relevant in the intraoperative setting, as the driving pressure has been shown to be the final mediator of the effects of ventilation settings on the rate of postoperative complications,[15] and optimization of dynamic respiratory system compliance has been advocated as a tool to titrate PEEP in the setting of general anesthesia.[17]

Second, with airway closure, real alveolar pressure at end expiration is unknown but can be very high and, ultimately, close to the airway opening pressure. Hence, alveolar pressure at end expiration is independent from applied PEEP if this is set below airway opening pressure. This should be taken into account when assessing the effects on obese patients of PEEP-setting strategies, such as those currently under evaluation in ongoing randomized studies during general anesthesia.[34–40] Of note, when PEEP is set below airway opening pressure, distal airways suffer from cyclic opening and closing, and this may yield bronchiolar injury.[41] Whether this may clinically jeopardize the population of surgical patients is unknown. Moreover, the high occult alveolar pressure, while preventing alveolar derecruitment, can generate detrimental hemodynamic effects,[42–44] whose mechanisms in the intraoperative setting could be misinterpreted.

Third, pneumoperitoneum in the head-down position can impair cerebral blood flow homeostasis,[45] with possible abnormal increases in intracranial pressure.[46] Whether and to what extent the high alveolar and intrathoracic pressure caused by airway closure may contribute to this is unknown and warrants further investigations.

Most important, airway closure is difficult detect in the clinical setting (*i.e.*, low-flow inflation is needed), occurred in patients with no apparent impairment in respiratory function, and determined alarmingly high airway opening pressure values. This raises concerns regarding the safety of pressure-controlled ventilation in this setting, even though it has been proposed with encouraging results and is used worldwide.[47–50] With airway closure, use of pressure-controlled modes with inspiratory pressure lower than airway opening pressure results in complete apnea. Furthermore, if airway opening pressure varies over time, use of the same inspiratory pressure may yield relevant hypo-/hyperventilation.

Our study has limitations. First, the study was not designed to assess the presence of airway closure in morbidly obese patients undergoing general anesthesia, but rather to determine the effects of ventilatory interventions on postoperative oxygenation. Hence, our conclusions are the result of a serendipity process. This should not alter, and could even strengthen, the significance of the current investigation, especially because measurements were performed according to a prespecified protocol, patients represent a homogeneous and externally reproducible population, and airway closure was documented with different PEEP levels and tidal volume sizes.

Second, reported data are limited to 11 cases, and all patients were females, which cannot ensure the reproducibility of the findings among male patients. However, previous investigations in different settings[1,4,23] clearly showed that males may be similarly affected.

Finally, our results should be seen as a "proof of concept" study, and we acknowledge that the low number of studied patients did not allow correction for multiple comparisons: we recognize it is not possible to draw conclusions from our results on the risk factors, exact prevalence, and eventual time course of this phenomenon or on its consequences on the postoperative period. Recently, expiratory flow limitation has been shown to affect up to 30% of the patients undergoing general anesthesia and has been linked to the risk of pulmonary complications[51]: to what extent development of airway closure contributes to this remains to be established.

Conclusions

Airway closure unpredictably affects a considerable proportion of obese patients undergoing general anesthesia. Pneumoperitoneum in the Trendelenburg position relevantly worsens this phenomenon, enormously increasing airway opening pressure and alveolar pressure at end expiration; this yields misinterpretation of respiratory mechanics and underestimation of end-expiratory alveolar pressure, which is markedly higher than measured PEEP, possibly equals airway opening pressure, and prevents alveolar derecruitment. Airway closure can be missed at the bedside, while this phenomenon generates a pressure threshold to inflate the lung that can reach high values; this raises concerns about the safety of pressure-controlled modes in this specific setting.

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Competing Interests

Dr. Grieco has received payments for travel expenses from Maquet (Rastatt, Germany), Getinge (Getinge, Sweden), and Air Liquide (Paris, France). Dr. Antonelli has received payments for board participation from Maquet, Air Liquide, and Chiesi (Parma, Italy). Drs. Antonelli and Grieco disclose an ongoing research grant received by General Electric Healthcare (Chicago, Illinois). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Grieco: Department of Anesthesiology and Intensive Care Medicine, Catholic University of The Sacred Heart, Fondazione "Policlinico Universitario A. Gemelli" IRCCS, L.go F. Vito, 00168, Rome, Italy. dlgrieco@outlook.it. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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