Application of the Novel Ventilation Mode FLow-Controlled EXpiration (FLEX): A Crossover Proof-of-Principle Study in Lung-Healthy Patients

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BACKGROUND: Traditionally, mechanical ventilation is achieved via active lung inflation during inspiration and passive lung emptying during expiration. By contrast, the novel FLEX (FLow-controlled EXpiration) ventilator mode actively decreases the rate of lung emptying. We investigated whether FLEX can be used during intraoperative mechanical ventilation of lung-healthy patients.
METHODS: In 30 adult patients scheduled for neurosurgical procedures, we studied respiratory system mechanics, regional ventilation, oxygenation, and hemodynamics during ventilation with and without FLEX at positive end-expiratory pressure (PEEP) of 5 and 7 cm H_2O. The FLEX system was integrated into the expiratory limb and modified the expiratory flow profile by continuously changing expiratory resistance according to a computer-controlled algorithm.
RESULTS: Mean airway pressure increased with PEEP by 1.9 cm H_2O and with FLEX by 1 cm H_2O (all $P < .001$). The expiratory peak flow was 42% lower with FLEX than without FLEX ($P < .001$). FLEX caused significant shifts in aeration from ventral to the dorsal lung regions. Respiratory mechanics, end-tidal carbon dioxide partial pressure, oxygenation, and hemodynamics were independent from FLEX and PEEP. We observed no critical incidents or FLEX malfunctions in any measurement that would have required an intervention or termination of the FLEX mode.
CONCLUSIONS: FLEX can be used in lung-healthy patients who are mechanically ventilated during general anesthesia. FLEX improves the homogeneous distribution of ventilation in the lungs.
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Mechanical ventilation during general anesthesia may lead to postoperative pulmonary complications.[1–4] Ventilator modes that minimize lung damage may thus improve outcomes during mechanical ventilation. Traditional forms of mechanical ventilation focus primarily on the inspiratory phase via modifying how gas is delivered into the lungs. Modifying the expiratory phase, however, has not been addressed in most modern ventilatory modes. The FLow-controlled EXpiration (FLEX) mode was recently introduced as a new approach to lung-protective ventilation.[5,6] FLEX modulates the otherwise passive expiration phase: reducing the initial high-expiratory peak flow and causing expiratory gas flow to persist throughout the expiratory phase. In an animal model of acute respiratory distress syndrome, FLEX reduced ventilation-induced lung damage, decreased severity of pulmonary edema and focal inflammation, increased dynamic compliance, and improved ventilation. Furthermore, FLEX may permit a lower PEEP as a result of better maintained airway expansion.[6]

The aim of this study was to test this ventilation mode during intraoperative anesthesia. We hypothesized that the new ventilation mode FLEX can be used for intraoperative ventilation without adverse effects on respiratory system mechanics, gas exchange, and hemodynamics in lung-healthy patients. Therefore, we investigated respiratory system mechanics, regional ventilation, oxygenation, and hemodynamics in patients ventilated with and without FLEX at PEEP of 5 and 7 cm H_2O.

METHODS

The study was approved by the ethics committee of the University of Freiburg (EK 163/15) and was registered at the German Register for Clinical Trials (DRKS00008555) before the study. Written informed consent was obtained from all patients before the intervention. The study included 30 consecutive patients (American Society of Anesthesiologists physical status I–III, age 20–87 years) who received controlled ventilation during elective neurosurgical procedures at the Medical Center—University of Freiburg. Exclusion criteria included lung diseases, pregnancy, cardiac pacemaker or other active implants, operations in an inclined or prone position, operations in the thoracic region, and anticipated surgery time <70 minutes. After primary recruitment, preoperative evaluation of lung function was performed by spirometry in which the forced vital capacity, the forced expiratory volume in 1-second capacity, and the ratio of both, that is, the Tiffeneau Index, were determined (Vitalograph 2120 Hand Held; Vitalograph, Ennis, Ireland).

Midazolam (3.75–7.5 mg, Dormicum; Roche Pharma AG, Grenzach-Wyhlen, Germany) was administered as oral

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premedication at least 1 hour before anesthetic induction. To perform electrical impedance tomography (EIT) measurements, an electrode belt with 16 electrodes was placed around the chest at the level of the fifth intercostal space. Routine monitoring (electrocardiography, SaO_2, noninvasive and invasive blood pressure measurement; Infinity Delta XL; Dräger Medical, Lübeck, Germany) was established, and anesthesia was induced using a standard protocol. All patients were preoxygenated before endotracheal intubation with an Fio_2 of 0.8. During anesthesia, the Fio_2 was set at 0.4. For the induction of anesthesia, 0.5–0.7 μg/kg sufentanil (Janssen-Cilag, Neuss, Germany) was administered, and propofol 1% was added through a target-controlled infusion with a target concentration (effective dose) of 5–6 μg/mL (Agilia, Schnider Model; Fresenius Kabi, Bad Homburg vor der Höhe, Germany).

Cisatracurium (0.1 mg/kg; Fresenius Kabi) was administered for endotracheal intubation. Neuromuscular monitoring was conducted with a mechanomyograph (Stimpod NMS450; Xavant Technology Ltd, Pretoria, South Africa). Endotracheal tubes with high-volume, low-pressure cuffs were used for intubation with an internal diameter of 7.0 (women) and 7.5 mm (men; Mallinckrodt Hallo-Contour Rohr; Covidien, Neustadt an der Donau, Deutschland). The cuff pressure was continuously monitored and kept below 20 cm H_2O. Anesthesia was maintained with a target-controlled infusion and a target concentration of 3–4 μg/mL propofol and a continuous infusion of remifentanil (0.1–0.2 μg/kg/min). Hypotension (mean arterial pressure <60 mm Hg) was treated with a continuous infusion of norepinephrine. Intraoperative fluid was administered with a crystalloid solution (8 mL/kg/h, Jonosteril; Fresenius Kabi).

After intubation, patients were ventilated using a volume-controlled mode (Primus IE; Dräger Medical, Lübeck, Germany) with an inspiration-to-expiration ratio of 1:2, tidal volume of 8 mL/kg predicted bodyweight, and respiratory rate set to maintain normocapnia (end-tidal carbon dioxide partial pressure between 4 and 5.3 kPa). The patient was initially ventilated with a PEEP of 5 cm H_2O.

After completion of surgical preparations and an equilibration phase of at least 10 minutes, each patient was subjected to 4 different ventilation settings in random order. The 4 settings included (1) PEEP 5 cm H_2O without FLEX; (2) PEEP 5 cm H_2O with FLEX; (3) PEEP 7 cm H_2O without FLEX; and (4) PEEP 7 cm H_2O with FLEX. PEEP levels of 5 and 7 cm H_2O were chosen because these are commonly used in clinical practice in our medical center. Moreover, previous animal work[6] suggested effects of FLEX comparable to a 2-cm H_2O change in PEEP. For reasons of patient safety, we kept the minimal standards of our medical center and omitted investigating a group with 0 PEEP. Each ventilator setting was maintained for 20 minutes. EIT images were recorded for 2 minutes at the end of each ventilator setting (PulmoVista 500, software version 1.10; Dräger, Lübeck, Germany). Oxygen saturation, heart rate, invasive blood pressure, and end-tidal partial pressure of carbon dioxide were recorded in 5-minute intervals throughout the measurements. At the end of each ventilation setting, arterial blood gas was measured (ABL800 FLEX; Radiometer, Copenhagen, Denmark).

The flow rate was measured using a pneumotachograph (Type 2, Fleisch; Dr Fenyves und Gut, Hechingen, Germany) and the airway pressure at the proximal end of the tracheal tube using a piezoresistive pressure transducer (Transmitter module Type 4; SI-special instruments GmbH, Nördlingen, Germany). Based on a measuring system developed in LabVIEW (version 7.1, Austin, TX), the measured respiratory data were recorded at a sampling rate of 200 Hz for postprocessing in offline analysis. Tracheal pressure was calculated from airway pressure by means of Rohrer's approach.[7] In brief, the pressure drop across the tracheal tube was calculated from the resistance coefficients of the tracheal tube and the measured flow rate. The tracheal pressure was then calculated as the difference between the airway pressure and the pressure drop across the tracheal tube. Based on the tracheal pressure (P_{trach}), dynamic respiratory compliance (C_{RS}) and resistance (R_{RS}) were calculated by multilinear regression analysis of the general equation of motion:

$$P_{trach} = 1/C_{RS} \cdot V + R_{RS} \cdot \dot{V} + P_0,$$

where V is volume, $\dot{V}$ is flow rate, and P_0 is the dynamic pressure base. The expiratory resistance of the artificial airways (R_{EX}) was calculated from expiratory airway pressure (P_{awEX}) and expiratory flow rate ($\dot{V}_{EX}$) by multilinear regression analysis of

$$P_{awEX} = R_{EX} \cdot \dot{V}_{EX} + P_0.$$

The FLEX device was developed and produced by our "Clinical Respiration Physiology" working group. A computer-controlled linear motor (PS01-23Sx80 und MS01-1/D; LinMot, Spreitenbach, Switzerland) modified the cross-section of a 30-mm inner diameter air duct via partial occlusion with a movable cone. The position of the cone then determined the additional expiratory resistance generated by the FLEX device (Figure 1). The FLEX system was integrated into the expiratory limb of the anesthesia machine's circuit. Inspiratory and expiratory phases were detected automatically and during inspiration the movable cone occluded the air duct. After the onset of expiration, the cone gradually opened the air duct progressively reducing expiratory resistance during inspiration. The cone thus created a gradually decreasing resistance.

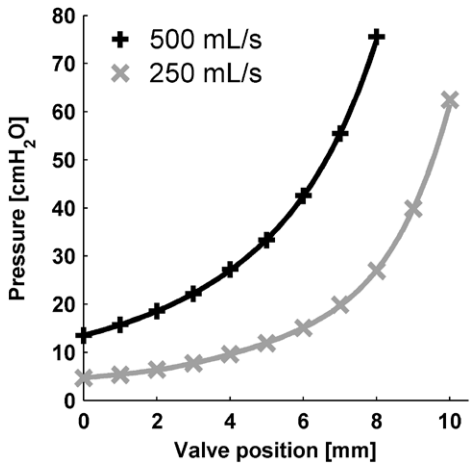

Figure 1. Flow- and position-dependent pressure drop across the FLEX system. The additional expiratory resistance of FLEX is determined by positioning of a cone inside an aperture. The resistance at a specific position equates the pressure drop divided by the respective flow rate. FLEX indicates flow-controlled expiration.

Analysis of EIT Data

Before evaluation of the EIT images, the lung area was determined for each patient as described by Zhao et al.[8,9] In brief, for each patient, frames of the data taken during the equilibrium phase were used to determine the active lung area. The standard deviation of each pixel over all calibration frames was calculated and pixels within 80% of the maximal standard deviation variation were identified. These pixels were subsequently mirrored left to right to correct for possible atelectasis, and finally, the heart region was subtracted by filtering in the frequency domain. Tidal EIT images were generated for each patient by calculating the difference between the images at the end and start of inspiration.[10,11]

To compare the applied PEEP/FLEX combinations (PEEP 5 cm H_2O versus PEEP 7 cm H_2O, PEEP 5 cm H_2O with versus without FLEX, and PEEP 7 cm H_2O with versus without FLEX), differential functional images were calculated by subtracting the tidal images of the corresponding measurements from each other. The differential images were divided in a ventral and dorsal region of interest. For both regions, the relative number of positive (ventilation gain) and negative (ventilation loss) pixels was calculated as percentage of the total number of pixels. Gain and loss represent the changes in impedance (Z) and hence in ventilation within a lung region.[10] Thus, the difference between gain and loss (ΔZ) represents the total change in ventilation of the lung region. If ΔZ is positive, gain is larger than loss, and thus, the lung region is better ventilated; by contrast, if ΔZ is negative, the ventilation is worse.

Statistical Analysis

Statistical analyses were performed using the statistical software package R (version 3.3.1, The R Foundation, Vienna, Austria). For all tests, a P value <.05 was considered statistically significant. The effects of the factors FLEX and PEEP on the measured variables were calculated based on a linear mixed model including the interaction between the factors. Unless stated otherwise, the results are reported as mean value with the corresponding confidence interval. Box plots show mean, interquartile ranges, and minimal and maximal values.

Previous studies were not available to use in estimating sample size. Therefore, the sample size was considered reasonable on the basis of a hypothetical difference in compliance between 2 treatments. We assumed that the difference in compliance between treatment with or without FLEX would be clinically relevant if it equaled the standard deviation of the compliance. With 30 patients, such difference in compliance would be detected with a power of 0.972 at an α level of .05.

RESULTS

Forty-three patients were screened from June to July 2015. Nine were excluded from the study, because the inclusion criteria were not met (n = 2), the operation was cancelled (n = 4), or an unplanned intraoperative position shift was necessary (n = 3). Of the 34 remaining data sets, 4 could not be analyzed as a result of artifacts in the measurement signals. Demographic data for the 30 patients included in the study are shown in Table 1.

Table 1. Basic Demographic Data of the Patients (n = 30) Included in the Study

Sex (n), female/male	17/13
Age (y; range)	58 (20–87)
Height (cm; range)	169 (160–183)
Weight (kg; range)	75 (54–114)
Body mass index (kg/m^2; range)	27 (20.2–39.4)
ASA I/II/III (n)	1/22/7
Smoker (n), yes/no	7/23
Preoperative pulmonary function	
VC (% predicted [SD])	89 (17)
FEV1 (% predicted [SD])	90 (20)
FEV1/FVC (% predicted [SD])	106 (12)
Surgery duration (min [range])	257 (170–485)

Abbreviations: ASA I/II/III, physical status according to the American Society of Anesthesiologists; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; SD, standard deviation; VC, vital capacity.

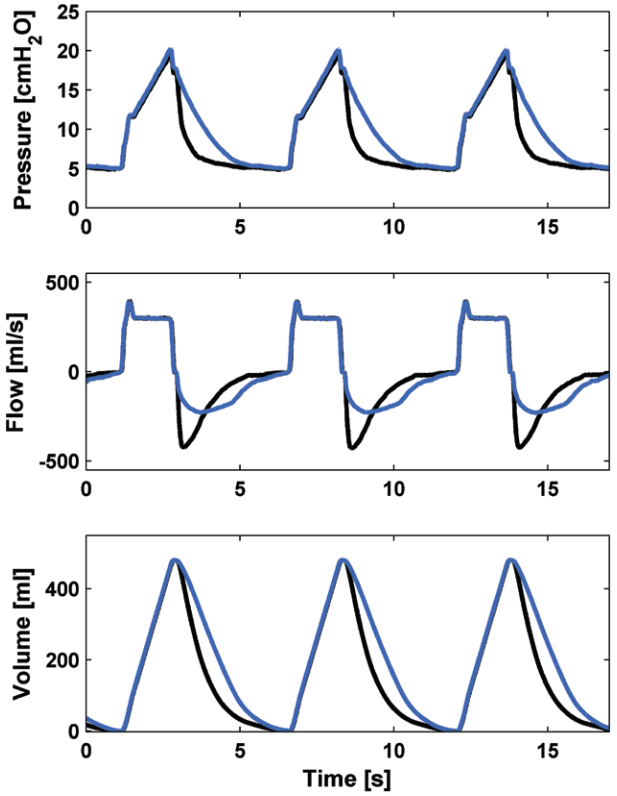

Figure 2. Airway pressure, flow, and volume curves of a representative patient ventilated with (blue) and without FLEX (black) at PEEP 5 cm H_2O over 3 breaths. FLEX is characterized by a reduced expiratory peak flow and a linearized expiratory flow curve, a decelerated expiratory volume decrease, and airway pressure. FLEX indicates flow-controlled expiration; PEEP, positive end-expiratory pressure.

Two data sets had to be excluded from the EIT analysis as a result of artifacts in the signal, leaving 28 EIT data sets for full analysis.

Both PEEP and FLEX affected airway pressure and gas flow rate in expiration, but not in inspiration (Figure 2). The mean expiratory resistance was 5-fold higher with FLEX compared with without FLEX (P < .001). Accordingly, the expiratory peak flow did not change with PEEP but decreased by 42% with FLEX compared with without FLEX (P < .001). Peak and plateau pressure increased by approximately 2 cm

Table 2. Intraoperatively Measured Physiologic Variables During the Individual Ventilation Settings

	PEEP 5 cm H_2O		PEEP 7 cm H_2O			
	Control	FLEX	Control	FLEX	P_{PEEP}	P_{FLEX}
Ventilation variables						
VF (beats/min)	12.4 (11.9, 12.9)	12.5 (11.9, 13.1)	12.3 (11.8, 12.8)	12.4(12.0, 12.8)	0.797	0.440
V_T (mL/kg)	7.1 (6.7, 7.5)	7.1 (6.6, 7.6)	7.1 (6.7, 7.5)	7.1 (6.6, 7.6)	0.114	0.341
C_{RS} (mL/cm H_2O)	52 (47, 56)	51 (47, 55)	52 (48, 56)	51 (47, 55)	0.708	0.199
R_{RS} (cm H_2O/s/L)	7.3 (6.8, 7.9)	7.4 (6.9, 7.9)	7.3 (6.8, 7.8)	7.3 (6.8, 7.9)	0.525	0.797
R_{EX} (cm H_2O/s/L)	7.6 (7.1, 8.1)	37.2 (33.9, 40.6)	6.8 (6.4, 7.2)	34.9 (31.7, 38.1)	0.541	<0.001
Peak $flow_{exp}$ (mL/s)	−429 (−457, −401)	−244 (−256, −232)	−426 (−453, −399)	−240 (−252, −228)	0.654	<0.001
Peak $flow_{insp}$ (mL/s)	469 (449, 489)	471 (453, 489)	470 (450, 491)	472 (453, 491)	0.864	0.736
P_{trach_peak} (cm H_2O)	16.3 (15.5, 17.1)	16.2 (15.4, 17.0)	18.2 (17.4, 19.0)	18.3 (17.5, 19.1)	<0.001	0.501
$P_{plateau}$ (cm H_2O)	16.2 (15.3, 17.1)	16.1 (15.3, 16.9)	18.1 (17.3, 18.9)	18.1 (17.2, 19.0)	<0.001	0.539
P_{mean} (cm H_2O)	8.6 (8.3, 8.9)	9.5 (9.1, 9.9)	10.5 (10.2, 10.8)	11.4 (11.1, 11.7)	<0.001	<0.001
$Petco_2$ (mm Hg)	36.2 (35.7, 36.7)	36.4 (35.8, 37.0)	36.2 (35.5, 36.9)	36.4 (35.7, 37.1)	0.969	0.533
Horowitz index (mm Hg)	395 (363, 426)	389 (359, 418)	396 (368, 423)	390 (360, 420)	0.866	0.466
Hemodynamic variables						
HR (beats/min)	54 (51, 58)	54 (50, 58)	53 (49, 57)	55 (51, 59)	0.451	0.957
MAP (mm Hg)	81 (78, 84)	79 (76, 82)	78 (75, 81)	78 (75, 83)	0.046	0.193
Catecholamine dose (ng/kg/min)	26 (16, 36)	26 (16, 36)	24 (14, 34)	25 (15, 35)	0.044	0.839

Data are given as mean (standard deviation).

Abbreviations: C_R, compliance of the respiratory system; Horowitz index, ratio of partial pressure of oxygen and the inspiratory fraction of oxygen; HR, heart rate; FLEX, flow-controlled expiration; MAP, mean arterial pressure; P_{mean}, mean airway pressure; P_{trach_peak}, tracheal peak pressure; $P_{plateau}$, plateau pressure; Peak $flow_{exp}$, maximum expiration flow; Peak $flow_{insp}$, maximum inspiration flow; PEEP, positive end-expiratory pressure; $Petco_2$, end-tidal carbon dioxide partial pressure; R_{EX}, mean expiratory airway resistance; R_{RS}, resistance of the respiratory system; VF, ventilation frequency; V_T, tidal volume.

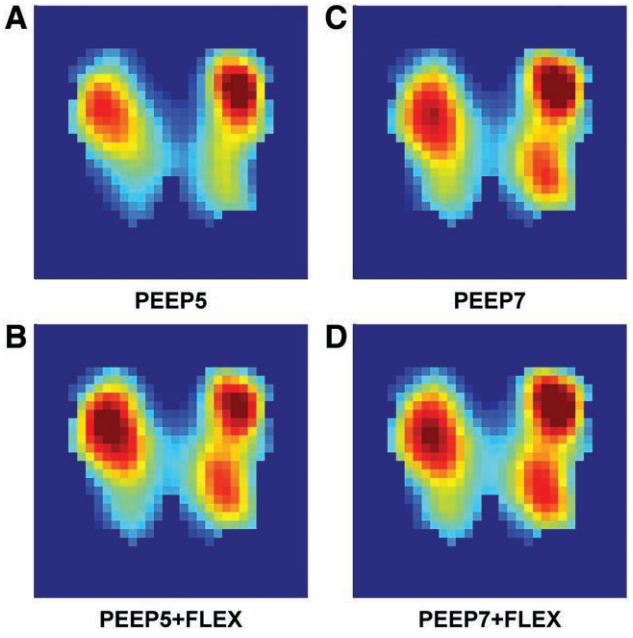

Figure 3. Example of a typical differential functional EIT image. The images display the regional differences in impedance between end and start of inspiration at ventilation with PEEP 5 cm H_2O (A), 5 cm H_2O + FLEX (B), 7 cm H_2O (C), and 7 cm H_2O + FLEX (D). Before generating the image, a mirroring technique[8] was applied to determine the lung area. EIT indicates electrical impedance tomography; FLEX, FLow-controlled EXpiration; PEEP, positive end-expiratory pressure.

H_2O with PEEP 7 cm H_2O compared with PEEP 5 cm H_2O but did not change with FLEX (Table 2; details to statistical calculations are given in Supplemental Digital Content, Table 1, http://links.lww.com/AA/B692).

Ventilation frequency and inspiratory flow rate were also not influenced by FLEX or PEEP. Mean airway pressure increased with PEEP by 1.9 cm H_2O and with FLEX by 1 cm H_2O (all $P < .001$). Inspiratory peak flow, compliance and respiratory system resistance, end-tidal carbon dioxide partial pressure, and the Horowitz index were independent of both FLEX and PEEP. In addition, heart rate, mean blood pressure, and norepinephrine dose were not significantly influenced by FLEX. Mean blood pressure was lower and norepinephrine dose higher with higher PEEP levels (Table 2).

FLEX caused significant shifts in ventilation from ventral to dorsal lung regions (Figure 3). Increases in dorsal region ventilation were higher than for the ventral region, and decreases in dorsal ventilation were lower than in the ventral region (Figure 4).

Increases in ventilation in the dorsal region and decreases in ventral ventilation were significantly larger with PEEP 7 cm H_2O than with PEEP 5 cm H_2O and with FLEX than without FLEX at both PEEP levels (Figure 5).

We observed no critical incidents or FLEX malfunctions in any measurement that would have required an intervention or termination of the measurement.

DISCUSSION

When FLEX was applied to patients undergoing neurosurgery, expected effects were easily observable in respiratory measurement parameters and ventilation curves, especially the early peak expiratory flow. FLEX increased ventilation in the dorsal-dependent lung regions, thereby homogenizing the ventilation distribution. At the same time, FLEX did not affect hemodynamics or oxygenation. The principal findings of the study indicate that FLEX improves the distribution of inspired ventilation as a consequence of more uniform homogeneous lung emptying during expiration and can be used in adult patients under controlled mechanical ventilation during general anesthesia.

FLEX decreased early expiratory peak flow and FLEX increased late expiratory flow. In contrast, during conventional expiration lung emptying is rapid with a sudden pressure drop. As a consequence, FLEX increased mean airway pressure by 1 cm H_2O. By contrast, increasing PEEP

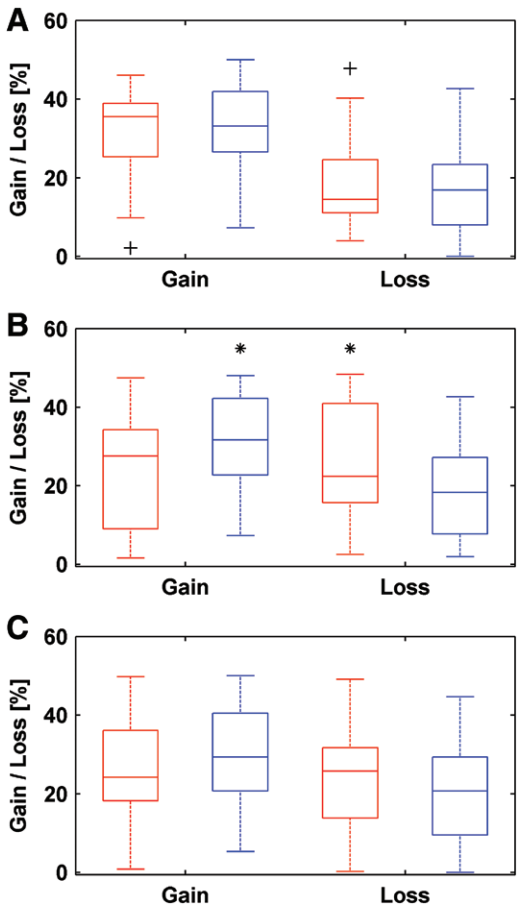

Figure 4. Relative number of EIT pixels with impedance gain and loss in the ventral (red) and dorsal (blue) region of the ventilated lung, respectively. The 3 comparisons show PEEP 7 cm H_2O versus PEEP 5 cm H_2O (A), PEEP 5 cm H_2O with FLEX versus without FLEX (B), and PEEP 7 cm H_2O with FLEX versus without FLEX (C). Increasing PEEP led to an increased gain in the ventral as well as in the dorsal regions of the lung. With FLEX at PEEP 5 cm H_2O, the gain in the dorsal (dependent) region was significantly higher ($P = .037$) than in the ventral (nondependent) region and the loss in the dorsal region was significantly lower ($P = .037$) than in the ventral region. *$P < .05$. "+" show outliers. EIT indicates electrical impedance tomography; FLEX, FLow-controlled EXpiration; PEEP, positive end-expiratory pressure.

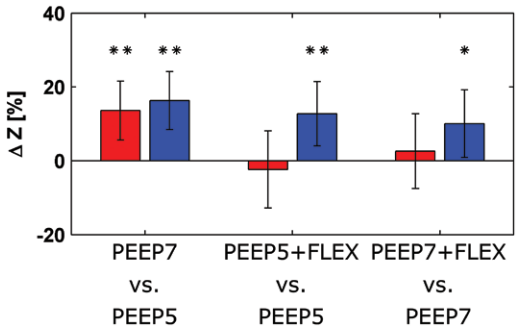

Figure 5. Relative changes in ventilation (ΔZ) in the ventral (nondependent, red) and dorsal (dependent, blue) lung regions. Higher PEEP resulted in a significant improvement in ventilation in the ventral and the dorsal part of the lung. FLEX resulted in an improvement in ventilation in the dorsal part of the lung. *$P < .05$, **$P < .01$. Whiskers indicate confidence intervals. FLEX indicates flow-controlled expiration; PEEP, positive end-expiratory pressure.

from 5 to 7 cm H_2O shifted all pressure levels and thus mean airway pressure by the amount of the PEEP increase, that is, by 2 cm H_2O.

Analysis of regional ventilation revealed in our patients in supine position, a typical shift from ventral (nondependent) to dorsal (dependent) regions of the lungs with PEEP 7 cm H_2O compared with 5 cm H_2O.[12] Similarly, FLEX shifted ventilation from ventral to dorsal regions, improving overall regional ventilation in the same fashion as an increased PEEP but without increasing peak and plateau airway pressures.

FLEX is a relatively new procedure, and to date, no published studies in humans exist. We also did not evaluate pulmonary hemodynamics or cardiac output in our study because the invasiveness of such measurements was not justifiable for such an experimental device. However, in our study, we found no FLEX-dependent effects on heart rate, mean arterial blood pressure, or catecholamine demand. In our study, in pigs with artificial lung injury, we also found no adverse effects of FLEX on heart rate, mean arterial pressure, central venous pressure, the cardiac index, or resistance in the systemic circulatory system.[6] Under FLEX, only the mean pulmonary blood pressure and the pulmonary capillary wedge pressure were decreased. In another initial study with FLEX[13] in healthy conscious volunteers, we also observed no hemodynamic effects. The current study supports our hypothesis that FLEX is hemodynamically neutral.

In lung-injured pigs, FLEX was associated with several lung protective effects: after 6 hours of mechanical ventilation, decarbonization was improved and various markers of ventilation-induced lung injury were lower with FLEX compared with conventional ventilation. Furthermore, to reach a comparable Pao_2 at the same FIo_2, 20% lower PEEP was required with FLEX than without.[6] Although the mechanism for this PEEP effect is unclear, one possibility is that FLEX may stabilize dependent areas of the lung previously recruited by plateau pressure and prevented from derecruitment during expiration. Potential positive effects of FLEX such as improved gas exchange with limited effect on hemodynamics may then be a consequence. However, in the current study with lung-healthy patients, we found no significant effects of FLEX or PEEP on gas exchange. Further studies are required to investigate the potentially beneficial effects in patients with less favorable preconditions.

It is a paradigm of nearly all mechanical ventilation modes that expiration is passive and therefore governed by the mechanical characteristics of the respiratory system. Thus, in patients with stiff lungs (ie, low compliance), expiration is relatively rapid compared with that in patients with high compliance like in chronic obstructive pulmonary disease. Furthermore, because expiration is not normally managed by the attending physician, expiratory time is not normally considered a target for potential therapy. In patients with restrictive lung injury, expiratory peak flow rates during passive expiration are often very high, and lung emptying proceeds within a few hundred milliseconds.[14] This rapid lung emptying means that fast and slow compartments empty in an inhomogeneous fashion that probably increases shear stress in the lung parenchyma. Such patients may benefit from a more homogenous lung emptying as a result of controlled expiration.

In patients with obstructive lung diseases, flow limitation and air trapping result from caliber reductions of small airways in response to high local flow rates.[15] These patients are often trained to exhale against pursed lips to increase airway pressure during expiration. In the unconscious patient with furthermore intubated/bridged airways, this breathing technique is not applicable. During mechanical ventilation, FLEX may be a mechanical surrogate for pursed lip breathing by "externally" reducing expiratory flow rate and increasing airway pressure during expiration. However, because we excluded these patient groups from our study, the potential effects need to be investigated in appropriate trials.

Earlier approaches have also aimed at decelerating expiration by adding a constant expiratory resistance.[16,17] Although the ideas behind these approaches are similar to that of FLEX, the constant expiratory resistance increases expiratory time. Incomplete expiration might therefore have prevented clinically relevant benefits[17,18] In contrast, FLEX does not prolong expiration time to a large extent. With FLEX, the expiratory flow is limited in the early expiration. As a consequence, the lung volume empties in a decelerated fashion and an expiratory gas flow is achieved nearly throughout expiration. During late expiration, however, the pressure in the lung decreases to a level at which the "targeted" flow rate cannot be achieved any more and the flow rate drops to 0. Dynamic hyperinflation may thus be detected by expiratory gas flow at the end of expiration immediately before the subsequent inspiration begins.

Our patient population and sample size do not allow us to evaluate lung-protective effects of FLEX. Longer intervention times may also be needed to show detectable differences in the application of FLEX with respect to an improvement in oxygenation.

This study is the first step in the evaluation of FLEX in patients under controlled ventilation. Our findings suggest potential benefits for different patient groups (eg, chronic obstructive pulmonary disease, acute respiratory distress syndrome, increased intra-abdominal pressure). Our principle-of-proof study was not designed to investigate outcome variables, and in our patients, effects of FLEX were limited on the homogenized ventilation. However, the homogenizing effects of FLEX may be considered lung protective. Because no adverse effects on hemodynamics were observed, FLEX may be another ventilatory option for lung-protective ventilation.

With our proof-of-principle study, we could not investigate all aspects of controlled expiration. FLEX offers various modalities. FLEX may be applied only to reduce the initial expiratory peak flow or to maintain a linearized flow throughout the full expiration phase. Furthermore, other than linear expiratory flow profiles, for example, sine-shaped, may be applied. Further studies are needed to clarify the effects of FLEX on other ventilator parameters.

SUMMARY

In our pilot study of 34 patients, FLEX increased mean airway pressure moderately. Comparable to an increase of PEEP, FLEX improved the ventilation in the dorsal areas and thus homogenized regional ventilation, however, without changing PEEP and peak pressure. We found no adverse effects of FLEX on hemodynamic parameters. Patients with impaired lung function of various origins may potentially benefit from ventilation with FLEX.

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DISCLOSURES

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Name: Silke Borgmann, PhD.
Contribution: This author helped analyze the data (EIT) and write the manuscript.
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Name: Stefan Schumann, PhD.
Contribution: This author helped conceptualize and design the study, interpret the data, and write the manuscript.
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