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Effects of Different Levels of Pressure Support Variability in Experimental Lung Injury

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Background: **Noisy pressure support ventilation has been reported to improve respiratory function compared to conventional assisted mechanical ventilation. We aimed at determining the optimal level of pressure support variability during noisy pressure support ventilation.**

Methods: **Twelve pigs were anesthetized and mechanically ventilated. Acute lung injury was induced by surfactant depletion. At four levels of pressure support variability (coefficients of variation of pressure support equal to 7.5, 15, 30, and 45%, 30 min each, crossover design, special Latin squares sequence), we measured respiratory variables, gas exchange, hemodynamics, inspiratory effort, and comfort of breathing. The mean level of tidal volume was constant among variability levels.**

Results: **Compared to conventional pressure support ventilation, different levels of variability in pressure support improved the elastance of the respiratory system, peak airway pressure, oxygenation, and intrapulmonary shunt. Oxygenation and venous admixture benefited more from intermediate (30%) levels of variability, whereas elastance and peak airway pressure improved linearly with increasing variability. Heart rate as well as mean arterial and pulmonary arterial pressures decreased slightly at intermediate to high (30–45%) levels of variability in pressure support. Inspiratory effort and comfort of breathing were not importantly influenced by increased variability in pressure support.**

Conclusion: **In a surfactant depletion model of acute lung injury, variability of pressure support improves lung function. The variability level of 30% seems to represent a reasonable compromise to improve lung functional variables during noisy pressure support ventilation.**

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IN patients suffering from the acute respiratory distress syndrome, mechanical ventilation may be required to treat severe gas exchange impairment and avoid fatigue of respiratory muscles. Volume assist-control is the most common ventilator mode used in this scenario.[1] However, controlled ventilation requires deep sedation and sometimes muscle paralysis, which can result in diaphragmatic dysfunction.[2–4] Different studies suggest that a certain amount of spontaneous ventilatory effort may be beneficial during mechanical ventilation, not only by avoiding diaphragm dysfunction, but also by improving respiratory mechanics and regional ventilation/perfusion matching.[5–8] More recently, the variation of the breathing pattern, *i.e.*, the use of noise, has been reported to improve lung function during both controlled[9,10] and pressure support ventilation.[11]

The degree of variability of tidal volumes (V_T) and respiratory frequency (RR) may differently affect lung functional variables. Suki and coworkers postulated that the lungs behave like a stochastic resonance system.[12] According to this hypothesis, the level of noise in V_T, which represents the input of the system, may influence the amplitude of its output, most notably the oxygenation. Accordingly, excessive as well as lack of variability in V_T may worsen lung function. In controlled mechanical ventilation, it has been suggested that variation of V_T within 40 to 60% of mean value resulted in improved respiratory system mechanics and oxygenation in endotoxin-induced lung injury.[13]

In the surfactant depletion model of acute lung injury (ALI), we found that noise in pressure support leading to approximately 20% variation in V_T (coefficient of variation [CV], normal distribution) was able to improve oxygenation compared to conventional assisted mechanical ventilation.[11] We termed that novel mode of assisted mechanical ventilation "noisy pressure support ventilation (noisy PSV)." However, we did not assess the effects of different degrees of V_T variability with noisy PSV.

Basically, noisy PSV differs from other assisted mechanical ventilation modes that may also increase the variability of the respiratory pattern (*e.g.*, proportional assist ventilation) by the fact that the variability does not depend on changes in the patient's inspiratory efforts; rather, it is generated externally by the mechanical ventilator. Thus, noisy PSV is able to guarantee a given level of variability by generating different pressure support values, even if the patient is not able to vary the respiratory pattern due to the underlying disease or sedation.

The aim of this study was to determine the optimal variability for noisy PSV in experimental ALI based on its

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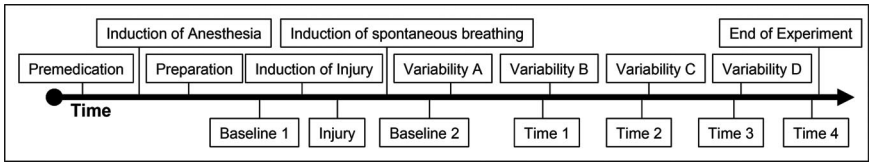

Fig. 1. Time course of interventions. Variabilities *A, B, C and D* correspond to the levels of variability in pressure support ventilation (noisy PSV) that were tested in random sequence according to a special Latin squares sequences (see Protocol of Measurements in the Material and Methods section).

effects on respiratory mechanics, breathing comfort, gas exchange, and hemodynamics. We hypothesized that noise in pressure support leads to variations in V_T that are able to improve lung function and that physiologic variables respond differently to the degree of variability in pressure support.

Materials and Methods

The protocol was approved by the Institutional Animal Care Committee and the Government of the State of Saxony, Germany. Figure 1 shows the sequence of interventions performed, which are described in detail in this section. Throughout this work, variability is used as a synonym for CV, unless stated otherwise.

Anesthesia and Mechanical Ventilation

Twelve juvenile female pigs with a mean bodyweight of 29.0 kg (range 26.6–31.0 kg) were premedicated with 10 mg/kg ketamine (ketamin-ratiopharm; Ratiopharm, Ulm, Germany) and 1 mg/kg midazolam (midazolam-ratiopharm, Ratiopharm). Animals had their trachea intubated with a cuffed 8.0-mm ID endotracheal tube (Malinckrodt, Athlone, Ireland). Anesthesia was deepened and maintained by means of continuous intravenous application of midazolam (initial bolus of 0.5–1.0 mg · kg^{-1}; maintenance with 1.5–6 mg · kg^{-1} · h^{-1}) and ketamine (initial bolus of 3–4 mg · kg^{-1}; maintenance with 5–30 mg · kg^{-1} · h^{-1}). Animals were kept in the supine position during the whole experiment. Paralysis was achieved by administration of 4 mg of pancuronium (pancuronium-ratiopharm, Ratiopharm) before baseline and injury measurements. Volume-controlled mechanical ventilation was performed using an intensive care respirator (EVITA XL 4Lab; Dräger Medical, Lübeck, Germany). The ventilator settings during baseline and injury were as follows: fraction of inspired oxygen (F_{IO_2}) = 1.0; V_T = 10 ml/kg; positive end-expiratory pressure (PEEP) = 5 cm H_2O; ratio of inspiratory to expiratory time (I:E) = 1:1 to minimize inspiratory pressures. RR was adjusted to achieve P_{aCO_2} in the range of 35–45 mmHg. Volume status was maintained with infusion of a crystalloid solution (E153: osmolarity = 303 mOsm/L, Na = 140 mM, K = 5 mM, Ca = 2.5 mM, Mg = 1.5 mM, Cl = 104.5 mM, acetate = 50 mM; Serumwerke Bernburg, Bernburg, Germany) at 20–40 ml · kg^{-1} · h^{-1} to keep pulmonary capillary wedge pressure constant below 14 mmHg.

Instrumentation and Sensor Placement

After surgical preparation of the right internal carotid artery and the right external jugular vein, an indwelling catheter was inserted into the carotid artery to measure the arterial blood pressure (BP) continuously and obtain blood samples. A pulmonary artery catheter (Abbott, Abbott Park, IL) was advanced through the external jugular vein until typical pulmonary artery pressure waveforms could be observed.

The signals of airway pressure, esophageal pressure and airway flow were acquired continuously as described elsewhere.[11,14] Briefly, a heated pneumotachograph (Fleisch No. 2; Fleisch, Lausanne, Switzerland) connected to a differential pressure transducer (PXL12X5DN; Sensortechnics, Troy, NY) was placed between the Y-piece of the mechanical ventilator tubing and endotracheal tube to determine $\dot{V}$. Airway pressure was monitored by a second pressure transducer (SCX01DNC; SenSym ICT, Milpitas, CA.) placed at the proximal end of the endotracheal tube. An esophageal balloon catheter (Erich Jaeger, Höchberg, Germany) was advanced into the mid chest and connected to a pressure transducer (SCX01DNC, SenSym ICT). The signals of airway pressure, esophageal pressure, and airway flow were acquired by a LabVIEW-based data acquisition system (National Instruments, Austin, TX).

Blood Gases and Hemodynamics

Arterial and mixed venous blood samples were analyzed using a standard blood gas analyzer (ABL 505; Radiometer, Copenhagen, Denmark). Oxygen saturation and hemoglobin concentration were measured using an OSM 3 Hemoximeter (Radiometer) calibrated for swine blood. Heart rate, mean arterial BP, and mean pulmonary arterial BP were measured using a commercial monitor (CMS; Agilent, Böblingen, Germany). Cardiac output was determined by the conventional bolus thermodilution method as described elsewhere.[14] Venous admixture ($\dot{Q}_{va}/\dot{Q}_t$) was calculated using standard formulae.

Respiratory Mechanics and Derived Parameters

Dynamic respiratory mechanics and derived parameters were calculated offline from continuous recordings (2 min during controlled ventilation and 5 min during assisted ventilation) of airway pressure, esophageal pressure, and airway flow, as described in detail before.[14] The product of esophageal pressure over time was calculated during inspiration, taking the first value at the beginning of the respiratory cycle as offset. Airway pressure at 100 ms after

beginning of inspiration ($P_{0.1}$) was determined and used as surrogate of the central respiratory drive. Inspiratory pressure time product and $P_{0.1}$ values were averaged throughout the whole acquisition periods. Comfort of breathing was evaluated with the Aachen Breathing Comfort Score as proposed by Henzler *et al.*[15]

Noisy PSV

Normalized sets of 600 randomly generated, normally distributed pressure values with mean ± SD = 1 ± 0.075, 1 ± 0.15, 1 ± 0.30, and 1 ± 0.45 were created, correspondeding to the levels of variability of 7.5, 15, 30, and 45%, respectively. The minimal level of variability of pressure support was 7.5% because it is only slightly higher than the intrinsic variability observed during traditional PSV in our previous study.[11] The highest level of variability of pressure support was 45% to avoid Ppeak incompatible with clinical use.

To obtain the sequence of pressure support levels to be effectively used during the experiments, each set of normalized values was multiplied by the target mean pressure support. The target mean pressure support represented the value needed to obtain a V_T of 6 ml/kg. After completion of a cycle of 600 breaths, the system looped itself. For safety reasons, the pressure limit of the ventilator was set at 40 cm H_2O throughout the whole experiment.

Protocol of Measurements

Initially, the lungs were recruited with an inspiratory pressure of 30 cm H_2O for 30 s, and the animals were allowed to stabilize for 15 min. Then, baseline measurements were obtained under volume-controlled mechanical ventilation (*Baseline volume controlled*).

Acute lung injury was induced by repetitive lung lavage of surfactant with warmed (37°C) 0.9% saline.[16] Injury was considered stable if Pa_{O_2}/F_{IO_2} was less than 100 mmHg for at least 30 min. Thereafter, measurements of acute lung injury under volume controlled mechanical ventilation (*Injury*) with the same settings of *Baseline volume controlled* were performed.

To resume spontaneous breathing, the depth of anesthesia was decreased (midazolam = 1–2 $mg \cdot kg^{-1} \cdot h^{-1}$, ketamine = 5–15 $mg \cdot kg^{-1} \cdot h^{-1}$). When inspiratory efforts could be observed in the esophageal pressure signal, the mechanical ventilation mode was changed to conventional PSV with the following settings: $F_{IO_2} = 0.7$, PEEP = 10 cm H_2O (stepwise change), inspiratory pressure = adjusted to reach a V_T of 6 ml/kg, flow trigger = 2 l/min. PEEP was increased to permit lung recruitment and stabilization, reproducing usual clinical practice. After a stabilization period of 30–60 min, the ventilator was set at the continuous positive airway pressure mode with PEEP of 5 cm H_2O for 2 min to reset the pulmonary volume history (derecruitment maneuver). Thereafter, PSV was resumed for 30 min with the same settings as described above, being followed by baseline measurements during acute lung injury and assisted mechanical ventilation (baseline PSV). The derecruitment maneuver was repeated after baseline PSV as well as after every subsequent variability level of noisy PSV in order to restore the pulmonary volume history and minimize possible carryover effects among the different variability levels within the crossover design. Animals were ventilated with different degrees of pressure support variability (noisy PSV 7.5%, 15%, 30%, and 45%, respectively) for 30 min, and measurements were taken at the end of each level of variability. Except to the degree of variability, the settings of noisy PSV were the same as described for baseline PSV.

The sequence of variability modes in this crossover design was determined for each animal according to a special 4 × 4 (therapies × animals) Latin square.[11] The following sequences were used: A-B-C-D; B-D-A-C; D-C-B-A; C-A-D-B, where A, B, C, and D represent the degrees of variability tested. Each sequence was repeated 3 times, for a total of 12 animals. According to this design, a given degree of variability is never preceded or followed by the same degree of variability twice within a block of 4 animals, and all animals are treated with all degrees of variability to balance for possible carryover effects.

At the end of the experiment, animals were killed by bolus injection of 2 g of thiopental (Altana, Konstanz, Germany) and 50 ml of KCl 1M (Serumwerke Bernburg).

Statistical Analyses

Values are given as mean ± SD or median and 25–75% interquartiles for the CV of selected variables. Comparisons of selected CVs at baseline PSV, and different levels of variability were tested nonparametrically with the Wilcoxon test. The response of the respiratory system to different levels of noisy PSV variability as compared to conventional PSV was assessed by paired *t* tests. Multiple comparisons in univariate tests were adjusted according the Bonferroni procedure. General linear model statistics were used to determine the effects of the four levels of variability on functional variables of the respiratory system (within-subjects factor = four degrees of variability; planned contrasts for the degree of variability = linear and quadratic). Multiple measurements were adjusted according to Sidak.[17] All statistical tests were performed using the Software SPSS (Vers. 15.0, Chicago, IL). Statistical significance was accepted at $P < 0.05$ (two-tailed for all tests).

Results

Figure 2 shows typical recordings of airway pressure and $\dot{V}$ signals obtained with the different levels of

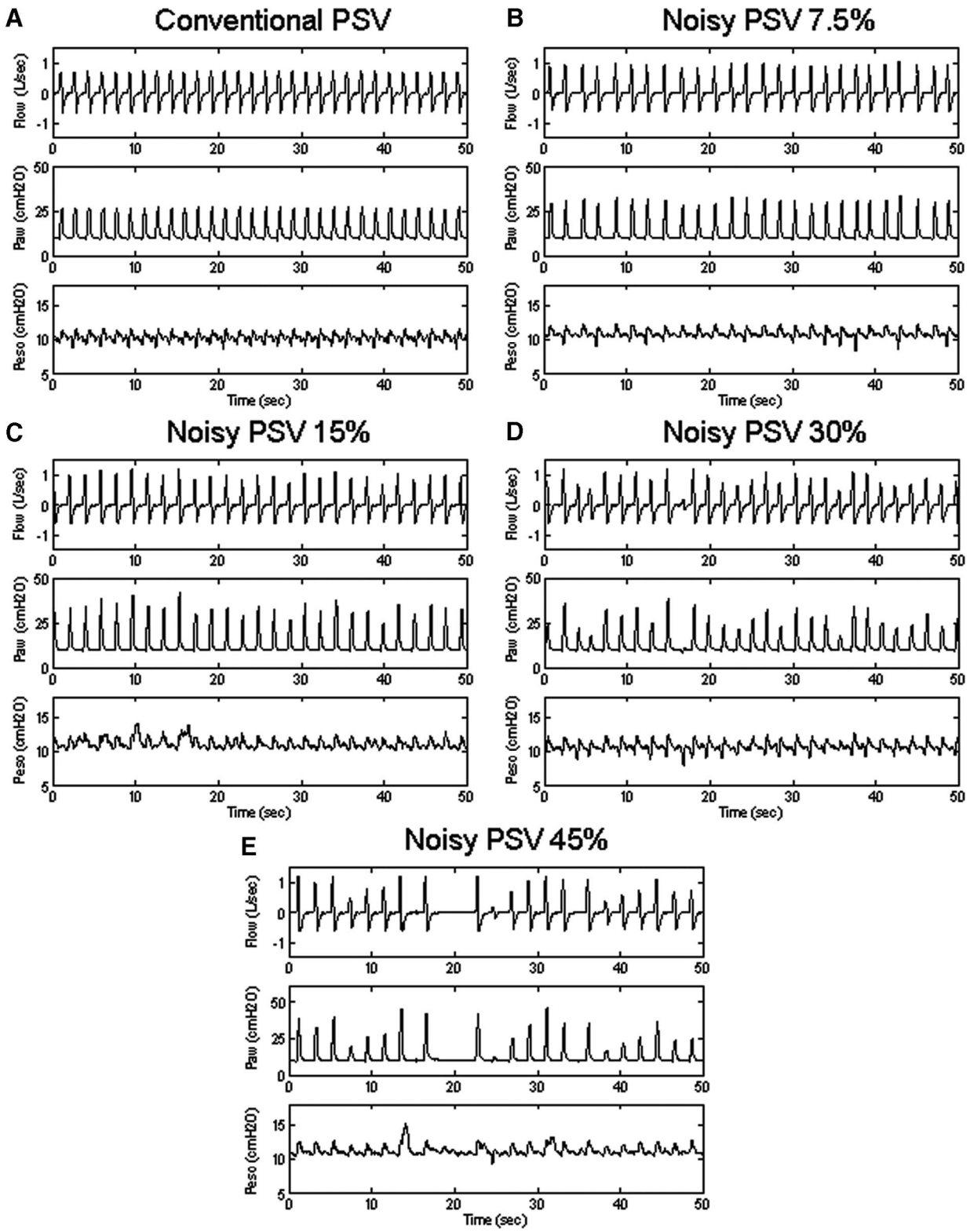

Fig. 2. Recordings of airway flow (*Flow*), airway pressure (*Paw*), and esophageal pressure (*Peso*) in one representative animal. (*A*) Conventional pressure support ventilation (conventional PSV); (*B–E*) variable pressure support ventilation (noisy PSV) with different degrees of pressure support variability (7.5, 15, 30, and 45%—coefficient of variation, normal distribution).

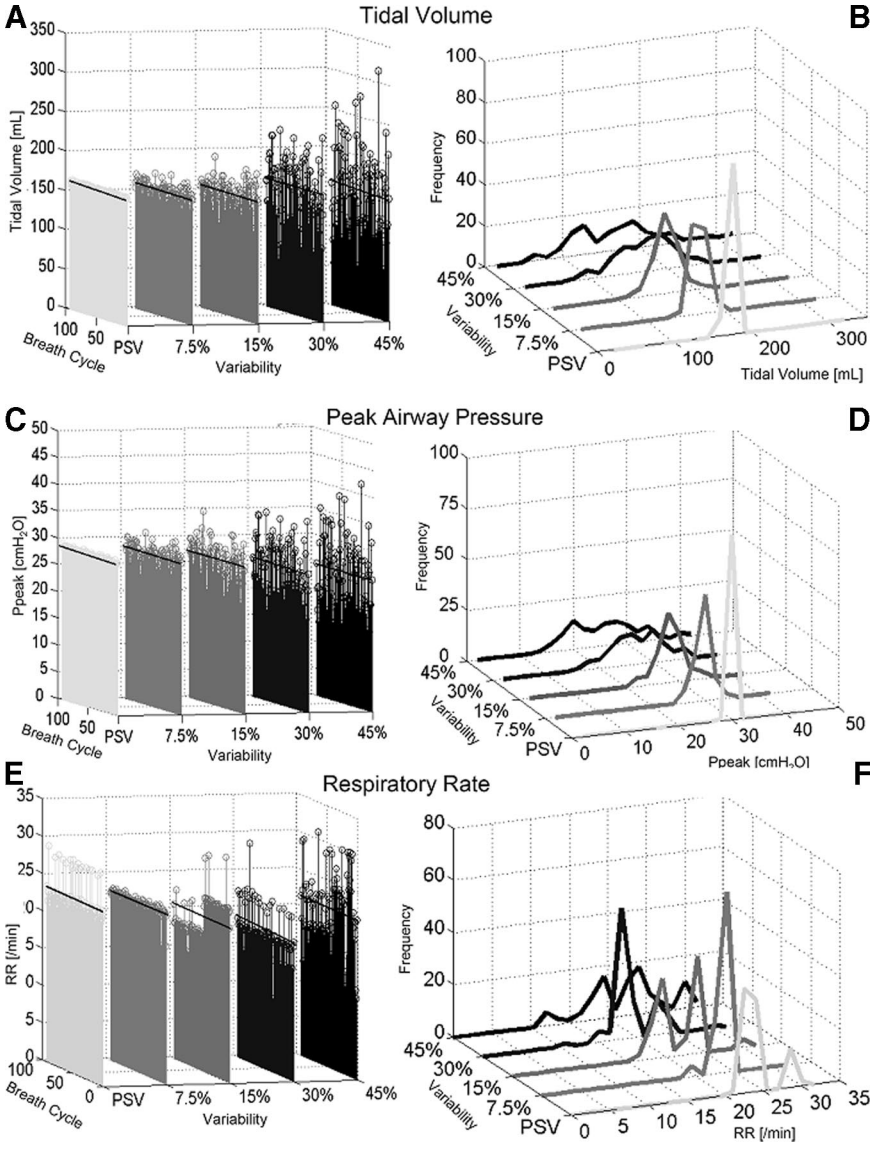

Fig. 3. Recordings of tidal volume (*A, B*), peak airway pressure (Ppeak - *C, D*), and respiratory rate (RR - *E, F*) in one representative animal. *A, C,* and *E* represent breath-by-breath recordings (*horizontal lines* indicate means). *B, D,* and *F* represent respective frequency distributions.

variability during PSV. While conventional PSV resulted in an almost monotonic respiratory pattern, noisy PSV led to a polymorph pattern which heterogeneity increased with the variability in pressure support.

Figure 3 shows typical recordings of V_T, Ppeak, and RR for the different levels of variability in pressure support in one representative animal. Although mean V_T remained unchanged, the dispersion of V_T became higher with increasing variability in pressure support. A similar increase in dispersion could be observed with Ppeak and RR. Mean values of Ppeak decreased with increasing variability, whereas RR evidenced a nadir at a variability level of 30%.

As shown in table 1, the CV of V_T, Ppeak, and RR increased with variability of pressure support, although they were lower than the variability of the input signal set at the ventilator. Whereas the CV of Ppeak began to

Table 1. Coefficients of Variation

	Baseline PSV	Noisy PSV 7.5%	Noisy PSV 15%	Noisy PSV 30%	Noisy PSV 45%
CV V_T (%)	1 (1–5)	6 (5–7)	10 (9–11)*†	23 (21–27)*†‡	38 (36–40)*†‡§
CV Ppeak (%)	1 (1–1)	5 (5–5)*	9 (9–10)*†	18 (17–19)*†‡	25 (24–28)*†‡§
CV RR (%)	14 (8–18)	10 (6–17)	13 (9–19)	17 (12–20)	23 (20–26)*†

Data are presented as median and interquartiles (25–75%). Data were tested with the Wilcoxon test and adjusted for multiple comparisons by the Bonferroni procedure.

* $P < 0.05$ *vs.* baseline PSV. † $P < 0.05$ *vs.* noisy PSV 7.5%. ‡ $P < 0.05$ *vs.* noisy PSV 15%. § $P < 0.05$ *vs.* noisy PSV 30%.

CV V_T = coefficient of variation of tidal volume; CV Ppeak = coefficient of variation of peak airway pressure; CV RR = coefficient of variation of respiratory rate; PSV = conventional pressure support ventilation; noisy PSV = pressure support ventilation with variable pressure support levels.

Table 2. Respiratory Variables

	Baseline VCV	Injury	Baseline PSV	Noisy PSV 7.5%	Noisy PSV 15%	Noisy PSV 30%	Noisy PSV 45%	GLM $P < 0.05$
RR, /min	14 ± 1	14 ± 1	34 ± 6	32 ± 5	29 ± 5	30 ± 6	29 ± 6	NS
MV, L/min	4 ± 0	4 ± 0	6 ± 1	6 ± 1	5 ± 1*	5 ± 1*	5 ± 1*	§
V_T, mL	286 ± 3	283 ± 15	172 ± 9.1	177 ± 17	181 ± 14*	179 ± 16	178 ± 18	NS
Ppeak, cm H_2O	18.7 ± 1.3	35.4 ± 3.5	28.9 ± 2.6	29.1 ± 2.2	28.7 ± 2.8	27.5 ± 2.7*	26.2 ± 2.5*†‡	§‖
Pmean, cm H_2O	10.3 ±.7	17.2 ± 1.3	13.2 ± .5	13.2 ± .8	12.9 ± .4*	13.0 ± .7	12.9 ± .5*	NS
Peso, cm H_2O	6.5 ± .6	7.3 ± 1.2	8.5 ± 1.4	9.1 ± 1.4	9.1 ± 1.4	9.2 ± 1.2	9.1 ± 1.0	NS
Ers, cm H_2O/L	34.1 ± 5.2	92.4 ± 11.9	111.5 ± 18.4	107.2 ± 16.1	102.7 ± 16.0	96.0 ± 20.1*†	85.9 ± 14.1*†‡	§‖
PTP, cm H_2O · sec/min			10.2 ± 11.7	13.2 ± 19.5	7.2 ± 7.4	11.1 ± 13.1	10.6 ± 8.3	NS
$P_{0.1}$, cm H_2O			0.7 ± .5	0.6 ± .3	0.5 ± .3	0.7 ± .4	0.7 ± .4	NS
ABC score, 0–60			47 ± 3	49 ± 2	49 ± 2	50 ± 2*	49 ± 2	NS

Data are presented as mean ± SD. Baseline PSV *vs.* different variability levels was tested with paired *t* tests adjusted by means of the Bonferroni procedure (* $P < 0.05$ *vs.* baseline PSV). Differences among variability levels were tested with general linear model statistics (GLM; within-subjects factor = 4 degrees variability; planned contrasts for the degree of variability = linear and quadratic) († $P<.05$ *vs.* 7.5%; ‡ $P<.05$ *vs.* 15%). Statistical significance of global tests is indicated by § $P<.05$ based on within-subject effects or ‖ $P<.05$ based on linear contrasts.

ABC Score = Aachen Breathing Comfort Score; Ers = elastance of the respiratory system; PSV = conventional pressure support ventilation; Ppeak = peak airway pressure; Pmean = mean airway pressure; Peso = esophageal pressure; PTP = pressure time product; $P_{0.1}$ = airway pressure 100 ms after beginning of inspiration; RR = respiratory rate; MV = minute ventilation; NS = not significant; noisy PSV = pressure support ventilation with variable pressure support levels; VCV = volume controlled ventilation; V_T = tidal volume.

increase at the pressure support variability level of 7.5%, CVs of V_T and RR started to increase at 15% and 45% variability levels, respectively.

Table 2 depicts the effects of variability of PSV on respiratory variables. RR did not show significant differences among variability levels or as compared to baseline PSV. Minute ventilation was lower at 15%, 30%, and 45% PSV variability as compared to baseline PSV and differed significantly among variability levels. V_T was comparable among variability levels. Levels of variability in pressure support of 30% and 45% were associated with lower Ppeak compared to baseline PSV. Mean Ppeak differed among variability levels and decreased linearly with increasing variability. Pmean decreased by only 0.3 cm H_2O at variability levels of 15 and 45% compared to baseline PSV. No significant differences in Pmean were detected among the different levels of pressure support variability.

Figure 4 shows typical recordings of elastance of the respiratory system (Ers) at each level of variability in pressure support in one representative animal. Dispersion of Ers increased, while mean values decreased with variability. As shown in table 2, mean Ers decreased with variability levels of 30 and 45% compared to Baseline PSV. In addition, Ers values differed significantly among variability levels, improving linearly with increasing variability.

Variability in pressure support did not result in significant changes in inspiratory pressure time product and $P_{0.1}$ compared to baseline PSV (table 2). Also, inspiratory pressure time product and $P_{0.1}$ did not differ among

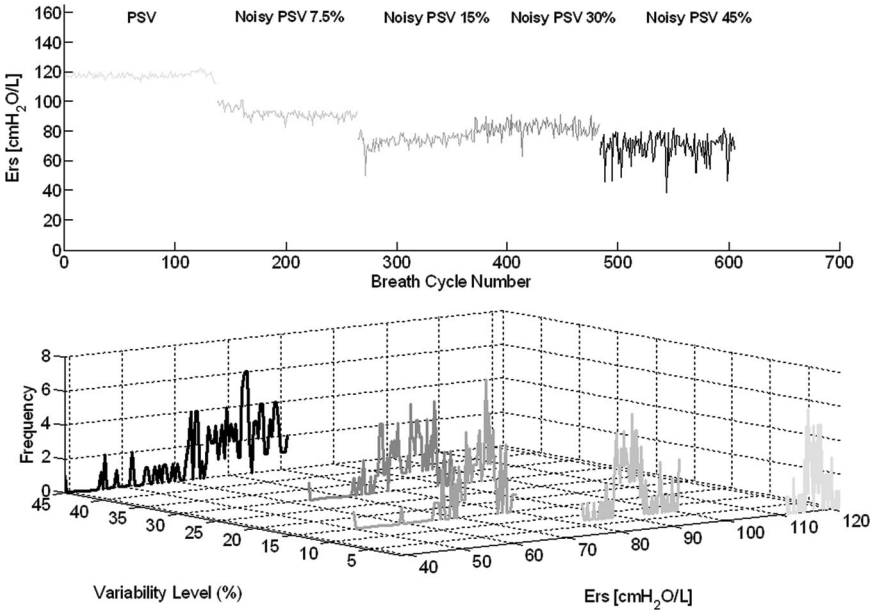

Fig. 4. The *two-dimensional plot* shows the elastance of the respiratory system (Ers) at different levels of pressure support variability in one representative animal. In the *three-dimensional plot*, the corresponding changes in mean values as well as the increasing dispersion with increasing variability are illustrated. The increased variability of the output variable (Ers) is related to the noise of the input signal (variability of pressure support). The different degrees of variability are displayed as *grayscale values* ranging from conventional pressure support ventilation (PSV, *bright gray*) to noisy pressure support ventilation with a coefficient of variation of the pressure support of 45% (noisy PSV 45%, *black*).

Table 3. Gas Exchange and Hemodynamics

	Baseline VCV	Injury VCV	Baseline PSV	Noisy PSV 7.5%	Noisy PSV 15%	Noisy PSV 30%	Noisy PSV 45%	GLM, $P < 0.05$
Pao_2/Fio_2, mmHg	540 ± 22	61 ± 13	295 ± 75	371 ± 55*	374 ± 69*	395 ± 49*	372 ± 52*	#
$Paco_2$, mmHg	43 ± 2	60 ± 5	52 ± 7	50 ± 7	48 ± 8	50 ± 9	50 ± 7	NS
pH	7.41 ± .02	7.28 ± .04	7.36 ± .05	7.40 ± .05	7.41 ± .05	7.40 ± .05	7.39 ± .05	NS
Q_{VA}/Q_t, %	13 ± 4	58 ± 14	22 ± 6	16 ± 4*	15 ± 3*	14 ± 3*	16 ± 3*	#
CO, l/min	4 ± 1	4 ± 1	3 ± 1	3 ± 0	3 ± 0	3 ± 1	3 ± 1	NS
HR, /min	94 ± 10	85 ± 13	76 ± 13	75 ± 12	73 ± 11	71 ± 12	69 ± 13*†‡	§‖
MAP, mmHg	76 ± 12	80 ± 11	81 ± 12	85 ± 10	86 ± 9	83 ± 12†	81 ± 10	§‖
MPAP, mmHg	24 ± 2	35 ± 5	31 ± 3	31 ± 3	30 ± 3	29 ± 2*†	29 ± 2*	§‖

Data are presented as mean ± SD. Baseline PSV *vs.* different variability levels was tested with paired *t* tests adjusted by means of the Bonferroni procedure (* $P < 0.05$ *vs.* baseline PSV). Differences among variability levels were tested with general linear model statistics (GLM; within-subjects factor = 4 degrees variability; planned contrasts for the degree of variability = linear and quadratic) († $P < 0.05$ *vs.* 7.5%; ‡ $P < 0.05$ *vs.* 15%). Statistical significance of global tests is indicated by § $P < 0.05$ based on within-subject effects, ‖ $P < 0.05$ based on linear contrasts or # $P < 0.05$ based on quadratic contrasts.

CO = cardiac output; HR = heart rate; MAP = mean arterial blood pressure; MPAP = mean pulmonary arterial blood pressure; noisy PSV = pressure support ventilation with variable pressure support levels; NS = not significant; Pao_2/Fio_2 = ratio of arterial partial pressure of oxygen and inspired oxygen fraction; $Paco_2$ = arterial partial pressure of carbon dioxide; PSV = conventional pressure support ventilation; Q_{VA}/Q_t = venous admixture; = VCV, volume controlled ventilation.

different pressure support variability levels. The Aachen Breathing Comfort Score indicated a relatively high degree of breathing comfort (≥ 43 of 60) with both conventional and noisy PSV. The variability level of 30% was associated with a slightly higher improvement in breathing comfort compared to Baseline PSV.

The effects on gas exchange and hemodynamics are shown in table 3. All variability levels improved Pao_2/Fio_2 and $\dot{Q}_{va}/\dot{Q}_t$, but not $Paco_2$, as compared to baseline PSV. Contrast analysis showed more pronounced effects on Pao_2/Fio_2 and $\dot{Q}_{va}/\dot{Q}_t$ at intermediate levels (15 to 30%) of variability. Heart rate, mean arterial BP, and pulmonary arterial BP decreased linearly with increasing variability levels in pressure support.

Discussion

Our major findings were that: (1) compared to conventional PSV, different levels of variability in pressure support improved Ers, Ppeak, Pao_2/Fio_2, and $\dot{Q}_{va}/\dot{Q}_t$ without influencing $Paco_2$; (2) Pao_2/Fio_2 and $\dot{Q}_{va}/\dot{Q}_t$ benefitted more from intermediate (30%) levels of variability, but Ers and Ppeak improved linearly with increasing variability; (3) heart rate, mean arterial BP, and pulmonary arterial BP decreased slightly at intermediate (30%) to high (45%) levels of variability in pressure support; and (4) inspiratory effort and comfort of breathing were not importantly influenced by increased variability in pressure support.

Biologic systems seem to benefit from noise, and the loss of variability is usually associated with organ dysfunction.[12,18] During controlled mechanical ventilation, the use of biologic variable respiratory patterns are associated with improved lung function under conditions as different as ALI,[10] asthma,[19] atelectasis,[20,21] and one-lung ventilation.[22] Suki *et al.*[12] suggested that the respiratory system may function as a stochastic resonance system, where variability of the input signal (*e.g.*, breathing pattern) influences the amplitude of the output signal (*e.g.*, gas exchange and lung mechanics). According to this hypothesis, the variability of V_T and RR can be tuned to improve the respiratory variables.

PSV represents the most used form of assisted ventilation.[1] During PSV, the subject is able to initiate the inspiratory cycle by triggering the ventilator, partially controlling the inspiratory time through the inspiratory and expiratory muscular activity. However, being the pressure support level and the inspiratory effort constant due to use of sedation and/or underlying disease, the variability of the respiratory pattern may be reduced. Recently, we showed that noisy PSV is superior to conventional PSV to improve respiratory function.[11] The present study confirms that finding. Moreover, we found that the level of variability in pressure support affects the breathing pattern, Ers, and oxygenation.

Noisy PSV cannot be considered simply as a combination of sighs with conventional PSV. Patroniti *et al.*[23] showed that intermittent sighs during PSV may improve respiratory function in clinical ALI. However, in our previous work, noisy PSV was found to improve oxygenation compared to PSV+sighs.[11] Theoretically, variability could also be applied to other settings of PSV to yield a variable respiratory pattern. For example, the cycling-off criteria could be modulated to obtain variable V_T. We opted for variation of pressure support because of its direct association with V_T and ease of remote control.

Effects on Breathing Pattern

The increased variability of pressure support was associated with a progressive increase in the variability of V_T. The variability of Ppeak also increased, but absolute values were lower than those set for pressure support due to the fact that the maximal inspiratory pressure was

limited to 40 cm H_2O to protect the lungs against excessive inflation. The fact that CV of V_T was higher than CV of Ppeak is most probably explained by the lung pressure-volume curve, which may make the distribution curve of V_T flatter than that of Ppeak values. Surprisingly, we found that the variability levels of pressure support of 7.5, 15, and 30% were not associated with higher variability in RR than conventional PSV. This suggests that the respiratory center triggered the inspiration at variable time intervals, whereas V_T and Ppeak depended more importantly on the levels of pressure support. This hypothesis is supported by our previous finding that the inspiratory effort does not correlate with V_T during noisy PSV.[11]

Effects on Respiratory Variables

Noisy PSV markedly reduced Ers and Ppeak, as compared to conventional PSV. Different hypotheses can explain this observation: (1) recruitment of previously collapsed lung regions; (2) different distribution of alveolar inflation; (3) structural changes in the mechanical properties of the lung tissue. In our previous study, we did not find evidence of recruitment during noisy PSV.[11] However, PEEP levels used in that study were lower than in the present one (5 *vs.* 10 cm H_2O). It is possible that the level of PEEP as used in the present study (10 cm H_2O) was enough to keep the lungs open after recruitment induced by noisy PSV. We cannot exclude that more homogeneous redistribution of ventilation and/or structural changes in the mechanical properties of the lung tissues induced by noisy PSV could have contributed to this finding. During controlled mechanical ventilation, Arold *et al.* also found a progressive decrease in tissue elastance with increased variability.[13]

Minute ventilation decreased with increasing variability of pressure support as compared to conventional PSV mainly due to a reduction in mean RR with constant mean V_T. The reduction in RR during noisy PSV could be explained by the Hering-Breuer reflex; higher end-inspiratory volumes in the lungs occurred more frequently at higher variability levels of pressure support.

The fact that noisy PSV did not lead to clinically relevant effects on inspiratory effort and breathing comfort is in agreement with our previous data showing that variability in pressure support of 30% does not change inspiratory pressure time product or $P_{0.1}$ compared to conventional PSV.[11]

Effects on Gas Exchange and Hemodynamics

We confirmed our previous finding that the use of noisy PSV improves $Pa_{O_2}/F_{I_{O_2}}$ and $\dot{Q}_{va}/\dot{Q}_t$ without affecting Pa_{CO_2} compared to conventional PSV.[11] In addition, we observed that the variability of pressure support of 30% optimized oxygenation, although absolute $Pa_{O_2}/F_{I_{O_2}}$ values were relatively high. This is likely the result of recruitment due to increase of PEEP. Since one important mechanism of improvement of oxygenation during noisy PSV seems to be redistribution of perfusion towards the better aerated nondependent areas of lungs,[11] our data suggest that the variability of pressure support does not have a relevant effect on regional perfusion. In addition, we used higher PEEP levels than in our previous evaluation of noisy PSV (10 *vs.* 5 cm H_2O); it is therefore likely that lung recruitment did play a role in the improvements observed in the present study, with increased variability of pressure support, as supported by the improvement in Ers. Unfortunately, we cannot distinguish between recruitment and perfusion-distribution effects. However, it was beyond the scope of this study to the address the mechanisms of noisy PSV.

At highest (45%) levels of pressure support variability, inspiratory pressures could have been high enough to squeeze out regional intrathoracic blood volume, contributing to mismatch of ventilation-perfusion ratio[24] and explaining the decrease in $Pa_{O_2}/F_{I_{O_2}}$ at that level. However, the fact that Pa_{CO_2} did not change despite decreased minute ventilation suggests that ventilation-perfusion matching improved and dead space decreased at higher pressure support variability. Thus, it is likely that even at the lowest (7.5%) level of pressure support variability, inspiratory pressures in isolated breath cycles were higher than local opening pressures in some lung areas.[25]

The decrease in mean pulmonary arterial BP with increased variability could be explained by redistribution of pulmonary blood flow towards vascular areas with lower impedance[11] and also increased cross-sectional lung capillary area.

Possible Implications in Clinical Practice

The intrinsic variability of the respiratory drive may be reduced due to the underlying disease and use of sedation; therefore, noisy PSV could prove useful to increase the variability of the respiratory pattern as a means to improve lung function during assisted spontaneous breathing. Obviously, noisy PSV should not replace judicious dosing of sedative drugs.

Limitations

Our study has several limitations. First, the lung injury model used does not reproduce all complex clinical features of ALI and, therefore, precludes direct extrapolation of our results to other ALI models and the clinical scenario. Second, we limited our observational period to 30 min for each level of variability in pressure support. Experimental models of ALI may be unstable, and we focused on functional variables, so we tried to keep the observational time as short as possible to allow comparability among the different levels of variability. Third, baseline PSV was not performed in randomized sequence; therefore, we cannot exclude that improvement

of gas exchange in noisy PSV was biased by certain instability of the lung injury model over time. However, we compensated for that by using a Latin square design and periodically derecruitment maneuvers before each level of variability. Fourth, the range of variability in V_T was no higher than approximately 40%; however, the variability of V_T in normal subjects is situated in the range of 20–30%.[18,26] Moreover, higher variability in V_T could promote lung injury by excessive stretching, which could limit the clinical applicability of our results. Fifth, although the use of a crossover design increased the power of the analysis of functional variables, it precluded the measurement of inflammatory response. Thus, before noisy PSV can be considered for clinical use, its impact on lung inflammation must be determined.

Conclusion

In an experimental surfactant depletion model of acute lung injury, variability of pressure support improved the respiratory function. High variability (45%) levels of pressure support improved Ppeak and Ers, and moderate variability (30%) levels improved Pa_{O_2}/F_{IO_2} and $\dot{Q}_{va}\dot{Q}_t$. In addition, variability of pressure support had no clinical relevant influence on inspiratory effort or comfort of breathing. Our findings suggest that a variability level of 30% in pressure support represent the best compromise to improve pulmonary function during noisy PSV.

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