



Literature List Variable Pressure Support –

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INDEX

Writer	Subject	Publication	Page
de Magalhães R.F. et al.	Variable ventilation improves pulmonary function and reduces lung damage without increasing bacterial translocation in a rat model of experimental pneumonia.	Respir Res. 2016 Nov 25;17(1):158.	4
Gama de Abreu M. et al.	Noisy pressure support ventilation: a pilot study on a new assisted ventilation mode in experimental lung injury.	Crit Care Med. 2008 Mar;36(3):818-27. doi: 10.1097/01.CCM.0000299736.55039.3A.	5
Huhle R. et al.	Variable ventilation from bench to bedside.	Crit Care. 2016 Mar 15;20:62. doi: 10.1186/s13054-016-1216-6.	6
Mauri T. et al.	Effects of Variable Pressure Support ventilation on regional homogeneity and aeration.	10.1164/rccm.201609-1806IM	6
Morawiec E. et.	Comparative Effects of Variable Pressure Support, Neurally Adjusted Ventilatory Assist (NAVA) and Proportional Assist Ventilation (PAV) on the Variability of the Breathing Pattern and on Patient Ventilator Interaction.	American Journal of Respiratory and Critical Care Medicine 2015;191:A3163	7
Mutch W.A. et.	Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung.	Am J Respir Crit Care Med. 2000 Jul;162(1):319-23.	8
Naik B.I. et al.	Variability in Mechanical Ventilation: What's All the Noise About?	Respir Care. 2015 Aug;60(8):1203-10. doi: 10.4187/respcare.03794. Epub 2015 Feb 17.	9
Rentzsch I. et al.	Variable stretch reduces the proinflammatory response of alveolar epithelial cells.	10.1371/journal.pone.0182369	10
Shimabukuro D.W. et al.	Noisy mechanical ventilation: listen to the melody.	Anesthesiology. 2009 Feb;110(2):214-5. doi: 10.1097/ALN.0b013e3181945b63.	10

Spieth P.M. et al.	Short-term effects of noisy pressure support ventilation in patients with acute hypoxemic respiratory failure.	Crit Care. 2013 Oct 31;17(5):R261. doi: 10.1186/cc13091.	11
Spieth P.M. et al.	Effects of different levels of pressure support variability in experimental lung injury.	Anesthesiology. 2009 Feb;110(2):342-50. doi: 10.1097/ALN.0b013e318194d06e	12
Vassilakopoulos T. et al.	When mechanical ventilation mimics nature.	Crit Care Med. 2008 Mar;36(3):1009-11. doi: 10.1097/CCM.0B013E3181650592.	12
Wysocki M. et al.	Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation.	Crit Care Med. 2006 Aug;34(8):2076-83	13

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	<p>de Magalhães R.F.</p>	<p>Variable ventilation improves pulmonary function and reduces lung damage without increasing bacterial translocation in a rat model of experimental pneumonia.</p>	<p>Respir Res. 2016 Nov 25;17(1):158.</p>
<p>Background: Variable ventilation has been shown to improve pulmonary function and reduce lung damage in different models of acute respiratory distress syndrome. Nevertheless, variable ventilation has not been tested during pneumonia. Theoretically, periodic increases in tidal volume (VT) and airway pressures might worsen the impairment of alveolar barrier function usually seen in pneumonia and could increase bacterial translocation into the bloodstream. We investigated the impact of variable ventilation on lung function and histologic damage, as well as markers of lung inflammation, epithelial and endothelial cell damage, and alveolar stress, and bacterial translocation in experimental pneumonia.</p> <p>Methods: Thirty-two Wistar rats were randomly assigned to receive intratracheal of <i>Pseudomonas aeruginosa</i> (PA) or saline (SAL) (n = 16/group). After 24-h, animals were anesthetized and ventilated for 2 h with either conventional volume-controlled (VCV) or variable volume-controlled ventilation (VV), with mean VT = 6 mL/kg, PEEP = 5cmH₂O, and FiO₂ = 0.4. During VV, tidal volume varied randomly with a coefficient of variation of 30% and a Gaussian distribution. Additional animals assigned to receive either PA or SAL (n = 8/group) were not ventilated (NV) to serve as controls.</p> <p>Results: In both SAL and PA, VV improved oxygenation and lung elastance compared to VCV. In SAL, VV decreased interleukin (IL)-6 expression compared to VCV (median [interquartile range]: 1.3 [0.3-2.3] vs. 5.3 [3.6-7.0]; p = 0.02) and increased surfactant protein-D expression compared to NV (2.5 [1.9-3.5] vs. 1.2 [0.8-1.2]; p = 0.0005). In PA, compared to VCV, VV reduced perivascular edema (2.5 [2.0-3.75] vs. 6.0 [4.5-6.0]; p < 0.0001), septum neutrophils (2.0 [1.0-4.0] vs. 5.0 [3.3-6.0]; p = 0.0008), necrotizing vasculitis (3.0 [2.0-5.5] vs. 6.0 [6.0-6.0]; p = 0.0003), and ultrastructural lung damage scores (16 [14-17] vs. 24 [14-27], p < 0.0001). Blood colony-forming-unit (CFU) counts were comparable (7 [0-28] vs. 6 [0-26], p = 0.77). Compared to NV, VCV, but not VV, increased expression amphiregulin, IL-6, and cytokine-induced neutrophil chemoattractant (CINC)-1 (2.1 [1.6-2.5] vs. 0.9 [0.7-1.2], p = 0.025; 12.3 [7.9-22.0] vs. 0.8 [0.6-1.9], p = 0.006; and 4.4 [2.9-5.6] vs. 0.9 [0.8-1.4], p = 0.003, respectively). Angiotensin-2 expression was lower in VV compared to NV animals (0.5 [0.3-0.8] vs. 1.3 [1.0-1.5], p = 0.01).</p>			
<p>Conclusions: In this rat model of pneumonia, VV improved pulmonary function and reduced lung damage as compared to VCV, without increasing bacterial translocation.</p>			

	<p>Gama de Abreu M. et al.</p>	<p>Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung.</p>	<p>Crit Care Med. 2008 Mar;36(3):818-27. doi: 10.1097/01.CCM.0000299736.55039.3A.</p>
<p>Objectives: To describe and evaluate the effects of the new noisy pressure support ventilation (noisy PSV) on lung physiologic variables.</p> <p>Design and subjects: Crossover design with four modes of mechanical ventilation. A total of 12 pigs weighing 25.0-36.5 kg.</p> <p>Interventions: Animals were anesthetized, the trachea was intubated, and lungs were ventilated with a mechanical ventilator (volume-controlled mode). Acute lung injury was then induced by surfactant depletion. Biphasic intermittent airway pressure/airway pressure release ventilation (BIPAP/APRV) was initiated, and anesthesia depth was decreased to allow spontaneous breathing. After that, each animal was ventilated with four different modes of assisted mechanical ventilation (1 hr each, Latin squares sequence): 1) PSV, 2) PSV combined with intermittent sighs (PSV + Sighs), 3) BIPAP/APRV + spontaneous breathing, and 4) noisy PSV with random variation of pressure support (normal distribution). The mean level of pressure support was set identical in all PSV forms.</p> <p>Measurements and Main Results: We found that noisy PSV increased tidal volume variability compared with PSV and PSV + Sighs (19% vs. 5% and 7%, respectively, $p < .05$) independently from the inspiratory effort; improved oxygenation and reduced venous admixture but did not affect the amount of nonaerated lung tissue as compared with other assisted ventilation modes; reduced mean airway pressure at comparable minute ventilation; redistributed pulmonary blood flow toward nondependent lung regions similar to other PSV forms, whereas BIPAP/APRV + spontaneous breathing did not; and reduced the inspiratory effort and cardiac output in comparison with BIPAP/APRV + spontaneous breathing.</p>			
<p>Conclusions: In the surfactant depletion model of acute lung injury, the new noisy PSV increased the variability of the respiratory pattern and improved oxygenation by a redistribution of perfusion toward the ventilated nondependent lung regions with simultaneous lower mean airway pressure, comparable minute ventilation, and no increase in the inspiratory effort or cardiac output.</p>			

	Huhle R. et al.	Variable ventilation from bench to bedside.	Crit Care. 2016 Mar 15;20:62. doi: 10.1186/s13054-016-1216-6.
<p>Abstract: Biological systems constantly adjust their inner condition according to the external environment in order to achieve a steady state that allows their adaptation to the environment. Healthy biological systems are able to quickly adapt to changing environmental conditions and exhibit intrinsic fluctuations in function within each subsystem, for example the cardiovascular [1] and respiratory [2] systems, during steady-state conditions. In diseased biological systems, however, such intrinsic functional fluctuation (variability) is usually reduced. In fact, reduced variability of the heart rate in patients with coronary heart disease [3], of blood pressure during pre-eclampsia [4], of heart rate and blood pressure during pathological sleep [5], and of respiratory rate and tidal volume in patients with chronic obstructive pulmonary disease (COPD) [6] and prolonged weaning [7] have been documented.</p> <p>Different from most biological systems, the variability of the respiratory system can be easily influenced in an attempt to improve its function. In controlled, as well as in assisted mechanical ventilation, the variability of tidal volume and/or respiratory rate may be modulated externally by the mechanical ventilator to reproduce certain characteristics of spontaneous breathing in healthy subjects. Because mechanical ventilation represents a common intervention in intensive care and emergency medicine, interest in modes that can enhance the variability of the respiratory pattern has increased in recent years.</p>			
<p>Conclusions: In this article, we will review the rationale and mechanisms of variable ventilation, and provide a comprehensive review of the literature for both controlled and assisted variable mechanical ventilation. We will focus mainly on the translational aspects that may be relevant for the clinical practice of mechanical ventilation.</p>			

	Mauri et al.	Effects of variable pressure support ventilation on regional homogeneity and aeration	10.1164/rccm.201609-1806IM
<p>Results: The amount of tidal volume distending each region of interest (ROI1-4) became more homogeneously distributed...especially by relative increase in ROI2. Moreover, during vPSV, ΔEELV increased, mostly in ROI2. Improved ventilation homogeneity and lung aeration during vPSV were also associated with increased oxygenation and CO₂ clearance.</p> <p>Conclusions: The present case generates the hypothesis that vPSV might improve regional lung mechanics increasing aeration and ventilation homogeneity.</p>			

	<p>Morawiec E. et al.</p>	<p>Comparative Effects of Variable Pressure Support, Neurally Adjusted Ventilatory Assist (NAVA) and Proportional Assist Ventilation (PAV) on the Variability of the Breathing Pattern and on Patient Ventilator Interaction</p>	<p><i>American Journal of Respiratory and Critical Care Medicine 2015; 191:A3163</i></p>
<p>Rationale: Breathing is characterized by a cycle to cycle variability that proceeds from the complexity of the central breathing command. Mechanical ventilation induces a reduction of the variability of breathing, which is associated with negative outcomes. Restoring the variability of breathing is a new issue in mechanical ventilation. “Proportional” modes of ventilation, namely PAV and NAVA tailor the level of assistance to the demand of the patient estimated with instantaneous activity of the respiratory muscles (PAV) or the electromyographic activity of the diaphragm (NAVA). PAV and NAVA restore some of the intrinsic variability of breathing and in addition prevent lung overdistension and reduce patient-ventilator asynchrony. Variable Pressure Support Ventilation (V-PSV) is a mode that introduces some extrinsic variability through a “random” variation of the level of assistance on a cycle-by-cycle basis. The impact of extrinsic variability on breathing pattern variability and patient ventilator interaction are not known, and have never been compared to the effects of PAV and NAVA.</p> <p>Objectives: To compare the impacts of PSV, NAVA, PAV and two levels of V-PSV on: 1) the variability of breathing pattern, 2) patient-ventilator asynchrony, 3) the risk of lung overdistension defined by the prevalence of $VT > 10\text{ml/kg}$, 4) blood gases</p> <p>Patient and Methods: Cross-over, prospective, randomized controlled trial conducted in a ten-bed ICU. In 12 patients, PSV, NAVA and PAV were set for a tidal volume (VT) of 6-8 ml/kg. Two conditions of V-PSV were studied by applying a variability level of 30 and 80% (V-PSV30 and V-PSV80) to the chosen level of PSV. The five conditions were randomly applied for 1 hour each. Airway flow and pressure and the electrical activity of the diaphragm (EAdi) were measured. Were calculated: VT, inspiratory time (TI), peak (EAdi), the coefficient of variation (CV) of the pressure peak (Pmax), VT, Ti and EAdi, and the prevalence of the main patient-ventilator asynchronies.</p> <p>Main Results: 1) The variability of the breathing pattern increased in V-PSV80 and NAVA ($p < 0.05$), in a similar range (see figure: coefficient of variation of VT); 2) The overall prevalence of asynchronies was similar among conditions, with the exceptions of double triggering that were more frequent in NAVA than in PSV ($p < 0.05$); 3) there were no differences in the prevalence of $VT > 10\text{ml/kg}$; 4) blood gases were similar among conditions.</p>			
<p>Conclusions: V-PSV80 induces the same increase in breathing pattern variability than NAVA, without including more patient-ventilator asynchrony or lung overdistension.</p>			

	<p>Mutch W.A. et.</p>	<p>Biologically variable or naturally noisy mechanical ventilation recruits atelectatic lung.</p>	<p>Am J Respir Crit Care Med. 2000 Jul;162(1):319-23.</p>
<p>Abstract: Biologically variable mechanical ventilation (Vbv)-using a computer-controller to mimic the normal variability in spontaneous breathing-improves gas exchange in a model of severe lung injury (Lefevre, G. R., S. E. Kowalski, L. G. Girling, D. B. Thiessen, W. A. C. Mutch. Am. J. Respir. Crit. Care Med. 1996;154:1567-1572). Improved oxygenation with Vbv, in the face of alveolar collapse, is thought to be due to net volume recruitment secondary to the variability or increased noise in the peak inspiratory airway pressures (Ppaw). Biologically variable noise can be modeled as an inverse power law frequency distribution (y approximately 1/f(a)) (West, B. J., M. Shlesinger. Am. Sci. 1990;78:40-45). In a porcine model of atelectasis-right lung collapse with one-lung ventilation-we studied if Vbv (n = 7) better reinflates the collapsed lung compared with conventional monotonously regular control mode ventilation (Vc; n = 7) over a 5-h period. We also investigated the influence of sigh breaths with Vc (Vs; n = 8) with this model. Re-inflation of the collapsed lung was significantly enhanced with Vbv-greater Pa(O₂) (502 +/- 40 mm Hg with Vbv versus 381 +/- 40 mm Hg with Vc at 5 h; and 309 +/- 79 mm Hg with Vs; mean +/- SD), lower Pa(CO₂) (35 +/- 4 mm Hg versus 48 +/- 8 mm Hg and 50 +/- 8 mm Hg), lower shunt fraction (9.7 +/- 2.7% versus 14.6 +/- 2.0% and 22.9 +/- 6.0%), and higher respiratory system compliance (Cr_s) (1.15 +/- 0.15 ml/cm H₂O/kg versus 0.79 +/- 0.19 ml/cm H₂O/kg and 0.77 +/- 0.13 ml/cm H₂O/kg)-at lower mean Ppaw (15.7 +/- 1.4 cm H₂O versus 18.8 +/- 2.3 cm H₂O and 18.9 +/- 2.8 cm H₂O). Vbv resulted in an 11% increase in measured tidal volume (VT(m)) over that seen with Vc by 5 h (14.7 +/- 1.2 ml/kg versus 13.2 ml/kg). The respiratory rate variability programmed for Vbv demonstrated an inverse power law frequency distribution (y approximately 1/f(a)) with a = 1.6 +/- 0.3.</p>			
<p>Conclusions: These findings provide strong support for the theoretical model of noisy end-inspiratory pressure better recruiting atelectatic lung. Our results suggest that using natural biologically variable noise has enhanced the performance of a mechanical ventilator in control mode.</p>			

	Naik B.I.	Variability in Mechanical Ventilation: What's All the Noise About?	Respir Care. 2015 Aug;60(8):1203-10. doi: 10.4187/respcare.03794. Epub 2015 Feb 17.
<p>Abstract: Controlled mechanical ventilation is characterized by a fixed breathing frequency and tidal volume. Physiological and mathematical models have demonstrated the beneficial effects of varying tidal volume and/or inspiratory pressure during positive-pressure ventilation. The addition of noise (random changes) to a monotonous nonlinear biological system, such as the lung, induces stochastic resonance that contributes to the recruitment of collapsed alveoli and atelectatic lung segments. In this article, we review the mechanism of physiological pulmonary variability, the principles of noise and stochastic resonance, and the emerging understanding that there are beneficial effects of variability during mechanical ventilation.</p>			
<p>Conclusions: The current ventilatory strategy for the management of ARDS is to improve oxygenation and reduce intrapulmonary shunt by recruitment of previously collapsed alveoli. In addition, uninjured lung units must be protected from the deleterious effects of positive-pressure ventilation. Based on the best evidence to date, this involves ventilating with low VT (6 mL/kg of predicted normal body weight) and limiting plateau pressures to < 30 cm H₂O to prevent barotrauma while optimizing PEEP to reduce cyclical alveolar opening- and closing-related atelectrauma. There is less clear evidence regarding the optimum type of recruitment maneuver to perform when protective lung ventilation is employed.</p> <p>Recruitment maneuvers include intermittent sustained inflation breaths, incremental increases in PEEP, prone positioning, and intermittent large VT breaths. The choice of the recruitment maneuver is influenced by the nature of the lung injury (primary vs secondary ARDS), extent of the lung injury, hemodynamic stability, and clinician experience. However, any recruitment maneuvers associated with high inspiratory pressures may result in deleterious cardiorespiratory changes.</p> <p>Variable ventilation offers a new physiological approach to lung recruitment without the negative hemodynamic effects from markedly elevated intrathoracic pressures. Although human data for variable ventilation are limited, animal data with variable ventilation in ARDS and non-ARDS models are encouraging. Larger prospective human studies utilizing this novel strategy are needed to confirm the benefits shown by early animal data.</p>			

	Rentsch et al.	Variable stretch reduces the proinflammatory response of alveolar epithelial cells	10.1371/journal.pone.0182369
<p>Background: Mechanical ventilation has the potential to increase inflammation in both healthy and injured lungs. Several animal studies have shown that variable ventilation recruits the lungs and reduces inflammation. However, it is unclear which cellular mechanisms are involved in those findings.</p> <p>Methods: We hypothesized that variable stretch of LPS-stimulated alveolar epithelial cells (AECs) reduces the production of pro-inflammatory cytokines compared to non-variable stretch. AECs were subjected to non-variable or variable cyclic stretch (sinusoidal pattern), with and without LPS stimulation. The expression and release of interleukin-6, CXCL-2 and CCL-2 mRNA were analyzed after 4 hours. The phosphorylation of the MAPKs ERK1/2 and SAPK/JNK was determined by Western Blot analysis at 0, 15, 30, 45 and 60 min of cyclic stretch.</p> <p>Results: In LPS-stimulated AECs, variable cyclic cell stretching led to reduced cytokine expression and release compared to non-variable cell stretching. Furthermore, the phosphorylation of the MAPK ERK1/2 was increased after 30 minutes in non-variable stretched AECs, whereas variable stretched cells demonstrated only the non-stretched level of phosphorylation. After the 4h period of cyclic cell stretch and inhibition of the ERK1/2, but not the SAPK/JNK, signaling pathway, the gene expression of investigated cytokines increased in variable stretched, and decreased in non-variable stretched AECs.</p> <p>Conclusions: We conclude that in LPS-stimulated AECs, variable stretch reduced the pro-inflammatory response compared to non-variable stretch. This effect was mediated by the ERK1/2 signaling pathway, and might partly explain the findings of reduced lung inflammation during mechanical ventilation modes that enhance breath-by-breath variability of the respiratory pattern.</p>			

	Shimabukuro D.W. et al.	Noisy mechanical ventilation: listen to the melody.	Anesthesiology. 2009 Feb;110(2):214-5. doi: 10.1097/ALN.0b013e3181945b63.
<p>Controlled mechanical ventilation provides, for the most part, a breathing pattern that is very monotonous. It is against our nature, our behavior, to sustain this for a prolonged period of time. Thus, from an evolutionary standpoint, noisy pressure support ventilation may be an important component in the future treatment of ARDS/ALI.</p> <p>This study by Spieth and colleagues reminds us of the importance of variability in normal human physiology. Should we be trying to achieve “normal” physiology in an individual with severe systems dysfunction?</p> <p>Conclusions: Stochastic resonance would suggest that we make a little noise; the time is here to translate these studies to the bedside.</p>			

	Spieth P.M. et al.	Short-term effects of noisy pressure support ventilation in patients with acute hypoxemic respiratory failure.	Crit Care. 2013 Oct 31;17(5):R261. doi: 10.1186/cc13091.
<p>Introduction: This study aims at comparing the very short-term effects of conventional and noisy (variable) pressure support ventilation (PSV) in mechanically ventilated patients with acute hypoxemic respiratory failure.</p> <p>Methods: Thirteen mechanically ventilated patients with acute hypoxemic respiratory failure were enrolled in this monocentric, randomized crossover study. Patients were mechanically ventilated with conventional and noisy PSV, for one hour each, in random sequence. Pressure support was titrated to reach tidal volumes approximately 8 mL/kg in both modes. The level of positive end-expiratory pressure and fraction of inspired oxygen were kept unchanged in both modes. The coefficient of variation of pressure support during noisy PSV was set at 30%. Gas exchange, hemodynamics, lung functional parameters, distribution of ventilation by electrical impedance tomography, breathing patterns and patient-ventilator synchrony were analyzed.</p> <p>Results: Noisy PSV was not associated with any adverse event, and was well tolerated by all patients. Gas exchange, hemodynamics, respiratory mechanics and spatial distribution of ventilation did not differ significantly between conventional and noisy PSV. Noisy PSV increased the variability of tidal volume ($24.4 \pm 7.8\%$ vs. $13.7 \pm 9.1\%$, $P < 0.05$) and was associated with a reduced number of asynchrony events compared to conventional PSV (5 (0 to 15)/30 min vs. 10 (1 to 37)/30 min, $P < 0.05$).</p>			
<p>Conclusions: In the very short term, noisy PSV proved safe and feasible in patients with acute hypoxemic respiratory failure. Compared to conventional PSV, noisy PSV increased the variability of tidal volumes, and was associated with improved patient-ventilator synchrony, at comparable levels of gas exchange.</p>			

	Spieth P.M. et al.	Effects of different levels of pressure support variability in experimental lung injury.	Anesthesiology. 2009 Feb;110(2):342-50. doi: 10.1097/ALN.0b013e318194d06e
<p>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.</p> <p>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.</p> <p>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.</p>			
<p>Conclusions: 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.</p>			

	Vassilakopoulos T. et al.	When mechanical ventilation mimics nature.	Crit Care Med. 2008 Mar;36(3):1009-11. doi: 10.1097/CCM.0B013E3181650592.
<p>Explains stochastic resonance: When the end-inspiratory pressure is varied from inflation to deflation—that is, when fluctuations in the form of symmetrically distributed random noise are added to the end-inspiratory airway pressure, called “noisy ventilation,”—the mean end-inspiratory airway pressure does not change. Higher end-inspiratory pressures than the mean will recruit additional lung volume (gain), whereas lower end-inspiratory pressures will lead to derecruitment of lung volume (loss) (1, 7). Because of the nonlinearity of the pressure-volume curve, the gain is far greater than the loss, and the recruited volume available for gas exchange increases.</p>			
<p>Conclusions: However, this experimental data suggest that physicians may acquire a new tool (noisy pressure support ventilation) to artificially support the ventilatory pump that may be beneficial by being more natural, that is, by exhibiting more variability, as nature does.</p>			

	<p>Wysocki M. et al.</p>	<p>Reduced breathing variability as a predictor of unsuccessful patient separation from mechanical ventilation</p>	<p>Crit Care Med. 2006 Aug;34(8):2076-83</p>
<p>Objectives: To compare descriptors of the breath-to-breath respiratory variability during a 60-min spontaneous breathing trial in patients successfully and unsuccessfully separated from the ventilator and the endotracheal tube and to assess the usefulness of these predictors in discriminating these two categories of patients.</p> <p>Design and Patients: Prospective observational study. A total of 51 consecutive patients mechanically ventilated for >24 hrs.</p> <p>Measurements and Main Results: Tidal volume, respiratory period, inspiratory time, expiratory time, mean inspiratory flow (tidal volume/inspiratory time), and duty cycle (inspiratory time/respiratory period) were obtained from the flow signal. Breath-by-breath variability was expressed in terms of their coefficients of variation (CV), the number of breaths among which a significant correlation was found (lag), and the autocorrelation coefficient between one breath and the following one. Five patients were excluded because of nonstationarity of the data, leaving 46 cases for analysis. Between-group comparison was conducted with the Mann-Whitney test, and a nonparametric classification and regression tree was used to identify variables discriminating "success" (n = 32) and "failure" patients (n = 14). All coefficients of variation were significantly higher in success patients, who also exhibited significantly less respiratory autocorrelation (shorter "short memory"). The classification and regression tree analysis allocated all success patients to a group defined by a coefficient of variation of tidal volume/inspiratory time of > or =19% and a coefficient of variation of inspiratory time/respiratory period of > or =10% that did not contain any failure patient. All failure patients belonged to a group with coefficient of variation of tidal volume/inspiratory time of <19%, a lag tidal volume of > or =11, and that contained no success patient.</p>			
<p>Conclusion: In intensive care unit patients undergoing a spontaneous breathing trial, breathing variability is greater in patients successfully separated from the ventilator and the endotracheal tube. Variability indices are sufficient to separate success from failure cases.</p>			