Biologically Variable or Naturally Noisy Mechanical Ventilation Recruits Atelectatic Lung

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Biologically variable mechanical ventilation ($\dot{V}$bv)—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 $\dot{V}$bv, 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 ($y \propto 1/f^a$) (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 $\dot{V}$bv (n = 7) better reinflates the collapsed lung compared with conventional monotonously regular control mode ventilation ($\dot{V}$c; n = 7) over a 5-h period. We also investigated the influence of sigh breaths with $\dot{V}$c ($\dot{V}$s; n = 8) with this model. Reinflation of the collapsed lung was significantly enhanced with $\dot{V}$bv—greater Pa_{O_2} (502 ± 40 mm Hg with $\dot{V}$bv versus 381 ± 40 mm Hg with $\dot{V}$c at 5 h; and 309 ± 79 mm Hg with $\dot{V}$s; mean ± SD), lower Pa_{CO_2} (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 (Crs) (1.15 ± 0.15 ml/cm H_2O/kg versus 0.79 ± 0.19 ml/cm H_2O/kg and 0.77 ± 0.13 ml/cm H_2O/kg)—at lower mean Ppaw (15.7 ± 1.4 cm H_2O versus 18.8 ± 2.3 cm H_2O and 18.9 ± 2.8 cm H_2O). $\dot{V}$bv resulted in an 11% increase in measured tidal volume (V_{T_m}) over that seen with $\dot{V}$c by 5 h (14.7 ± 1.2 ml/kg versus 13.2 ml/kg). The respiratory rate variability programmed for $\dot{V}$bv demonstrated an inverse power law frequency distribution ($y \propto 1/f^a$) with a = 1.6 ± 0.3. 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.

Recruitment of atelectatic lung units and maintenance of alveolar patency is an integral goal of mechanical ventilation. We have recently developed a new mode of mechanical ventilation called biologically variable ventilation ($\dot{V}$bv). This computer-controlled ventilator mimics the normal spectrum of breathing by incorporating breath-to-breath variability in respiratory rate (f) and tidal volume (V_T). Using $\dot{V}$bv we have demonstrated improved arterial oxygenation (Pa_{O_2}) without an increase in mean airway pressure ($\overline{Paw}$) in a porcine model of severe lung injury (1). Suki and colleagues (2) postulate that $\dot{V}$bv improves Pa_{O_2} owing to recruitment of collapsed alveoli, which open in bursts or avalanches (3). They speculate that $\dot{V}$bv is an example of stochastic resonance—the addition of noise to an input signal (variable peak airway pressure [Ppaw]) to amplify output (Pa_{O_2}) in a nonlinear system (4). With the noisy input signal seen with $\dot{V}$bv, the volume gained at higher Ppaw greatly exceeded the volume lost at lower pressures over time, the net result being improved oxygenation without an increase in airway pressure ($\overline{Paw}$).

To test the hypothesis that $\dot{V}$bv enhances recruitment of collapsed alveoli, we developed a porcine model of stable unilateral lung collapse and compared lung reinflation over 5 h using $\dot{V}$bv versus conventional control mode ventilation ($\dot{V}$c) at similar minute ventilation.

We also examined if the addition of sigh breaths to $\dot{V}$c was effective in recruiting collapsed alveoli. We programmed the sigh breaths to occur at the same interval with the same delivered volume as the largest breaths with $\dot{V}$bv. If sighs programmed in this manner were as efficacious as $\dot{V}$bv, then the more complicated variability programmed with $\dot{V}$bv would be unnecessary.

METHODS

The Committee for Animal Experimentation at the University of Manitoba approved the study. When depth of anesthesia was adequate (isoflurane 1.5 minimal alveolar concentration [MAC] in 100% O_2), a tracheostomy was done and a double-lumen endotracheal tube was placed in the airway. Correct positioning was confirmed by fibreoptic bronchoscope. Mechanical ventilation by $\dot{V}$c was instituted with an Ohio 7000 anesthesia ventilator (Ohio Instruments, Madison, WI) with f approximately 15 breaths/min and minute ventilation adjusted to maintain the end-tidal CO_2 at approximately 35 mm Hg. Catheters were placed for blood sampling and pressure measurements. Airway pressures and volumes were measured by pneumotachograph (Hans Rudolph, Kansas City, MO). After baseline measurements, the right side of the double-lumen endotracheal tube was opened to air to allow the right lung to collapse. A minithoracotomy (pleural opening 2.5 cm) permitted complete collapse and observation of the lung. The lung remained collapsed for 1 h. At this point, the double-lumen tube was removed and replaced with a cuffed tracheostomy tube for reexpansion of the right lung. Animals were randomly allocated to continue with $\dot{V}$c or switched to $\dot{V}$bv. Conceptually, this is equivalent to flipping a switch: on = biological variability; off = no variability. Before the switch was flipped in those animals receiving $\dot{V}$bv, f and measured tidal volume (V_{T_m}) were the same in each group. The delivered minute ventilation remained unchanged from baseline and continued with either mode for the next 5 h. Blood gases and O_2 contents (arterial and mixed venous) and expired gas samples were measured (Radiometer ABL3 and Radiometer OSM3, Copenhagen NV, Denmark). Static respiratory system compliance (Crs) was measured by transiently clamping the expiratory limb of the ventilatory circuit at

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end inspiration. Calculated indices included shunt fraction ($\dot{Q}S/\dot{Q}T$), and Crs ($\Delta V/\Delta P$).

Computer-controlled Ventilation

The computer-controller and software for the ventilator have been previously described (1). Data for the modulation file were obtained from an awake, spontaneously breathing animal. The variability file used with Vbv is shown in Figure 1.

Computer-controlled Sigh Ventilation

Examination of Figure 1 reveals four instantaneous breaths below 10 breaths/min. To deliver computer-controlled sighs, a modulation file was written so that all instantaneous breaths were set to 15 breaths/min except at the four time periods where the instantaneous breaths were < 10 breaths/min. At these times the instantaneous breath rate was programmed as shown in Figure 1. Thus, each of these low breath rates resulted in delivery of a large VT or sigh breath at the same interval and magnitude as those programmed for Vbv. In addition, the duration of the modulation file was the same as with Vbv before it looped to repeat itself. Experiments were done *post hoc* in this group. Every attempt was made to ensure that this group did not differ at baseline or with one-lung ventilation from the other two groups.

Post hoc Analysis

Data acquisition files of airway pressure and flows were processed to integrate the area under the pressure–time and flow–time curves to give $\overline{Paw}$ and volume. Mean Ppaw was also calculated.

Statistical Analysis

Data were analyzed by repeated measures analysis of variance (ANOVA). A p value ≤ 0.05 was considered significant for group × time interactions or differences between groups. Comparisons between and within groups were based on generated least-squares means matrices with Bonferroni's correction applied when multiple comparisons were made. Data are presented as mean ± SD unless otherwise noted.

Inverse power law analysis was done as follows: mean instantaneous f was determined, then each instantaneous f was subtracted from mean f, this value was squared, then log transformed. These data were partitioned into incremental bins of equal size to determine their frequency distribution. The probability of each frequency was determined by Ni/N where Ni = number of observations in a given frequency bin and N = total number of observations. A log transform of the probability distribution was derived. The log probability distribution versus log f variation was plotted. The confidence interval and correlation coefficient were derived by regression analysis.

RESULTS

Data were analyzed on 22 experiments (n = 7 with Vbv and Vc and n = 8 with Vs). Measured mean f was the same in all groups at baseline values and during the period of one-lung ventilation. At these times, there were only minor differences seen for any measured parameter between groups (Table 1). Importantly, at baseline there were no differences in Pa_{O_2}, Pa_{CO_2}, $\dot{Q}S/\dot{Q}T$, Ppaw, VT or Crs between groups. With one-lung ventilation, the Pa_{O_2} decreased significantly with approximately a 4-fold increase in $\dot{Q}S/\dot{Q}T$. The Ppaw nearly doubled. The Crs decreased to approximately 40% of baseline values. After 60 min both lungs were again ventilated. In the group receiving Vbv and Vs, the computer-controller was activated. In these two groups, the delivered minute ventilation was not changed from its baseline settings with Vc. Mean f was scaled to 15 breaths/min, the same mean rate as in the control group—measured rate with Vbv remained unchanged from baseline at 13.9 breaths/min; coefficient of variation 18%. At 5 h, Pa_{O_2} was significantly higher with Vbv than in the other two groups [group × time interaction (G × T); $p < 0.0001$]). Carbon dioxide clearance was superior with Vbv such that Pa_{CO_2} was significantly lower at 5 h than for the other two groups (G × T; $p < 0.0001$). Mean Ppaw was lower at 5 h with Vbv than with Vc or Vs (G × T; $p < 0.0001$). VT was significantly greater with Vbv at 5 h (G × T; $p < 0.0001$). Crs was much greater with Vbv by 5 h than in the other two groups (G × T; $p < 0.0001$).

Figure 2 shows the changes in Pa_{O_2} over time for each group from Time 0 (end one-lung ventilation) to experiment completion at 5 h. The Pa_{O_2} increases more rapidly with Vbv

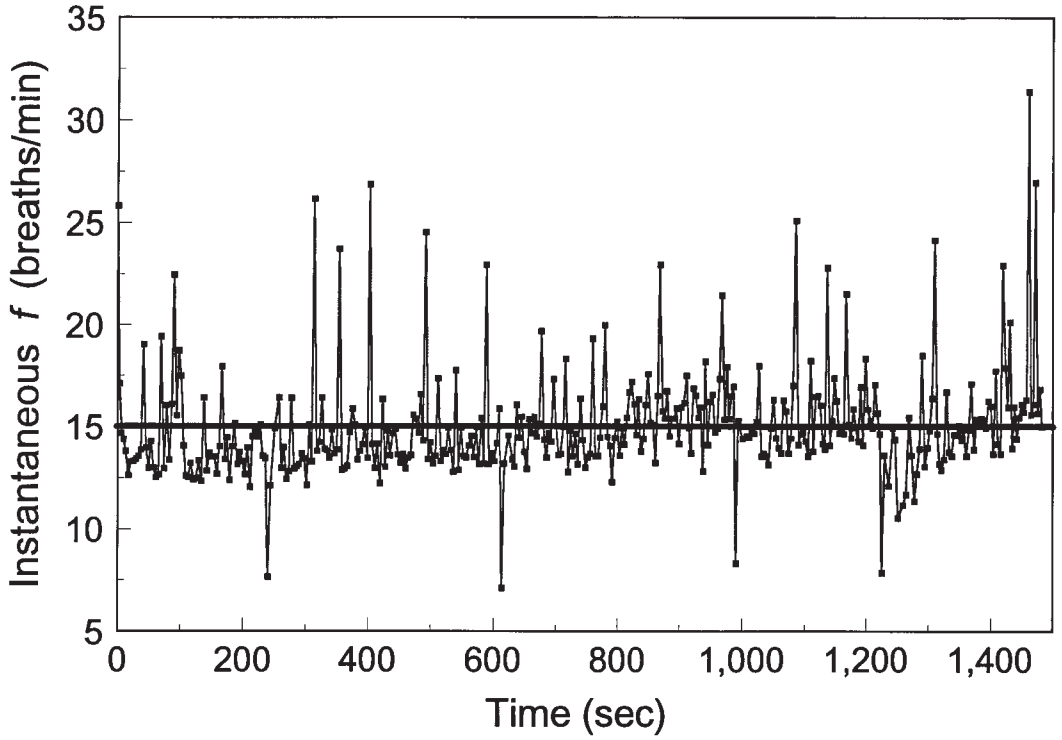

Figure 1. Modulation data file used to control f with Vbv. Instantaneous f (in breaths/min) versus time (s). There were 369 different f values over 24.7 min before the file looped to repeat itself. The mean programmed f was 15 breaths/min (*thick line*).

TABLE 1

COMPARISON OF V̇bv, V̇c, AND V̇s EXPERIMENTS*

	V̇bv Group (*n* = 7)	V̇c Group (*n* = 7)	V̇s Group (*n* = 8)
Pa_{O_2}, mm Hg			
Baseline	521 ± 25	515 ± 39	561 ± 34
One-lung ventilation	101 ± 15	109 ± 34	114 ± 18
5 h	502 ± 40†‡	381 ± 40§	309 ± 79
Pa_{CO_2}, mm Hg			
Baseline	34.7 ± 2.2	34.9 ± 2.4	38.2 ± 4.7
One-lung ventilation	60.3 ± 7.1†	60.3 ± 4.2§	67.0 ± 7.9
5 h	34.9 ± 3.7†‡	48.4 ± 8.4	50.2 ± 7.5
$\dot{Q}s/\dot{Q}T$, %			
Baseline	9.8 ± 3.5‡	9.2 ± 3.5§	6.9 ± 2.9
One-lung ventilation	40.1 ± 4.4	38.4 ± 9.5	39.8 ± 6.6
5 h	9.7 ± 2.7†‡	14.6 ± 2.0§	22.9 ± 6.0
Ppaw, cm H_2O			
Baseline	15.3 ± 1.7	14.9 ± 2.1	15.9 ± 3.3
One-lung ventilation	29.0 ± 5.4	27.7 ± 3.7	25.5 ± 3.7
5 h	15.7 ± 1.4†‡	18.8 ± 2.3	18.9 ± 2.8
VT, ml/kg			
Baseline	13.3 ± 0.8	13.9 ± 0.6	14.1 ± 0.9
One-lung ventilation	9.7 ± 2.0	9.9 ± 1.4	10.2 ± 0.9
5 h	14.7 ± 1.2†‡	13.2 ± 1.6	12.2 ± 0.8
Crs, ml cm H_2O^{-1} kg^{-1}			
Baseline	1.03 ± 0.13	1.11 ± 0.17	1.11 ± 0.15
One-lung ventilation	0.42 ± 0.16	0.44 ± 0.11	0.52 ± 0.10
5 h	1.15 ± 0.15†‡	0.79 ± 0.19	0.77 ± 0.13

* Values are expressed as mean ± SD.
† $p < 0.05$ V̇bv versus V̇c.
‡ $p < 0.05$ V̇bv versus V̇s.
§ $p < 0.05$ V̇c versus V̇s.

and reaches a higher asymptote ($p < 0.0001$ group × time interaction) than in the other two groups.

At baseline, during V̇c, minute ventilation, the product of f and V_{T_m} (f × V_{T_m}) was not different for V̇bv versus V̇c (186 ± 11 ml/kg with V̇bv and 187 ± 10 ml/kg with V̇c). With one-lung anesthesia with both groups on V̇c, measured VT decreased as airway pressure increased. This is compatible with the volume lost because of the compliance of the anesthesia circuit (circuit compression volume; 2 ml/cm H_2O/L in this case). With switch to V̇bv, the measured minute ventilation product increased despite unchanged ventilator settings. The f × V_{T_m} product increased solely as a consequence of an increase in measured VT. Measured f remains unchanged (> 75 instantaneous breath intervals and VT measured per observation with V̇bv). Measured VT was approximately 11% greater with V̇bv at 5 h compared with V̇c, such that $V\dot{V}bv = V\dot{V}c + \alpha V\dot{V}c$ with $\alpha = 0.11$.

In Figure 3 we have plotted log probability distribution versus log variability in f. An inverse power law frequency distribution was seen with slope −1.6 ± 0.3.

DISCUSSION

In this simple experimental model of reversible atelectasis—deflation of one lung in the pig—V̇bv resulted in more rapid and greater recruitment of collapsed lung. Our results are compatible with the theoretical model that "noisy" Ppaw would better recruit atelectatic lung units (2). With V̇bv, effective VT increased 11% under these experimental conditions. Suki and coworkers showed the probability functions for alveolar recruitment, which occur in avalanches (3, 5). These functions follow inverse power law frequency distributions ($y \propto 1/f^a$; examples of noise in natural phenomena) (6), with slopes of −1.1 to −2.5. We have plotted the probability distribution of the variability in f used with V̇bv (Figure 3). This function also follows an inverse power law frequency distribution with a negative slope of 1.6.

Suki and coworkers suggest that "both the magnitude and timing of pressure excursion applied at the airway entrance during artificial ventilation may be critical in triggering the avalanche process of alveolar recruitment" (3). As such, variable f and VT with V̇bv presumably facilitates this avalanche process. The increase in the f × V_{T_m} product is the fundamental change with V̇bv. The increase in measured VT is compatible with the improved Crs seen at 5 h with V̇bv. Gunnarsson and coworkers have shown a positive correlation between shunt fraction and the area of atelectasis as measured by computed tomography during anesthesia (shunt = 1.6 × atelectatic area + 1.7) (7). If such results apply to this experiment, V̇bv would have resulted in a net 3% greater atelectatic area recruited than with V̇c. Although of small magnitude, this change would represent 3 to 4 times greater area if such lung were aerated (8) (in this instance a difference in area of 9 to 12%). At 5 h, $\dot{Q}s/\dot{Q}T$ was returned to baseline with V̇bv but remained ele-

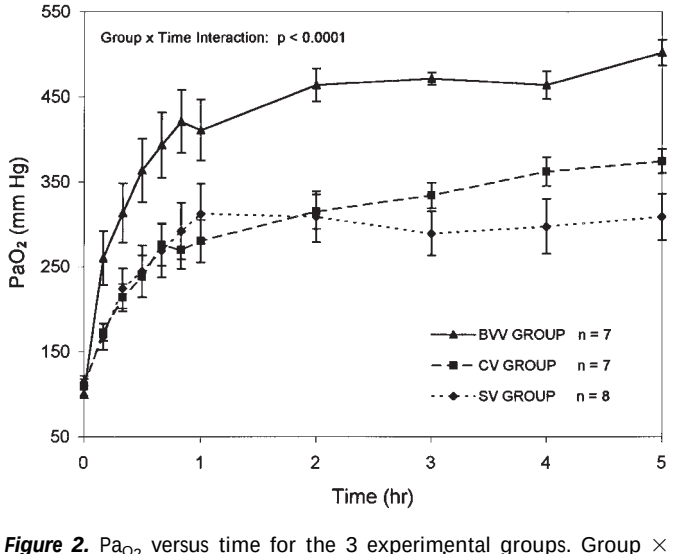

Figure 2. Pa_{O_2} versus time for the 3 experimental groups. Group × time interaction by ANOVA, $p < 0.0001$. With V̇bv, Pa_{O_2} increases more quickly and approaches a higher asymptote.

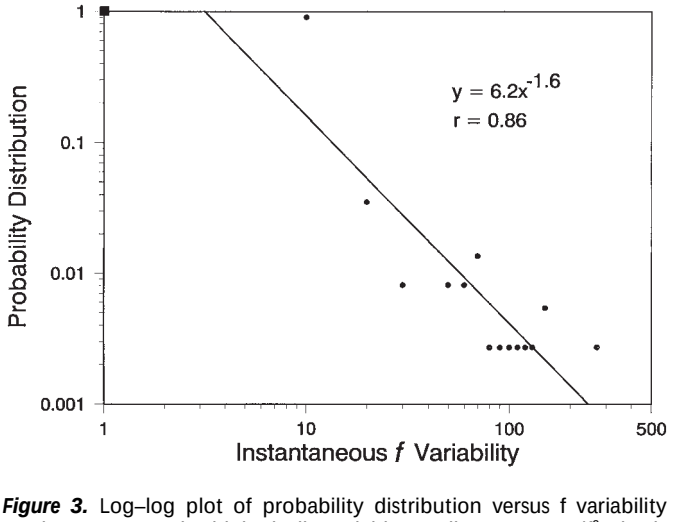

Figure 3. Log–log plot of probability distribution versus f variability used to program the biologically variable ventilator. A $y \propto 1/f^a$ plot is obtained with a = 1.6 ± 0.3. The solid box shows the probability distribution with V̇c. The probability is 1 with no f variability. The f variability is shown as 1 because the log of zero variability is undefined. The difference in the behavior of the two ventilatory modes is clear.

vated at almost 160% of normal with Vc and 330% of normal with Vs, suggesting near complete recruitment of atelectatic lung with "noisy" ventilation. The lower Pa_{CO_2} in the Vbv group also suggests better matching of ventilation to perfusion ($\dot{V}_A/\dot{Q}$).

Examination of Figure 1 reveals 4 low-frequency rates in the modulation file/cycle with instantaneous f approximately 7/min. As mean V_T in this group was 14.7 ml/kg, the calculated volume of the lowest breath rate would be (13.9/7 × 14.7) ml/kg or 29 ml/kg. Concern was raised that the large V_T with the low-frequency breaths represented sighs and that volume recruitment by this mechanism alone could account for the documented improvement in gas exchange during Vbv.

To address this issue, we examined eight additional animals (Vs group), ventilated in the same manner as the original Vc group, but submitted to programmed "sighs" of identical magnitude and frequency as the low-frequency, large V_T breaths in the Vbv group. Thus, this group of animals was exposed to the same inflation stress as the Vbv group but without the biologically variable noise of the Vbv group. Despite essentially identical measurements of gas exchange and respiratory mechanics at baseline values and during one-lung ventilation, Vs was not associated with any improvement in these parameters as seen with Vbv after 5 h of mechanical ventilation and conferred no advantage compared with Vc alone (*see* Table 1). Pa_{O_2} and shunt fraction were, in fact, worse with this ventilatory mode, with the proviso that this was a *post hoc* comparison.

Although the issue of sighs as an effective volume recruitment maneuver during prolonged ventilation is controversial, examination of the literature suggests that sighs are only effective when administered as a sustained inflation with high pressures under specific circumstances. Sighs of the magnitude seen during Vbv have not been shown to produce beneficial effects on Crs or gas exchange (9). Balsys and coworkers have shown that even larger sighs of 46 ml/kg resulted in unsustained increases in compliance and insignificant increases in Pa_{O_2} in healthy lungs in mechanically ventilated dogs (10). Bond and coworkers demonstrated that sustained inflation increased respiratory compliance only during conventional mechanical ventilation using low V_T (7 ml/kg) and low end-expiratory pressure. Sustained inflation was of no benefit during conventional ventilation with high V_T (14 to 17 ml/kg)—the range of the current study—or with low V_T and high end-expiratory pressure (11). Tusman and coworkers showed that a recruitment strategy (V_T up to 18 ml/kg coupled with increasing levels of positive end-expiratory pressure [PEEP] up to 15 cm H_2O) can improve arterial oxygenation after 40 min of anesthesia (12). Pelosi and coworkers demonstrated that gas exchange and respiratory mechanics were improved with 3 consecutive sighs/min at 45 cm H_2O plateau pressure over 1 h in patients with acute respiratory distress syndrome (ARDS) ventilated with a lung-protective strategy. The improvements seen were lost within 1 h after return of ventilatory parameters to baseline values (13). Thus, improvement in gas exchange occurs at the expense of increases in mean and Ppaw with sustained alveolar recruitment and it is not surprising that the relatively modest sighs delivered during Vs resulted in no benefit in the current study.

Biologically variable ventilation confers the advantage of improved gas exchange at an unchanged Paw and a lower Ppaw than either Vc or Vs. Exclusive to Vbv, the animals also received many small V_T/cycle with the potential for alveolar derecruitment.

Ongoing atelectasis is of significant concern during general anesthesia with mechanical ventilation (8). The near complete recovery of Pa_{O_2} and $\dot{Q}_S/\dot{Q}_T$ to baseline values with Vbv indicates better $\dot{V}_A/\dot{Q}$ matching over time during a lengthy period of anesthesia in the present study. As such, Vbv may be of clinical relevance for control mode ventilation during anesthesia (14).

All variability files used to date in the laboratory have demonstrated inverse power law frequency distributions and all have been obtained by lengthy collections of physiological signals such as heart rate (1), respiratory rate, and blood pressure (15). Variability in these physiological signals is ubiquitous in mammals (16–18). Further clarification is necessary to determine if biological variability is representative of stochastic resonance as defined by Suki and coworkers (2). If such turns out to be the case, then biological variability to recreate normal variation in V_T and f may be an example of tuned noise to enhance an output (Pa_{O_2}) in a nonlinear system (4). We have demonstrated that the programmed variability follows an inverse power law frequency distribution. This "noisy" behavior may explain the effectiveness of Vbv. It is important to realize that signals with inverse power law frequency distributions are not random ($\alpha = 0$ or white noise). Others have suggested that such biologically variable noise demonstrates deterministic behavior (19, 20). This experiment provides strong support for the theoretical proposal of how noisy Ppaw can increase recruitment of collapsed alveoli (2). It is uncertain if $\alpha = 0.11$ has optimized the benefits that can be obtained with Vbv in this context. Whether or not such a "noisy" mechanical ventilator has clinical utility must await further study. However, it is entirely possible that clinical life support systems may be improved by programming them for biologically variable or natural noise.

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