Convexity, Jensen's Inequality and Benefits of Noisy or Biologically Variable Life Support

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ABSTRACT

Life support with a mechanical ventilator is used to manage patients with a variety of lung diseases including acute respiratory distress syndrome (ARDS). Recently, management of ARDS has concentrated on ventilating at lower airway pressure using lower tidal volume. A large international study demonstrated a 22% reduction in mortality with the low tidal volume approach. The potential advantages of adding physiologic noise with fractal characteristics to the respiratory rate and tidal volume as delivered by a mechanical ventilator are discussed. A so-called biologically variable ventilator (BVV), incorporating such noise, has been developed. Here we show that the benefits of noisy ventilation - at lower tidal volumes - can be deduced from a simple probabilistic result known as Jensen's Inequality. Using the local convexity of the pressure-volume relationship in the lung we demonstrate that the addition of noise results in higher mean tidal volume or lower mean airway pressure. The consequence is enhanced gas exchange or less stress on the lungs, both clinically desirable. Jensen's Inequality has important considerations in engineering, information theory and thermodynamics. Here is an example of the concept applied to medicine that may have important considerations for the clinical management of critically ill patients. Life support devices, such as mechanical ventilators, are of vital use in critical care units and operating rooms. These devices usually have monotonous output. Improving mechanical ventilators and other life support devices may be as simple as adding noise to their output signals.
Key Words: acute respiratory distress syndrome, fractals, life support, mechanical ventilation, 1/f noise

1. INTRODUCTION

The importance of fluctuation and noise to medicine has been known for over 20 years. Pioneer work by Goldberger and colleagues demonstrated that noise was an index of cardiac health[1]. The nature of the healthy heart beat - so-called normal sinus rhythm has $1/f^1$ or fractal noise characteristics[2,3]. With disease, this pattern is altered; either simplified or changed in character; for example, atrial fibrillation, an abnormal rhythm often seen in clinical practice, is typified by white or $1/f^0$ noise. Many other biological processes have demonstrated fractal noise including blood flow to organs, and healthy breathing patterns[4,5].

With critical illness, the noisy output from organs is attenuated. A school of thought first postulated in the last decade suggests that degraded noisy communication between organs contributes to the high mortality with multiple organ failure[6,7]. In patients admitted to an intensive care unit, multiple organ dysfunction syndrome (MODS) is a common final pathway to death[8-10]. If greater than 3 organs are dysfunctional; and the individual organ dysfunction need only be relatively minor; mortality approaches 100 percent. Thus with each additional organ failing, lethality increases in a nonlinear manner.

With modern life support devices, physicians have become very adept at prolonging life when patients are critically ill, but less adept at reversing the consequences of chronic critical illness to restore the patient to health. Patients are maintained during critical illness by a number of life support devices, principal among them the modern mechanical ventilator. A ventilator with multiple microprocessor functions, can sustain life when patients cannot breathe for themselves. Other life support devices in the intensive care setting

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include i) perfusion pumps to deliver modified foodstuffs to provide nutrition when the gut has failed or deliver drugs to augment pumping action of the failing heart, ii) cardiac assist devices to provide even more advanced support with heart failure and iii) dialysis machines to cleanse the blood when the kidneys are failing. Such devices are used daily in operating rooms and intensive care units around the world. An important related device is the cardiopulmonary bypass pump used to sustain life during open-heart surgery; a procedure performed over one million times a year worldwide.

If MODS is, in part, a consequence of lost or degraded noisy communication between organs, then the management paradigm utilizing life support devices with monotonous output may be flawed, as the currently engineered devices usually eliminate such noise. An important question then: does the return of biological or fractal noise to the life support device improve its performance? This, in part, becomes a question of reverse engineering. Modern life support devices often use microprocessors to ensure their output is monotonously uniform. For example, mechanical ventilators have a mode called compliance compensation, which through on-line sensors detects small differences in expired gas volume, based on lung stiffness or compliance, and adjust ventilator output to equalize exhaled volume. If healthy breathing is associated with fractal fluctuation, then such mechanically enforced monotony would indeed appear counterproductive. Why not use the microprocessor to restore the natural noisy variation seen in health?[10] This is precisely the approach employed with a number of new life support devices including a mechanical ventilator and a roller pump that can be used for whole body perfusion during cardiopulmonary bypass and independent perfusion of individual organs. Our laboratory and others have demonstrated a benefit with such "biologically variable" or "noisy" life support devices. We will outline the various devices below:

2. BIOLOGICALLY VARIABLE VENTILATION (BVV)

With BVV a microprocessor restores normal fractal noise to the breathing pattern during mechanical ventilation[11-13]. A normal breathing pattern is shown in Figure 1. With conventional control mode ventilation (CMV), the mean value (shown in the figure as the solid line) would be the respiratory rate monotonously delivered with each breath. With CMV, this repetitive breath rate is delivered with a corresponding monotonous breath volume for hours or when the patient is critically ill, often for days to weeks; especially when such patients suffer from acute respiratory distress syndrome (ARDS).

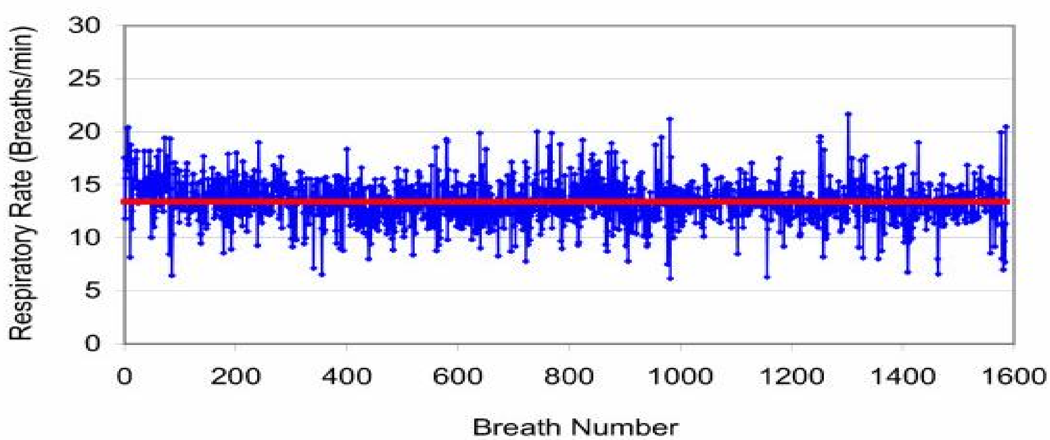

Figure 1: Human respiratory rate variability file. This is a typical variability file used to drive a ventilator programmed to deliver BVV. This data file was obtained from a spontaneously breathing healthy female volunteer. The mean rate is 13.4 ± 2.0 breaths/min (shown as the solid line). There are 1587 breaths in this file. With BVV, the ventilator is configured as a volume divider at fixed minute ventilation so that the respiratory rate × tidal volume product is constant. Thus the breath-by-breath volume related to instantaneous respiratory rate obtained from sequentially reading the above file is obtained from the minute ventilation/[(instantaneous breath rate/13.4) × chosen mean rate]. Analysis reveals that these data have fractal characteristics[13].

When BVV is used in an experimental model of ARDS (infusion of oleic acid to injure the lungs) the improvement in oxygenation and respiratory system compliance over CMV or CMV with a recruitment maneuver (CMV-RM; a sustained inflation of 40 cm H_2O inflation pressure for 40 seconds, administered hourly) is shown in Figure 2.

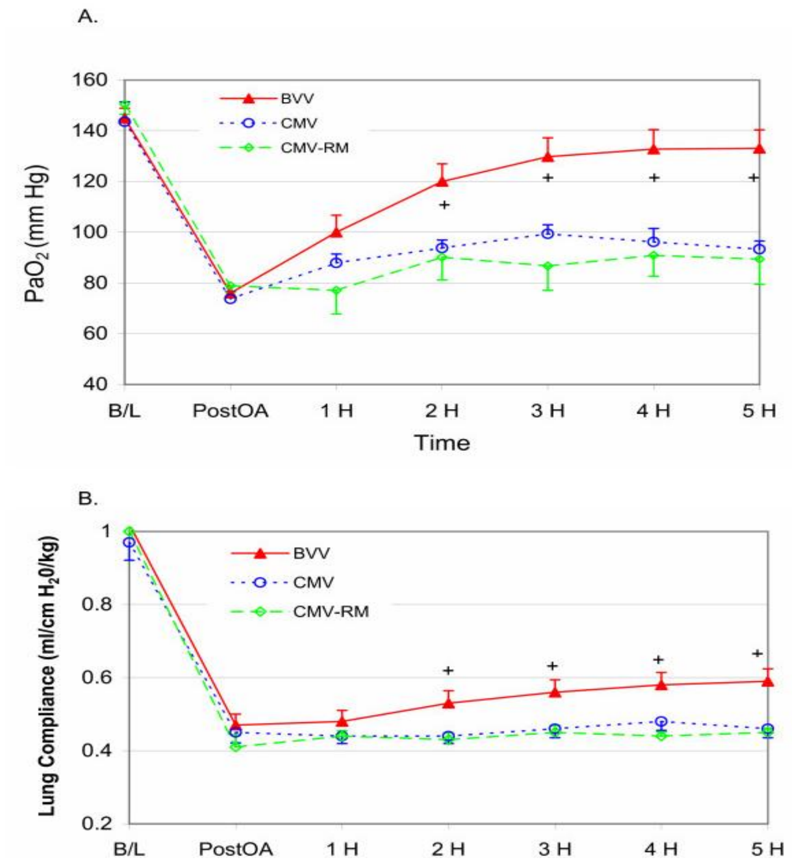

Figure 2: Arterial oxygenation and respiratory system compliance. Arterial oxygen tension (PaO_2) over time for the 3 groups discussed in the text: **(A)** The group × time interaction is p = 0.0001. No difference is seen between groups at baseline and following oleic acid (OA) infusion. By 2 hr the PaO_2 is greater with BVV (+). There is no difference between CMV and CMV-RM. Respiratory system compliance over time for the 3 groups: **(B)** The group × time interaction is p = 0.089. Least squares means tests revealed BVV had significantly greater compliance after 2 hr (+). There was no difference between CMV and CMV-RM[13].

The addition of biological or fractal noise thus appears to improve the performance of a mechanical ventilator. A number of explanations have been offered as to why this could be so, including i)the added variation is an example of stochastic resonance – the addition of noise to an input signal to enhance an output signal in a nonlinear system[14], ii)enhanced production of surfactant – the lipoprotein which maintains lung unit patency[15], iii)enhanced respiratory sinus arrhythmia[16], and iv)a demonstration of Jensen's Inequality when noisy ventilation is occurring on the convex portion of the pressure-volume (P-V) curve during ARDS[17].

The final explanation will be further developed. The current recommended management for ARDS is to ventilate these patients with small tidal volumes in the range of 6 mL/kg[18]. This approach to management decreases mortality by up to 22%. With ARDS, the static P-V curve can be shown to be convex in this range of tidal volumes. This static compliance curve, which describes the relationship between volume and pressure in the lungs, is central to the argument for the management of patients with ARDS. This curve is known to be sigmoidal in shape, and Venegas and colleagues[19,20] get excellent curve fits with a 4-parameter logistic equation of the form:

$$v = F(p) = a + b\frac{1}{1+e^{-(p-c)/d}}.$$

We have been able to fit this equation to our animal models of ARDS with precision: curve fits with R^2 values of > 0.995 are customarily seen. Such curve fits allow comprehensive study of ventilation protocols for ARDS.

3. JENSEN'S INEQUALITY

If ventilation is occurring on the convex portion of the P-V curve we can apply Jensen's Inequality to show that an advantage for BVV can be mathematically proven. Jensen's Inequality[21,22] applied to ventilation states that when individual pressures in a range of pressures (as with noisy BVV) are first transformed to volume over the convex portion of the P-V curve, the average volume will be greater than would result if individual pressures in the range of pressures with BVV are first averaged to equal the monotonous pressure with CMV and then transformed to volume. In mathematical terms, "if $F(P) = V$ is a convex function defined on an interval (r, s), and if pressure (P) is a random variable taking values in (r, s), then the expected value (E) at $F(P)$; $E(F(P)) > F$ at the expected value of P; $F(E(P))$." Such conditions are met with BVV since noisy ventilation provides a series of individualized observations of pressure (P), transformed to volume $F(P)$ as determined by Venegas curve fitting - Figure 3. Jensen's Inequality demonstrates that noisy ventilation will be beneficial under all circumstances where the inflation limb of the P-V curve is convex. Such is certainly the case with the current management for ARDS with low tidal volumes. Importantly, convexity is present at low inflation pressure in many lung conditions, suggesting BVV has broad applicability. Jensen's Inequality also shows where noisy ventilation can be harmful - on the concave portion of the P-V curve. Above point c, (the true inflection point; the static pressure where volume equals $(a+b)/2$) the curve becomes concave, so ventilation above this point reverses Jensen's Inequality and under these circumstances noisy ventilation may be deleterious. The one publication in the literature demonstrating no advantage of noisy ventilation was in a canine model of ARDS, when the lungs were severely damaged and a very noisy signal (skewed to the right) at high tidal volume was used to deliver airway pressure[23]. Under such circumstances ventilation may have been centered at or above point c on the logistic equation - with nil or negative benefit from additional noise.

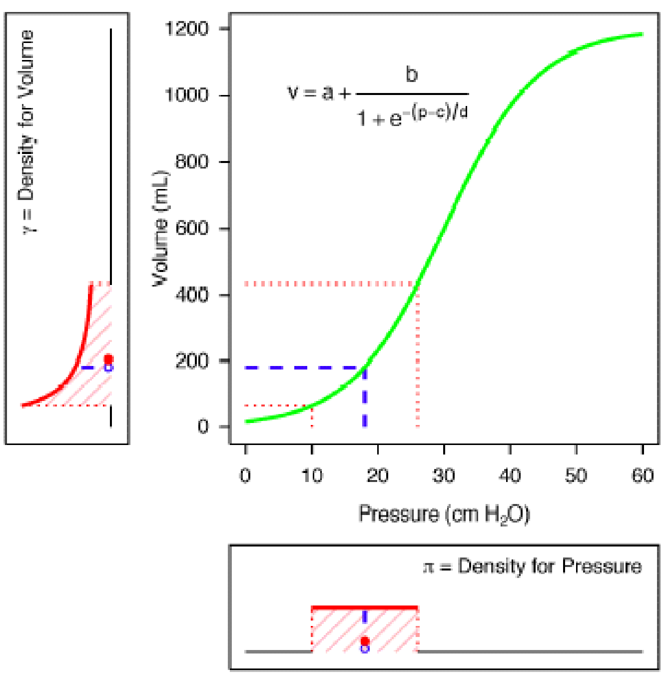

Figure 3: Comparison of noisy (BVV) and monotonous ventilation (CMV) strategies under a 4-parameter logistic model using the Venegas equation. Here a=0 mL (volume at lower asymptote), b=1200 mL (volume range), c=30 cm H_2O (pressure at inflection point) and d=7 cm H_2O (index of linear compliance). Pressure for monotonous strategy is 18 cm H_2O (open circle). Pressures for the noisy strategy are uniformly distributed between 10 and 26 cm H_2O, with mean 18 cm H_2O (solid circle). Probability density functions are on the margins (curves). Mean volume for noisy strategy is 205.7 ml (solid circle), greater than 183.1 ml; volume for the monotonous strategy (open circle).

Noisy ventilation can demonstrate Jensen's Inequality in two ways. Experiments have shown that, with BVV, mean tidal volume is greater at the same mean airway pressure or, conversely, that mean airway pressure is lower at the same mean tidal volume. That is, the noise can be introduced in either pressure or volume. In the latter case, the concavity of the inverse function is being exploited – see Figure 4.

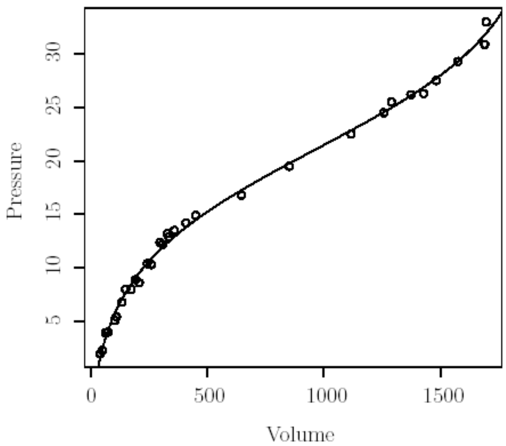

Figure 4: A plot of the V-P curve $G(v)$ which represents the inverse function of $F(p)$, given by:

$$p = G(v) = F^{-1}(v) = c + d * ln\left(\frac{v-a}{a+b-v}\right)$$

In this circumstance at a given mean delivered volume, the plateau pressure will be less with BVV than seen with CMV because ventilation is occurring on the concave portion of this curve. Ian Sturdy, MSc. thesis, University of Manitoba.

Thus, mathematically modelling can predict when BVV will and will not be beneficial. Here is a marriage of two mathematical models to answer an important question about mechanical ventilation for management of ARDS – P-V curve fitting using the Venegas equation and application of Jensen's Inequality in the face of noisy input with BVV to demonstrate the advantage of such noise. A demonstration of the impact of the inverse function described in Figure 4 is shown in Figure 5.

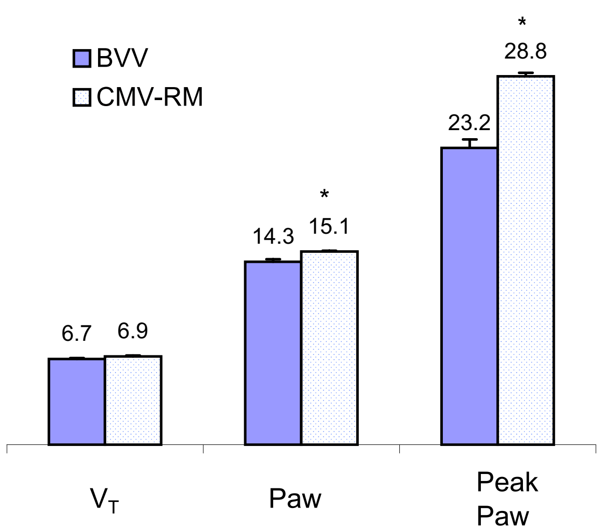

Figure 5: Ventilation with BVV compared to CMV-RM as defined in the text. At the same mean delivered tidal volume (V_T; mL/kg) the mean airway pressure Paw (cm H_2O) and mean peak airway pressure (Peak Paw) are lower with BVV. This is a consequence of Jensen's Inequality over the concave interval defined from the inverse equation given in Figure 4.

Collectively, the results indicate that the addition of biological noise can significantly enhance the function of a mechanical ventilator, one of the life support devices routinely used in modern medicine. A recently published clinical trial indicates that such improvements in gas exchange and respiratory mechanics can be demonstrated in patients as well[24].

4. BIOLOGICALLY VARIABLE CARDIOPULMONARY BYPASS

The addition of a biologically variable or noisy signal can potentially enhance the performance of the roller pump used to perfuse the body during cardiopulmonary bypass. We have demonstrated that adding fractal noise to this device – restoring the beat-to-beat variation in heart rhythm, fluctuations with blood pressure and respiratory rhythms can improve cerebral venous oxygenation[25,26], and attenuate renal injury following deep hypothermic circulatory arrest (DHCA)[27] – a technique where the body is cooled to 15-18 ^{o}C. When this temperature is reached, the bypass pump is stopped to allow repair of the pediatric heart or the great vessels in adult surgery. Such circumstances of 'suspended animation' can be maintained for up to an hour while the cardiac structures are repaired. Despite the safety of protective cooling, the body organs are at risk of damage. Any means to improve protection of the organs at risk would be clinically important.

5. BIOLOGICALLY VARIABLE CARDIOPLEGIA

During conventional open heart surgery, the heart is stopped to permit surgical repair to the heart valves or coronary arteries. In this situation, the heart is perfused with solutions to keep the heart arrested and to provide organ protection. Traditionally, the coronary arteries are perfused with the cardioplegia solution using a conventional roller pump delivering a monotonously regular apulsatile flow. Adding noise to the roller pump signal improves myocardial performance[28] with cessation of cardioplegia delivery and separation from cardiopulmonary bypass. Enhanced performance of an isolated organ following noisy perfusion raises the possibility such an approach could improve function of ex-vivo organs for transplantation.

6. CONCLUSION

The addition of physiologic or biological noise to life support devices improves their performance. Such reverse engineering, using microprocessors to add noise, not eliminate it, suggests that physiologic or fractal noise optimizes organ function. A new way of designing life support devices that incorporates the fractal noise seen in health is suggested.

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