JOURNAL OF THE ROYAL SOCIETY Interface

J. R. Soc. Interface (2005) **2**, 393–396
doi:10.1098/rsif.2005.0043
Published online 7 June 2005

REPORT

Convexity, Jensen's inequality and benefits of noisy mechanical ventilation

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Mechanical ventilators breathe for you when you cannot or when your lungs are too sick to do their job. Most ventilators monotonously deliver the same-sized breaths, like clockwork; however, healthy people do not breathe this way. This has led to the development of a biologically variable ventilator—one that incorporates noise. There are indications that such a noisy ventilator may be beneficial for patients with very sick lungs. In this paper we use a probabilistic argument, based on Jensen's inequality, to identify the circumstances in which the addition of noise may be beneficial and, equally important, the circumstances in which it may not be beneficial. Using the local convexity of the relationship between airway pressure and tidal volume in the lung, we show that the addition of noise at low volume or low pressure results in higher mean volume (at the same mean pressure) or lower mean pressure (at the same mean volume). The consequence is enhanced gas exchange or less stress on the lungs, both clinically desirable. The argument has implications for other life support devices, such as cardiopulmonary bypass pumps. This paper illustrates the benefits of research that takes place at the interface between mathematics and medicine.

Keywords: anaesthesiology; critical care; mechanical ventilation; noise; probability

Mechanical ventilation is standard treatment for the management of patients with a variety of lung diseases, including acute respiratory distress syndrome (ARDS). The principles of positive pressure ventilation include the use of inflation pressures that allow acceptable gas exchange while limiting overdistension of the lung (to prevent tissue damage). Recently, management of ARDS has concentrated on ventilating at low airway pressures using low tidal volumes. A large multi-centre study (The Acute Respiratory Distress Syndrome Network 2000) demonstrated a 22% reduction in mortality with the low tidal volume approach (see also Amato *et al.* 1998). Other studies have demonstrated the potential advantages of adding variability, or 'noise', to the signal in a mechanical ventilator and a biologically variable ventilator (BVV) that incorporates such noise has been developed (Mutch *et al.* 2000*a*). It has been argued that such a ventilator may increase measured lung volume based on the nonlinear opening characteristics of collapsed alveoli (Suki *et al.* 1998), enhance cardio-respiratory synchronization (Yasuma & Hayano 2004) and increase surfactant phospholipids levels (Arold *et al.* 2003). It has also been argued that, although continuous high pressures can be harmful, occasional high pressures resulting from the use of a noisy ventilator may not be, and that these occasional high pressures may help to open collapsed alveoli (Mutch *et al.* 2000*a*; Fujino *et al.* 2001). 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.

The static compliance curve, which describes the relationship between volume and pressure in the lungs, is central to the argument for managing patients with ARDS with noisy mechanical ventilation. This curve is known to be sigmoidal in shape and Venegas *et al.* (1998) obtained excellent curve fits with a four-parameter logistic equation of the form

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

Such a curve is shown in figure 1. In this figure, the parameters chosen are representative of a 27 kg animal used in an ARDS porcine experiment in which oleic acid has been used to induce injury to the lung (Boker *et al.* 2002). For ARDS patients, a weight-dependent scaled version of this curve is appropriate.

Before stating Jensen's inequality we will illustrate its impact on mechanical ventilation. Consider two ventilation strategies—one that is monotonously regular in delivery, as with conventional ventilation, and one that incorporates noise. In the first, pressure is set at 18 cm H_2O on every breath. In the second, pressures are randomly sampled from a uniform distribution on the interval $(p_{\min}, p_{\max}) = (10\ \mathrm{cm}\ H_2O, 26\ \mathrm{cm}\ H_2O)$, a range of 16 cm H_2O. In figure 1, the probability density function (PDF) for pressure under the noisy strategy is shown below the horizontal axis. The total area under a PDF is 1; thus, this uniform PDF is equal to 1/16 for pressures between 10 cm H_2O and 26 cm H_2O and is equal to 0 otherwise. Both strategies have the same mean pressure.

The induced PDF for volume under the noisy strategy is shown (rotated 90°) to the left of the vertical axis. The mean volume under the noisy strategy is larger than the volume under the monotonous strategy—even though the two strategies have the same mean pressure. The addition of noise results in a higher mean volume, which is associated with higher arterial oxygen tensions, more compliant lungs and enhanced gas exchange. The important point is that this happens

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Received 24 November 2004
Accepted 30 March 2005

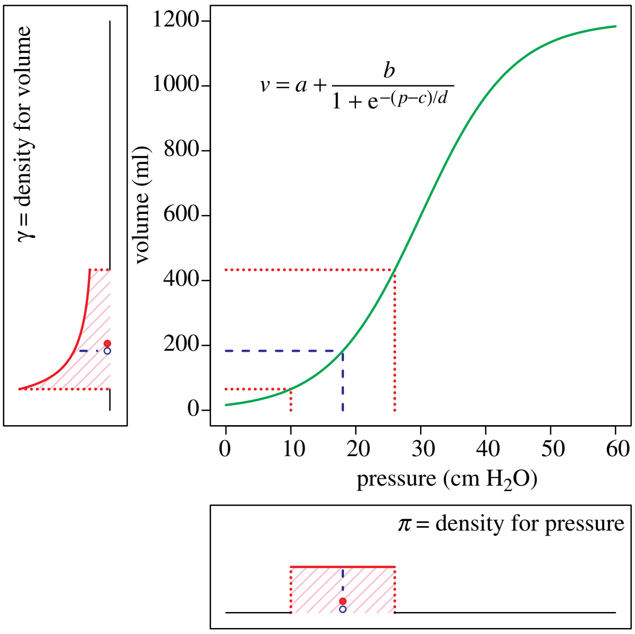

Figure 1. Comparison of noisy and monotonous ventilation strategies under a four-parameter logistic model. $a\!=\!0$ ml (volume at lower asymptote), $b\!=\!1200$ ml (volume range), $c\!=\!30$ cm H_2O (pressure at inflection point) and $d\!=\!7$ cm H_2O (index of linear compliance). The pressure for the monotonous strategy is 18 cm H_2O (open blue circle). The pressures for the noisy strategy are uniformly distributed between 10 and 26 cm H_2O, with a mean of 18 cm H_2O (red circle). Probability density functions are on the margins (red curves). The mean volume for the noisy strategy is 205.73 ml (red circle), greater than 183.13 ml, the constant (or mean) volume for the monotonous strategy (open blue circle).

without a corresponding increase in mean pressure, which would place additional stress on the lungs.

Jensen's inequality states: 'If X is a (non-degenerate) random variable taking values in an interval (r, s), and if $u(X)$ is a strictly convex function on (r, s), then mean$[u(X)] > u($mean$[X])$, providing that mean$[X]$ and mean$[u(X)]$ exist and are finite.' For a more detailed discussion of Jensen's inequality see the Electronic Appendix. To apply Jensen's inequality in our example, let P be a random variable representing the pressure of the noisy strategy and let $V\!=\!F(P)$ represent the induced volume. It should now be apparent why the mean volume under the noisy strategy is higher than the constant volume under the monotonous strategy—it is because the interval (10 H_2O, 26 H_2O) in which ventilation is taking place is within the convex portion of the curve F. In fact, the addition of (zero-mean) noise to any inflation pressure below the inflection point $c\!=\!30$ cm H_2O results in greater mean lung volume, provided that the individual inflation pressures are not permitted to exceed c.

Jensen's inequality demonstrates that noisy ventilation will be beneficial on the convex portion of the P–V curve. This is certainly the case with the current management of ARDS with low tidal volumes. Importantly, convexity is present at low inflation pressure in many lung conditions, suggesting BVV has broad applicability. Limited to the criterion under discussion, Jensen's inequality also shows where noisy ventilation may not be beneficial—on the concave portion of the P–V curve. The curve is concave above point c so Jensen's inequality is reversed and noisy ventilation may be deleterious. The one publication in the literature demonstrating no advantage of noisy ventilation was in a canine model of ARDS, where the lungs were severely damaged and a very noisy signal (skewed to the right) was used to deliver airway pressure (Nam *et al.* 2000). Under such circumstances ventilation may have been centred at or above point c on the logistic equation—with nil or negative benefit from additional noise.

Jensen's inequality provides us with an important tool for deciding whether noise will be beneficial or not. Indirectly, it also provides an indication of when the addition of noise will be most beneficial—if ventilation is centred at or near the point at which the convexity is largest or where the second derivative, $F''(p)$, is maximized. For the logistic equation, this point of maximal compliance change is at a pressure of $p\!=\!c\!-\!1.317d$ (Venegas *et al.* 1998; Electronic Appendix), corresponding to a volume of $v\!=\!a\!+\!0.211b$.

In figure 1, the noisy pressures are uniformly distributed on the interval (10 H_2O, 26 H_2O). This is only an example; many distributions could have been used instead. As there are a number of issues to consider in choosing an optimal noisy pressure distribution, the choice of distribution will not be considered here. However, in studying the consequences of different pressure distributions, it is useful to observe that, through F, the distribution for pressure induces a distribution for volume, and that the induced PDF for volume (γ) is given by

$$\gamma(v) = \pi(G(v))\,G'(v), \tag{2}$$

where π is the PDF for pressure and G is the inverse function of F, given by

$$p = G(v) = F^{-1}(v) = c + d\ln\left(\frac{v-a}{a+b-v}\right) \tag{3}$$

(see Electronic Appendix). The mean volume can be obtained from either π or γ,

$$\text{mean}[V] = \int_{p_{\min}}^{p_{\max}} F(p)\pi(p)\mathrm{d}p = \int_{F(p_{\min})}^{F(p_{\max})} v\gamma(v)\mathrm{d}v. \tag{4}$$

If P is uniformly distributed on the interval (10 H_2O, 26 H_2O), as in figure 1, then

$$\pi(p) = \begin{cases} 1/16 & \text{if } 10 \text{ cm } H_2O \le p \le 26 \text{ cm } H_2O, \\ 0 & \text{otherwise,} \end{cases} \tag{5}$$

and, thus, using equations (2) and (3),

$$\gamma(v) = \begin{cases} \dfrac{bd}{(p_{\max}-p_{\min})(v-a)(a+b-v)} & \\ \dfrac{525}{v(1200-v)} & \text{if } 65.18 \text{ ml} \le v \le 433.09 \text{ ml}, \\ 0 & \text{otherwise,} \end{cases} \tag{6}$$

since $F(10)=65.18$ and $F(26)=433.09$. Using numerical integration in equation (4), it can be shown that the mean volume under the noisy strategy is 205.73 ml, a 12.3% increase on the volume under the monotonous strategy ($F(18)=183.13$ ml). Such an increase would result in improved oxygenation (Suki *et al.* 1998).

For many mechanical ventilators it is convenient to introduce the noise in volume, rather than pressure. Jensen's inequality still applies (see Electronic Appendix). However, now the concavity of the inverse function $p=G(v)$ is exploited in the region of low volumes. In this case, the addition of noise decreases the mean airway pressure, while maintaining the same mean tidal volume. The fact that noise can be introduced in either pressure or volume is consistent with experimental results (Mutch *et al.* 2000*b*; Boker *et al.* 2002). If noise is introduced in volume using the PDF γ, then the induced PDF for pressure is given by

$$\pi(p) = \gamma(F(p))F'(p), \tag{7}$$

and the mean pressure is given by

$$\text{mean}[P] = \int_{v_{\min}}^{v_{\max}} G(v)\gamma(v)\mathrm{d}v = \int_{G(v_{\min})}^{G(v_{\max})} p\pi(p)\mathrm{d}p. \tag{8}$$

If the noisy strategy utilizes the PDF for the volume given in equation (6), as in figure 1, then the mean volume is 205.73 ml, the induced PDF for pressure is uniform on (10 cm H_2O, 26 cm H_2O) and the mean pressure is 18 cm H_2O. If the monotonous strategy uses a constant (or mean) volume of 205.73 ml, then the constant (or mean) pressure is $G(205.73)=18.97$ cm H_2O, larger than the mean pressure for the noisy strategy.

Note that 'noise' is used here in a non-pejorative sense; by a noisy ventilator we simply mean one in which random fluctuations, following some stochastic law, have been added to a monotonous signal. It is not necessary for the randomly selected pressures (or volumes) to be independent of one another for Jensen's inequality to hold, provided that the PDF for pressure (or volume) represents the long-run steady-state distribution. Thus, the noisy pressures (or volumes) could exhibit autocorrelation over time. In fact, normal breathing patterns exhibit autocorrelation and have fractal characteristics, so it is natural to speculate that a noisy ventilator with similar characteristics could be particularly beneficial. Another possibility is to base the noise on observed normal breathing patterns (figure 2). For a discussion of random fluctuations in physiological time-series, including those associated with the heart or lungs, see Bassingthwaighte *et al.* (1994).

In this report we have provided a framework for assessing the impact of noise on mechanical ventilation. Additional research is required in order to address a number of important issues. Some of these relate to the manner in which noise is introduced—the choice of the steady-state distribution, the nature of the autocorrelation over time, the (possibly noisy) distribution of times between successive breaths and, more generally, the specification of a probabilistic model for the relationship between breathing frequency and amplitude over time. Other issues are statistical in nature,

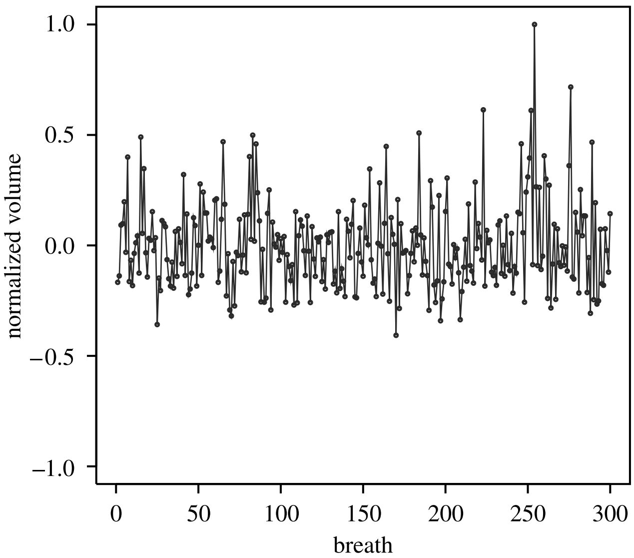

Figure 2. A normalized snapshot of a normal breathing pattern (300 breaths). Normal breathing patterns exhibit autocorrelation and have fractal characteristics. This figure is based on tidal volumes that were acquired from a healthy, spontaneously breathing individual over a number of breaths. The observed volumes were centred at zero (by subtracting the mean) and scaled to keep the resulting values within the range −1 to +1. Such a signal can drive a ventilator using engineered software and hardware, with an appropriately scaled version of the signal being added as noise to a monotonous tidal volume.

relating, for example, to the inclusion of residual variation in model (1) and the estimation of the model parameters. (With respect to the former, it should be noted that residual variation tends to be small (Venegas *et al.* 1998) and, if $v=F(p)+\epsilon$, where ϵ has mean 0, then the presence of ϵ has no impact on the mean volume or on Jensen's inequality. It does, however, affect the shape of the volume distribution and increase its variance.) Finally, another issue, that we cannot discuss in detail, concerns the distinction between the lung P–V curve and the total respiratory system P–V curve. (Both curves have been used in ARDS studies, with similar results. The use of the total respiratory system P–V curve, which recognizes that the inflation pressure must overcome both lung and chest wall compliances, could affect the position of the point of maximal compliance change but would not impact the applicability of Jensen's inequality.)

Other life support devices, also characterized by monotonous output, may be improved by adding noise to their output signals. Cerebral oxygenation is improved by using a noisy cardiopulmonary bypass pump (Mutch *et al.* 2000*c*). Noisy perfusion during the period of cardioplegic arrest results in better myocardial function after cardiopulmonary bypass (Graham *et al.* 2002). By extension, noisy perfusion of *ex vivo* organs may result in improved function after transplantation. In situations such as these, Jensen's inequality may help to identify the conditions under which the addition of noise will be beneficial.

Jensen's inequality has important considerations in engineering, information theory and thermodynamics. The medical example considered here may have an important influence on the clinical management of critically ill patients.

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The supplementary Electronic Appendix is available at http://dx.doi.org/10.1098/rsif.2005.0043 or via http://www.journals.royalsoc.ac.uk.