# Reports of Original Investigations

# Physiological noise versus white noise to drive a variable ventilator in a porcine model of lung injury

## *[Bruit physiologique versus bruit blanc pour entraîner un respirateur en mode variable dans un modèle porcin de lésion pulmonaire]*

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**Purpose:** Variable ventilation is superior to control mode ventilation in a number of circumstances. The nature of the breathing file used to deliver the variable rate and tidal volume has not been formally examined.

**Methods:** We compared two different noise files in a randomized prospective trial of variable ventilation. Pigs were anesthetized, intubated, and mechanically ventilated. Oleic acid was infused to introduce lung injury. The animals were ventilated at a tidal volume of 7 mL·kg$^{-1}$, in variable mode, with either physiologically-derived noise (variability file – 1,587 breath intervals– obtained from a spontaneously breathing volunteer; $n = 10$) or a variability file of identical length derived from computer-generated white noise ($n = 10$).

**Results:** The physiologically-derived noise had a power law $\alpha$-exponent of -0.27 and a Hölder exponent of -0.38, indicative of auto-correlated noise. The computer-generated noise had an $\alpha$-exponent of -0.52 and a Hölder exponent of -0.49, indicative of white noise. Both files showed multifractal characteristics. There were no differences between groups, at any time period, for $PaO_2$, $PaCO_2$, and static or dynamic respiratory system compliance. No differences were observed between groups for wet:dry lung weight ratios or for interleukin-8 in bronchoalveolar lavage fluid.

**Conclusion:** This study demonstrates that the nature of the variability files, chosen to drive the variable ventilator, had no effect on indices of gas exchange or respiratory mechanics in this model. A considerable overlap of the multifractal files existed. The potential to drive a variable ventilator using algorithm-derived files with multifractal characteristics, thereby eliminating the requirement to use physiologically-derived signals, is discussed.

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***Objectif** : La ventilation en mode variable est supérieure à la ventilation en mode contrôlée dans plusieurs situations. La nature du fichier de respiration utilisé pour engendrer la fréquence et le volume courant variable n'a pas été évaluée de façon formelle.*

***Méthode** : Nous avons comparé deux fichiers de bruit différents dans une étude prospective randomisée de la ventilation en mode variable. Les cochons ont été anesthésiés, intubés et ventilés mécaniquement. Ils ont reçu une perfusion d'acide oléique afin de provoquer une lésion pulmonaire. Les animaux ont été ventilés à un volume courant de 7 mL·kg$^{-1}$, en mode variable, avec soit du bruit de*

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*provenance physiologique (fichier de variabilité – 1587 intervalles de respiration – obtenus d'un volontaire respirant spontanément ; n = 10) ou un fichier de variabilité de longueur identique dérivé d'un bruit blanc généré par ordinateur (n = 10).*

***Résultats** : Le bruit d'origine physiologique avait un exposant $\alpha$ de la loi de puissance de -0,27 et un exposant de Hölder de -0,38, ce qui indique un bruit auto-corrélé. Le bruit généré par ordinateur avait un exposant $\alpha$ de -0,52 et un exposant de Hölder de -0,49, ce qui indique un bruit blanc. Les deux fichiers ont montré des caractéristiques multifractales. Il n'y a pas eu de différence entre les groupes, à n'importe quelle période de temps, pour la $PaO_2$, la $PaCO_2$, et la conformité statique et dynamique du système respiratoire. Aucune différence n'a été observée entre les groupes en ce qui touche aux rapports de poids œdème pulmonaire/poumon sec ou pour l'interleukine 8 dans le liquide de lavage bronchoalvéolaire.*

***Conclusion** : Cette étude démontre que la nature des fichiers de variabilité sélectionnés pour entraîner le respirateur en mode variable n'a pas eu d'effet sur les indices d'échange gazeux ou de mécanique respiratoire dans ce modèle. Un chevauchement considérable est apparu dans les fichiers multifractals. La possibilité d'entraîner un respirateur en mode variable avec des fichiers dérivés d'algorithmes avec des caractéristiques multifractales, éliminant ainsi le besoin de recourir à des signaux d'origine physiologique, est discutée ici.*

BIOLOGICAL signals are noisy.[1] This noise is associated with health and is responsible for the fluctuations seen in many physiological signals.[2,3] The inherent variability in these signals is known to decrement with age and deteriorating health.[4,5] These time series have been classified, in one respect, as $1/f$-phenomena, since their spectra demonstrate inverse power law in frequency or their probability distributions are inverse power law. Physiological signals often display some of the characteristics of true pink noise ($1/f^1$) - such that the probability distribution of the noise exhibits $1/f^{\alpha}$ characteristics with $0< \alpha \leq 1$, indicating a measure of auto-correlation. White noise ($1/f^0$) does not demonstrate this propensity, as the value at one instant is completely uncorrelated with its prior value.[6]

Increasingly, publications suggest that tracking time series variability in physiological signals can be predictive of a patient's course while in intensive care.[7–9] Returning a measure of variability to life support devices, which are usually monotonous in output, has been advanced as potentially restorative.[10] Based on this concept, we have demonstrated that mechanical ventilation can be improved, in terms of gas exchange and respiratory mechanics, by varying respiratory rate and tidal volume, when compared to the monotonous delivery observed with conventional ventilators.[11,12] This has been called biologically variable ventilation (BVV). To date, the breathing files have been acquired from healthy volunteers at rest. These physiological time series are then used to alter the breathing frequency in a modified mechanical ventilator. A recurring question regarding BVV is whether or not an optimal pattern of noise can be identified.

Mathematical modeling has demonstrated the conditions under which the addition of noise is advantageous when ventilating injured lungs.[13] The current paradigm of low tidal volume delivery, for patients with acute respiratory distress syndrome (ARDS), is such a circumstance.[14] In this prospective, randomized controlled trial, we set out to compare a physiologically-derived noise file to a computer-generated white noise file, with either used to drive the respiratory rate changes with BVV, in an established porcine model of ARDS.

## Methods

### *Experimental preparation*

The study was approved by the University of Manitoba Research Ethics Board. Healthy fasted pigs (20–30 kg) received atropine/midazolam/ketamine (0.02/0.5/10 $mg \cdot kg^{-1}$ *im*) prior to undergoing a mask induction with isoflurane 5% in $O_2$. The animals' tracheas were intubated with a 6.5-mm cuffed endotracheal tube, and mechanical ventilation was initiated with an Ohio 7000 ventilator (Ohio Medical, WI, USA), with minute ventilation adjusted to maintain a $PaCO_2$ of 35–45 mmHg. Anesthesia was maintained with 2.0% isoflurane in $O_2$ during surgical preparation. Neuromuscular blockade was achieved with pancuronium (0.2 $mg \cdot kg^{-1}$ *iv*) and maintained via continuous infusion (6 $mg \cdot hr^{-1}$). Lactated Ringer's solution was administered intravenously for the duration of the experiment.

A 7-Fr catheter was inserted in the right femoral artery for blood gas and hemodynamic monitoring. A 5-Fr single lumen femoral venous catheter was advanced into the inferior vena cava for infusion of oleic acid. A 7.5-Fr pulmonary artery thermodilution catheter was placed in the right external jugular vein and was advanced until a satisfactory pulmonary capillary wedge tracing was obtained with balloon inflation. The pulmonary artery catheter was used to obtain cardiac filling pressures and mixed venous blood samples, to monitor temperature, and to determine cardiac output (Edwards Lifesciences COM2, Irvine, CA, USA).

A standardized, total intravenous technique utilizing propofol/ketamine (12/3.5 $mg \cdot kg^{-1} \cdot hr^{-1}$) was

initiated as the isoflurane was discontinued. A bolus of fluid was administered to maintain central venous pressure >3 mmHg. An alveolar recruitment maneuver (30 cm $H_2O$ for 30 sec) was performed prior to switching the animals to an Esprit® ventilator (Respironics Inc, Vista, CA, USA) capable of delivering either BVV or conventional mode ventilation. The ventilator was set to deliver a square-wave inspiratory flow pattern with the following settings: tidal volume ($V_T$) = 10 mL·kg$^{-1}$, fractional inspired concentration of $O_2$ ($F_IO_2$) = 0 .3, inspiratory to expiratory ratio (I:E) = 1:2, and positive end expiratory pressure (PEEP) = 5 cm $H_2O$. Initially, the respiratory rate was set to 25 breaths·min$^{-1}$, then adjusted as necessary, to maintain a $PaCO_2$ between 35–45 mmHg.

After 15 min to stabilize, baseline measurements were obtained. Hemodynamic measurements included mean arterial pressure (MAP), heart rate (HR), cardiac output, central venous pressure (CVP), mean pulmonary artery pressure (MPAP), and pulmonary artery occlusion pressure (PAOP). All hemodynamic data were monitored continuously on a Gould 2600 Oscillograph (Gould, Cleveland, OH, USA). A pneumotachometer (Hans Rudolph 3700B series, Kansas City, MO, USA), with a sensor immediately distal to the endotracheal tube, intermittently recorded airway pressures, $V_T$, and flow using an advanced CODAS (Dataq Instruments, Akron, OH, USA) data acquisition system. A multimodal sensor (NICO 3700, Novametrics, Wallingford, CT, USA) was placed in the inspiratory limb of the respiratory circuit to record carbon dioxide tensions and measure airway resistance.

Arterial and mixed venous gases were analyzed using a Radiometer ABL 500 (Copenhagen NV, Denmark). Arterial and mixed venous oxygen content, oxygen saturation, and hemoglobin concentrations were measured with a Radiometer OSM3 (Copenhagen NV, Denmark) set for porcine blood.

At end expiration, respiratory system static compliance was measured in triplicate by the occlusion method. The plateau pressures were measured one second after occlusion. Pressure-volume loops were constructed, and dynamic compliance was calculated as the slope between end inspiratory and end expiratory zero flow.

Prior to initiating the oleic acid infusion, dopamine hydrochloride was started at 5 µg·kg$^{-1}$·min$^{-1}$ and titrated to keep the MAP > 60 mmHg. An oleic acid lung injury was initiated by infusion at 0.1 mL·min$^{-1}$. The infusion was stopped when $PaO_2$ decreased to < 80 mmHg. A subsequent blood gas measurement was obtained five minutes following the cessation of oleic acid infusion, to ensure the $PaO_2$ remained < 80 mmHg. When this oxygen tension was achieved, the PEEP was increased to 10 cm $H_2O$. Ten minutes after the increase in PEEP, an arterial blood gas sample was obtained to determine if $PaO_2$ had increased. This approach was considered to represent adequate lung injury, but also to indicate that collapsed alveoli could still be recruited with the additional PEEP. If the $PaO_2$ did not increase, the experiment was terminated. If the $PaO_2$ increased to a measure > 80% above the post-oleic acid baseline, additional oleic acid was infused.

Once an adequate oleic acid lung injury was established, a low $V_T$ (7 mL·kg$^{-1}$ plus 25 mL for equipment deadspace) protocol was initiated, and the respiratory rate was increased to 30 breaths·min$^{-1}$. If the $PaO_2$ remained stable, post-oleic acid hemodynamic, gas exchange, and respiratory system compliance measurements were obtained, and the animal was randomized (by selection of an unmarked envelop with notation of either white or physiological noise) into either group.

*Biologically variable ventilation*

Biologically variable ventilation is a form of noisy mechanical ventilation developed in this laboratory, which incorporates the normal variability in delivered $V_T$ and respiratory rate seen in healthy breathing patterns, to drive a standard mechanical ventilator using a computer-controller. In BVV mode, the Esprit® ventilator is driven by a software file. The file used for this study was derived from the breath-to-breath variability in frequency obtained from a spontaneously ventilating awake subject, captured by a data acquisition system and processed. Computer-generated files can also be adapted – as was the white noise file used in this study. The modulation file, in combination with the developed software and hardware, provide breath-to-breath control of the Esprit® ventilator using a laptop computer. Functions were developed to convert ventilator rate to voltage scaled to the chosen frequency. Voltage to the rate controller is altered, based on the next instantaneous rate, as read from the modulation file. Output to the control frequency is updated every 5 msec and changed accordingly. The ventilator functions as a volume divider – changes in frequency result in reciprocal changes in $V_T$ – such that minute ventilation remains fixed.

*Ventilation protocol*

The Esprit® ventilator (Respironics Inc, Vista, CA, USA) was switched from CMV to BVV mode. Immediately prior to this, the thorax of the animal was covered with an operating room drape to disguise the pattern of the tidal volume and respiratory rate being delivered.

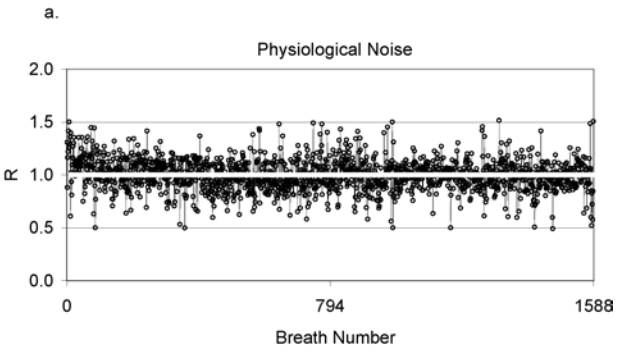


FIGURE 1a Physiologically-derived noise (PN) file. The breathing file was obtained from a healthy female volunteer, sitting quietly for a two-hour period. Instantaneous respiratory rate was obtained from analysis of the breathing file acquired to a digital acquisition system. The file has 1,587 breath intervals, normalized to a mean respiratory rate (R) of 1.000 with a standard deviation of 0.150. This file was uploaded to the Esprit® ventilator, with each breath interval multiplied by the selected respiratory rate (if the selected rate was 30 breaths·min$^{-1}$, then each value in this file was multiplied by 30 to give the instantaneous rate during mechanical ventilation).

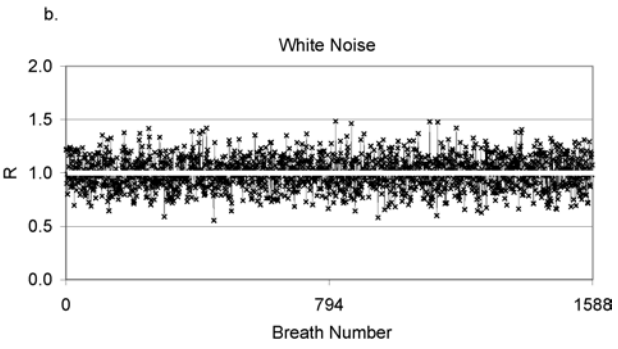


FIGURE 1b Computer-generated white noise (WN) file. The file has 1,587 breath intervals normalized to a respiratory rate (R) of 1.000 with a standard deviation of 0.149. This file was uploaded to the ventilator, as described in Figure 1a.

The animals were ventilated for four hours with either a physiologically-derived time series (PN; Figure 1a) or with a computer-generated white noise (WN; Figure 1b) with the same mean and standard deviation. The noise signals were pre-programmed into the Esprit® ventilator to deliver the same I:E ratio and minute ventilation over time for both groups. Hemodynamics, gas exchange, and respiratory system compliance measurements were repeated hourly for four hours, at which time the experiment was terminated.

*Wet:dry lung weight ratios*

At the end of the experiment, the animals were sacrificed with a lethal dose of euthanyl (115 mg·kg$^{-1}$), and a sternotomy was performed. The trachea was clamped at end inspiration; the heart and lungs were removed en bloc, and bronchoalveolar lavage (BAL) samples were obtained. The BAL samples were collected in heparinized saline and immediately frozen at -80°C. The lungs and previously collected BAL fluid were weighed, and the lungs were suspended and aerated overnight. The following day, the lungs were placed in an oven to dry, and following a stable dry measurement, wet:dry weight ratio was calculated.

*Cytokine assays for interleukin (IL)-8 ELISA*

The incubation times and washes were performed as specified in the kit: (BioSource International, Camarillo, CA, USA). An immunoassay kit for swine IL-8 was used. Sample incubation times were kept as constant as possible, by pre-plating on a blank 96 well plate before transferring to a coated assay plate. ELISA plates were read at 450 nm by an SLT Rainbow plate reader (Lab Instruments, Research Triangle Park, NC, USA). Standard curves and concentration calculations were performed according to kit directions.

*Signal analysis*

The physiologically-derived noise signal and the computer-generated noise signal were analyzed by two methods: relative dispersion and second moment diffusion analysis (SDA), as previously described.[15] Histograms, based on the frequency distribution of the Hölder exponents of each time series, were generated.

*Statistical analysis*

Parametric data were analyzed by repeated measures ANOVA using least squares means test matrices to identify differences within and between groups, from group × time or group effects. Bonferroni's correction was applied, where appropriate. In all circumstances, a $P$-value ≤ 0.05, corrected for multiple comparisons, was considered significant.

**Results**

Twenty-six experiments were undertaken. Six animals were not included, as three died during infusion of oleic acid, and three animals did not meet the criteria for an increase in $PaO_2$ with an increase in PEEP and were excluded prior to randomization. One hour after randomization, one animal died in the white noise group; nonetheless, it was included in the analysis, with data analyzed up to that point as intention-to-treat. Thus, data were analyzed on 20 experiments ($n$ = 10 in Group PN, and $n$ = 10 in Group WN).

TABLE I Hemodynamics

| | *Baseline Pre OA* | *Baseline Post OA* | *1 hr Post OA* | *2 hr Post OA* | *3 hr Post OA* | *4 hr Post OA* |
|---|---|---|---|---|---|---|
| *MAP* | | | | | | |
| WN | 96 ± 18* | 86 ± 26 | 91 ± 26 | 101 ± 27* | 101 ± 23* | 97 ± 23 |
| PN | 93 ± 16* | 80 ± 13 | 81 ± 16 | 92 ± 25* | 89 ± 21* | 79 ± 20 |
| *MPAP* | | | | | | |
| WN | 17.1 ± 1.9* | 36.6 ± 6.0 | 37.0 ± 6.7 | 34.4 ± 6.4 | 31.6 ± 5.6* | 29.8 ± 6.4* |
| PN | 18.5 ± 3.8* | 32.9 ± 4.1 | 33.2 ± 3.9 | 32.0 ± 2.4 | 30.4 ± 4.3* | 28.3 ± 6.1* |
| *PAOP* | | | | | | |
| WN | 6.6 ± 1.0* | 8.7 ± 1.7 | 8.9 ± 1.5 | 8.5 ± 0.9 | 8.5 ± 0.9 | 8.8 ± 1.0 |
| PN | 6.8 ± 1.5* | 9.0 ± 1.5 | 8.7 ± 1.3 | 8.9 ± 1.8 | 8.5 ± 1.4 | 8.7 ± 0.9 |
| *RAP* | | | | | | |
| WN | 4.4 ± 1.4* | 5.4 ± 1.6 | 5.3 ± 1.5 | 5.6 ± 1.9 | 5.7 ± 1.9 | 5.6 ± 1.8 |
| PN | 5.0 ± 1.8* | 6.1 ± 1.3 | 5.8 ± 2.0 | 5.9 ± 2.0 | 6.0 ± 1.9 | 6.0 ± 1.7 |
| *CO* | | | | | | |
| WN | 4.1 ± 0.4* | 2.7 ± 0.6 | 2.7 ± 0.6 | 2.9 ± 1.5 | 2.9 ± 1.0 | 2.6 ± 0.6 |
| PN | 4.7 ± 0.7* | 2.9 ± 0.8 | 2.3 ± 0.6 | 2.2 ± 0.5† | 2.3 ± 0.4 | 2.3 ± 0.5 |
| *PVR* | | | | | | |
| WN | 2.6 ± 0.5* | 11.3 ± 5.0 | 11.2 ± 4.1 | 10.2 ± 4.2 | 8.6 ± 3.0 | 8.3 ± 2.9 |
| PN | 2.5 ± 0.8* | 9.0 ± 3.7 | 11.2 ± 2.8 | 11.2 ± 2.9 | 10.0 ± 3.2 | 9.2 ± 4.4 |
| *HR* | | | | | | |
| WN | 127 ± 13* | 175 ± 35 | 178 ± 42 | 164 ± 40 | 163 ± 42 | 169 ± 42 |
| PN | 131 ± 20* | 179 ± 36 | 188 ± 38 | 177 ± 41 | 171 ± 43 | 171 ± 41 |
| *Temp* | | | | | | |
| WN | 37.0 ± 0.7 * | 37.6 ± 0.9 | 37.6 ± 1.1 | 37.7 ± 1.3 | 37.8 ± 1.3 | 37.8 ± 1.3 |
| PN | 36.8 ± 0.6* | 37.3 ± 0.9 | 37.6 ± 1.0 | 37.6 ± 1.2 | 37.6 ± 1.3 | 37.7 ± 1.3 |

WN = white noise variable ventilation; PN = physiological noise variable ventilation; MAP = mean arterial pressure (mmHg); MPAP = mean pulmonary artery pressure (mmHg); PAOP = pulmonary artery pressure (mmHg); RAP = right atrial pressure (mmHg); CO = cardiac output ($L \cdot min^{-1}$); PVR = pulmonary vascular resistance ($mmHg \cdot L^{-1} \cdot min^{-1}$). *$P < 0.05$ within groups *vs* baseline post OA. †$P < 0.05$ between groups. OA = oleic acid.

*Signal analysis*

Figure 2 shows the inverse power law relationship of the two files by relative dispersion analysis, with data fit to the equation $y = x^{\alpha}$. The physiologically-derived file had $\alpha = -0.27$, and the computer generated file had $\alpha = -0.52$. Figure 3 shows the analysis of the two data sets using SDA. The peak or supremum of the white noise series is at a Hölder exponent ($h$) of -0.49, while the supremum of the physiological noise series is -0.38. These values correspond to Hurst exponents ($H = h + 1$) of 0.51 and 0.62, respectively.[6]

*Temperature and hemodynamics*

Data are shown in Table I. All data are reported as mean ± SD, unless otherwise stated. The groups were not different at baseline, and similar changes occurred in temperature, HR, MAP, CVP, MPAP or PAOP, or pulmonary vascular resistance immediately following the oleic acid lung injury, but no group × time interaction (G × T) or group effects were seen. Cardiac output was significantly higher in the white noise group at two hours post oleic acid ($P = 0.037$), but subsequent comparisons showed no significant difference.

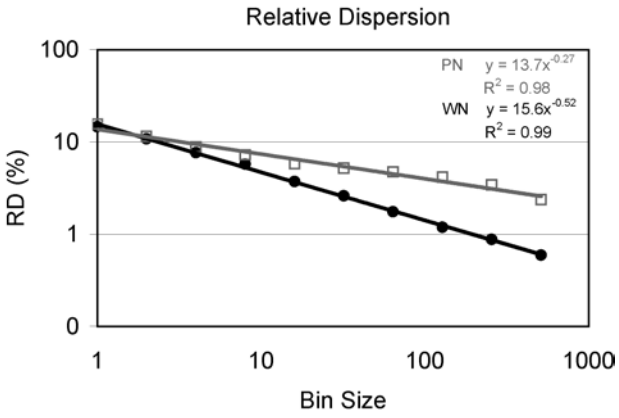


FIGURE 2 Relative dispersion (RD) analysis, as described by Glenny and colleagues.[15] An inverse power law relationship is seen for both files with data fitting an equation of the form $y = x^{\alpha}$. The physiologically-derived file had $\alpha = -0.27$ indicating auto-correlated noise. The computer-generated file had $\alpha = -0.52$, consistent with white noise. See text for further details.

*Respiratory gases and mechanics*

The changes in blood gases over time, for $PaO_2$ and $PaCO_2$ and for static and dynamic compliance, are shown in Figure 4a-d. There were no significant dif-

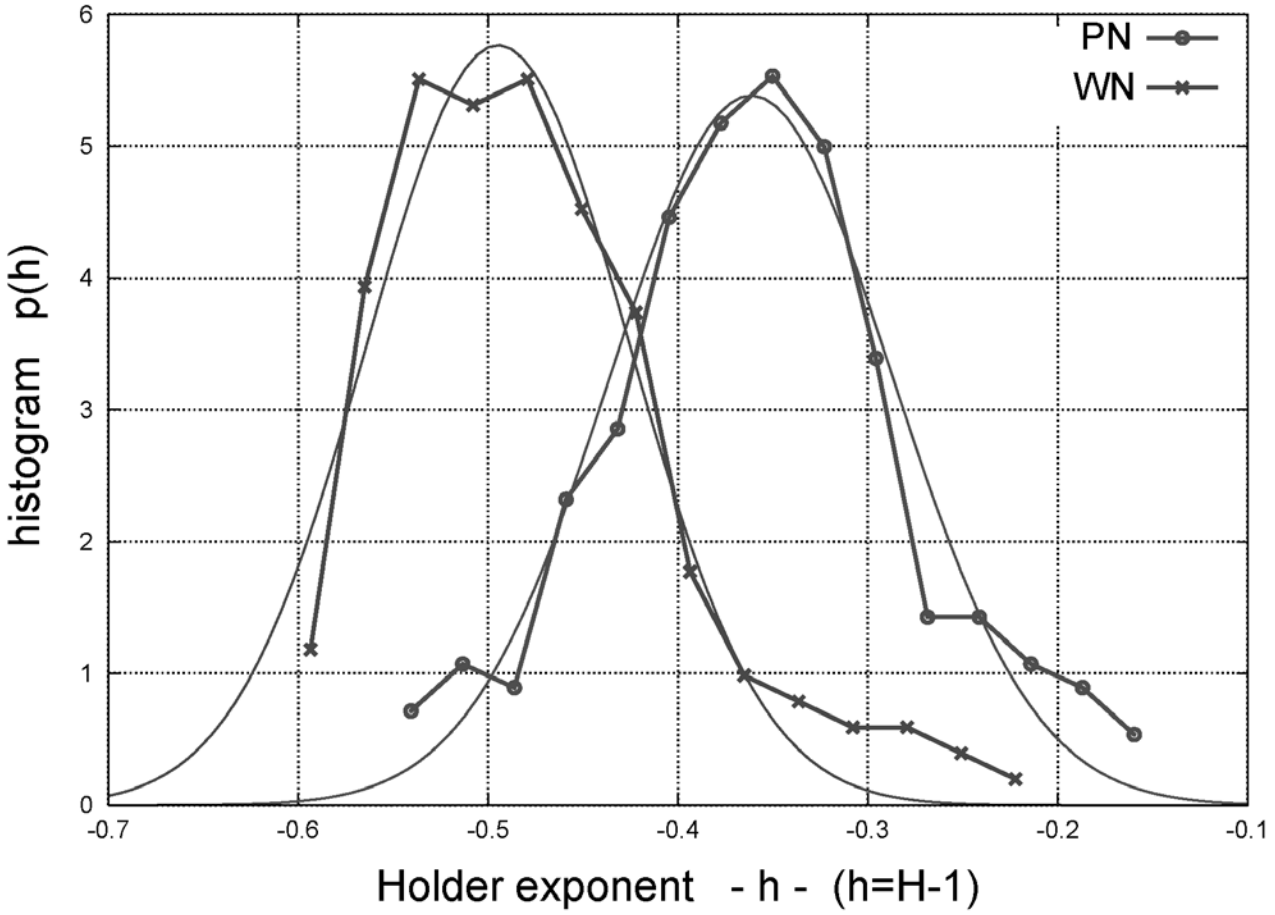


FIGURE 3 Hölder exponents *vs* probability histogram (p(h)) for the white noise and physiological noise files, based on a second moment diffusion analysis. In both circumstances, the files demonstrate multifractal behaviour (indicated by the width of the Gaussian envelop). The supremum (peak) for the white noise file is –0.49, and the supremum for the physiological noise file is –0.38. See text for further details.

ferences between any of these parameters, at any time period between groups. Both static and dynamic compliance increased in both groups following the oleic acid injury, but there was no significant difference between groups. Additional derived data are shown in Table II. In both the white noise and physiological noise groups, steady decreases were seen in deadspace ($V_D/V_T$) and shunt fraction ($Q_S/Q_T$) over the four hours following oleic acid, with no difference between groups. Airway pressures, compliance, and airway resistance data indicate no statistically significant differences between groups at baseline, and all showed a significant change from baseline to post oleic acid. The peak and mean airway pressures decreased significantly in both groups, at both two and four hours post oleic acid, with no difference at any point between groups.

*Wet:dry lung weight ratios*

The wet:dry weight ratio was 7.5 ± 0.7 in the white noise group and 7.3 ± 1.2 in the physiological noise group; ($P = 0.89$).

*Cytokine analysis*

The IL-8 concentration was 206 ± 273 pg·mL$^{-1}$ in the WN group and 132 ± 114 pg·mL$^{-1}$ in the PN group; ($P = 0.476$, by two-tailed *t* test).

## Discussion

Patients with ARDS require mechanical ventilation as part of their management. Mechanical ventilation, in and of itself, can further compound the lung injury by contributing to volutrauma, barotrauma, biotrauma, and atelectrauma.[16,17] Previous work using this animal model of ARDS has shown that BVV is superior in maintaining oxygenation to control groups ventilated with CMV,[11] or with CMV plus recruitment maneuvers.[18] When compared to control groups ventilated with CMV, BVV has also been shown to enhance

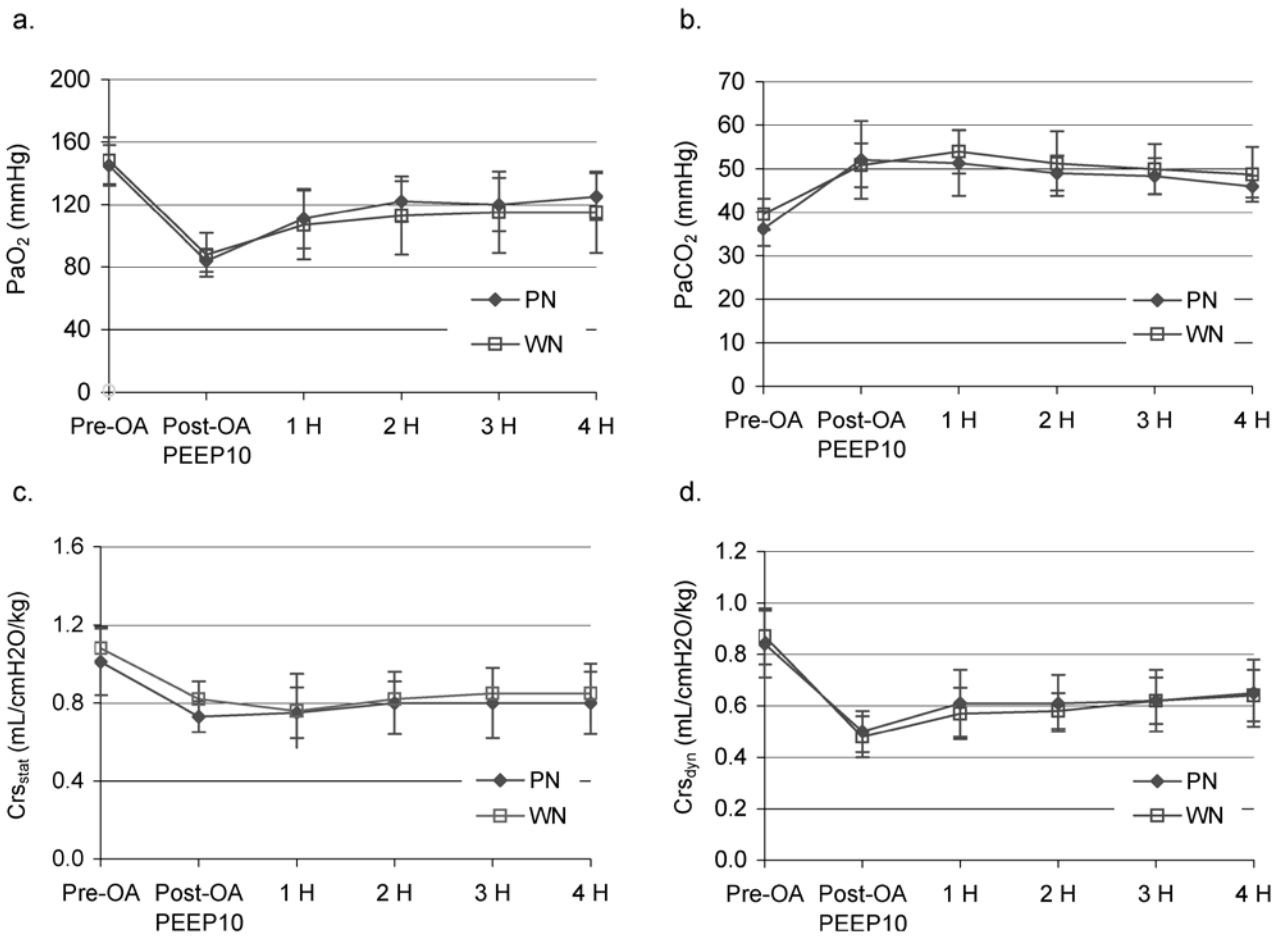


FIGURE 4a-d Blood gas and respiratory mechanics comparisons for the two experimental groups. There were no differences, at any time period, between groups for a) $PaO_2$, b) $PaCO_2$, c) static respiratory system compliance ($Crs_{stat}$), and d) dynamic respiratory system compliance ($Crs_{dyn}$).

recruitment of collapsed alveoli, thereby improving oxygenation and respiratory mechanics during, or following one-lung ventilation,[19,20] and providing superior gas exchange in a model of prolonged anesthesia.[21] When in BVV mode, compared to the control group with CMV, physiologically-derived respiratory rate variability, obtained from either an animal or human subject, was used to drive the ventilator in all of these experimental comparisons. In this study, we have compared BVV with either a physiologically-derived noisy respiratory rate file or a computer-generated white noise file, at the same mean value and standard deviation. A clear separation of the two time series is seen from the power-law $\alpha$-values obtained with the relative dispersion analysis. In contrast, save for a separation of their peaks or suprema, the SDA shows a significant overlap displayed by the Hölder exponent histograms. The distribution of Hölder exponents present in the histograms indicates that both files display multifractal behaviour.[6] The scaling properties of the fractal noise files generated here have probability distributions that fit an equation of the form:

$$P(f) = 1/f^{\alpha} = 1/f^{2h+1}$$

where $f$ is the frequency and $h$ is the mean of the Hölder exponent distribution for the time series. Thus, the computer-generated file fits the description of white noise with the exponent ($2h+1 = 0.02 \cong 0$), and the exponent is 0.24 for the physiologically-derived time series– indicative of auto-correlated noise. These results correspond to a Hurst exponent ($H = h+1$) of 0.51 for white noise and 0.62 for physiological noise. Increasing persistent behaviour or autocorrelation is seen when $0.5 < H \leq 1$. For this rate file, this finding indicates that, if an individual respiratory

TABLE II Respiratory gases, mechanics, and derived data

| | *Baseline Pre OA* | *Baseline Post OA* | *2 hr Post OA* | *4 hr Post OA* |
|---|---|---|---|---|
| *pH* | | | | |
| WN | 7.45 ± 0.03* | 7.30 ± 0.05 | 7.29 ± 0.09 | 7.33 ± 0.09* |
| PN | 7.47 ± 0.04* | 7.30 ± 0.06 | 7.30 ± 0.08 | 7.35 ± 0.04* |
| $Q_S/Q_T$ | | | | |
| WN | 2.9 ± 1.9* | 16.5 ± 7.4 | 10.5 ± 10.8* | 9.3 ± 8.0* |
| PN | 3.5 ± 2.0* | 17.2 ± 7.6 | 6.0 ± 3.1* | 4.3 ± 2.4* |
| $V_D/V_T$ | | | | |
| WN | 62.0 ± 4.5* | 75.2 ± 5.1 | 70.5 ± 5.7* | 68.8 ± 6.8* |
| PN | 60.0 ± 5.6* | 76.0 ± 6.2 | 72.4 ± 5.1* | 70.9 ± 5.5* |
| *Peak PAW* | | | | |
| WN | 20.0 ± 1.2* | 29.9 ± 2.5 | 26.7 ± 1.8* | 26.0 ± 2.1* |
| PN | 20.4 ± 2.6* | 30.2 ± 3.3 | 27.5 ± 4.3* | 26.7 ± 4.2* |
| *Mean PAW* | | | | |
| WN | 9.1 ± 0.4* | 15.2 ± 0.6 | 14.5 ± 1.0* | 14.4 ± 1.1* |
| PN | 9.1 ± 0.4* | 15.4 ± 1.4 | 15.1 ± 1.6* | 14.9 ± 1.6* |
| $V_T/kg$ | | | | |
| WN | 11.0 ± 0.4* | 8.8 ± 0.4 | 8.9 ± 0.4 | 8.9 ± 0.4 |
| PN | 10.9 ± 0.6* | 8.7 ± 0.5 | 8.5 ± 0.4 | 8.5 ± 0.3 |
| $R_{AW}$ | | | | |
| WN | 13.1 ± 1.3* | 16.7 ± 2.6 | 14.6 ± 2.1 | 14.6 ± 2.0* |
| PN | 13.2 ± 2.6* | 14.8 ± 2.9 | 15.2 ± 4.7 | 14.1 ± 3.9* |

WN = white noise variable ventilation; PN = physiological noise variable ventilation; pH = arterial blood gas pH; $Q_S/Q_T$= shunt fraction (%); $V_D/V_T$ = physiological deadspace ratio (%); Peak PAW = peak airway pressure (cm $H_2O$); mean PAW = mean airway pressure (cm $H_2O$); $V_T$/kg = tidal volume per kg (mL); $R_{AW}$ = airway resistance (cm $H_2O \cdot L^{-1} \cdot sec^{-1}$). *$P < 0.05$ within groups *vs* baseline post OA; †$P < 0.05$ between groups. OA = oleic acid.

rate had a low value, there was a greater than chance probability that the next rate would also have a low value; or vice versa. Antipersistent behaviour is seen for $0 \leq H < 0.5$.[6] In this situation, an individual respiratory rate with a low value would be followed by a respiratory rate with a higher value, at a greater than chance probability; or vice versa. During examination of HR variability comparing general anesthesia to the awake state, the potential of using Hurst exponents for analysis has recently been demonstrated and has been shown to be more discriminating than spectral indices.[22]

This experiment indicates no advantage in using a physiologically-derived, auto-correlated noise file over a computer-generated white noise file to drive the ventilator in BVV mode. We obtained the physiologically-derived file from data from a spontaneously breathing, healthy female, sitting at rest. From the above analysis, it is apparent that this respiratory rate file is only modestly auto-correlated, with considerable overlap of the two noise file histograms. If the auto-correlation were increased to a true pink noise distribution (a Hölder exponent of 0 and a Hurst exponent of 1), a clearer separation of the noise histograms would be expected. That said, work by Fadel *et al.*[23] examined the Hurst exponents in 20 spontaneously breathing subjects. They found 16 examples where the exponent was greater than 0.5, indicating persistent fluctuations in the breathing pattern, and four examples where the exponent was less than 0.5, indicating antipersistence in the breathing pattern. Thus, neither of the two files used to drive BVV were outside of previously demonstrated fractal characteristics for spontaneously breathing subjects.

Based on the two noise files studied, it is possible that the study was under-powered to detect true differences. However, the minimal differences between the two groups, for the variables examined in Figure 4a-d, suggest that, if a true difference does exist, a very large number of experiments would have been required to expose any statistical difference between groups. The relative differences are modest and unlikely to be of clinical significance. By way of example, the study was adequately powered, with nine experiments in each group, to detect a 25% lower mean value for arterial oxygen tension with white noise ventilation at four hours ($\alpha = 0.05$, $\beta = 0.2$, physiological noise projected to demonstrate a $PaO_2 = 120 \pm 30$ mmHg, and white noise projected to demonstrate a $PaO_2 = 90 \pm 15$ mmHg; two-tailed comparison). Prior work from the laboratory showed that BVV could improve $PaO_2$ up to 100% above values seen with control mode ventilation in this model of ARDS.[11] The most obvious difference between noise protocols was seen for $Q_S/Q_T$ at four hours, with the shunt being 116% greater with white noise. Due to the large standard deviation in the group ventilated with white noise, the calculated power is only 47% for a two-tailed comparison. With the means and standard deviations shown, 18 experiments in both groups would be required to reveal statistical significance for this observed difference. The difference at four hours, for any other variable studied, was markedly less. Thus, the fact that no differences were seen between noise protocols is not likely a consequence of an under-powered study (at least in the context of the noise files chosen to be compared here). It is not addressed whether or not differences would manifest if the experimental period were greater than four hours. This point may be best, and perhaps only, addressed by a comparison of noise protocols using BVV in patients ventilated in an intensive care setting for a protracted period of time.

Recently, we have mathematically demonstrated the

conditions under which the addition of a variable signal at end-inspiration, can be advantageous.[13] When ventilating on the convex portion of the static compliance curve, Jensen's inequality predicts that adding variability to the end-inspiratory pressure signal results in greater volume for a given mean end-inspiratory pressure, when compared to that seen with a monotonously delivered, and essentially constant end-inspiratory pressure. This mathematical model makes no prediction as to the nature of the noise signal which would be advantageous.

The optimal noisy signal for variable ventilation has not been previously investigated. Previous work from the laboratory has utilized breathing files with persistent fluctuations, and we speculated that such auto-correlated noise would be advantageous. That said, with increased auto-correlation, a greater temporal grouping of low value breath rates with true pink noise could potentially increase the risk of volutrauma with positive pressure ventilation, while the greater temporal grouping of high value breath rates could potentially increase the risk of atelectrauma. An optimal trade off is as yet to be determined. This study indicates that, when compared to white noise, a physiologically-derived signal with a modestly auto-correlated noise such that $P(f) = 1/f^{0.24}$ was not advantageous in regards to gas exchange or respiratory mechanics with BVV.

This study suggests potential ways to improve BVV. It is possible that computer-generated files of longer duration, with defined Hurst exponents, could be superior to drive a ventilator in BVV mode. The files used in this study were limited to a length of slightly less than 1,600 observations. The demonstration of multifractality may be, in part, a consequence of such a relatively brief file length. Files generated by computer algorithms with sufficient length, with no repeats over the course of an experiment, could be utilized (each file in this experiment was read approximately 5 times) and could possibly be advantageous. At present, BVV is limited to a fixed I:E ratio of 1:2, with a square-wave delivery of breathing volume so that the ratio of inspiration to expiration is always auto-correlated, and the inspiratory flow is fixed at a given minute ventilation for each breath delivered. True physiological variability would permit alteration in the breathing duty cycle and inspiratory flow rate.

In this experiment, we used human variability to provide the physiologically-derived noise file. It is possible that a porcine breath rate variability file may have been superior. Of interest is the consideration that interspecies differences may disappear when power law scaling is considered.[24]

As configured, this experiment shows that modestly auto-correlated noise provides no advantage over white noise, when used to drive a variable ventilator. Potential improvements for BVV are discussed in relation to these findings. Our study, using an ARDS model, shows that when applying a variable respiratory rate to control mode mechanical ventilation, the addition of multifractal variability, itself, may be more important than the specific temporal pattern of the signalling.

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