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Laboratory Investigation

LABORATORY INVESTIGATION

Comparison between neurally-assisted, controlled, and physiologically variable ventilation in healthy rabbits

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Abstract

Background: Various ventilation strategies have been proposed to reduce ventilation-induced lung injury that occurs even in individuals with healthy lungs. We compared new modalities based on an individualised physiological variable ventilation model to a conventional pressure-controlled mode.

Methods: Rabbits were anaesthetised and ventilated for up to 7 h using pressure-controlled ventilation with (Group PCS, n=10), and without (Group PC, n=10) regular sighs. Variable ventilation in the other two groups was achieved via a pre-recorded spontaneous breathing pattern [Group physiologically variable ventilation (PVV), n=10] or triggered by the electrical activity of the diaphragm [Group neurally adjusted ventilation assist (NAVA), n=9]. Respiratory elastance, haemodynamic profile, and gas exchange were assessed throughout the ventilation period. Cellular profile, cytokine content of bronchoalveolar lavage fluid, and wet-to-dry lung weight ratio (W/D) were determined after protocol completion. Lung injury scores were obtained from histological analysis.

Results: Marked deteriorations in elastance were observed (median and 95% confidence interval) in Group PC [48.6 (22)% increase from baseline], while no changes were detected in Groups PCS [3.6 (8.1)%], PVV [18.7 (13.2)%], and NAVA [−1.4 (12.2)%]. In comparison with Group PC, Group PVV had a lower lung injury score [0.29 (0.02) compared with 0.36 (0.05), P<0.05] and W/D ratio [5.6 (0.1) compared with 6.2 (0.3), P<0.05]. There was no difference in blood gas, haemodynamic, or inflammatory parameters between the groups.

Conclusions: Individualised PVV based on a pre-recorded spontaneous breathing pattern provides adequate gas exchange and promotes a level of lung protection. This ventilation modality could be of benefit during prolonged anaesthesia, in which assisted ventilation is not possible because of the absence of a respiratory drive.

Keywords: pulmonary gas exchange; respiratory mechanics; ventilator-induced lung injury

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Editor's key points

- Prolonged ventilation can damage even healthy lungs.
- Pressure-controlled ventilation was compared with variable ventilation based on pre-recorded spontaneous breathing patterns in rabbits.
- All ventilation modes provided adequate gas exchange.
- Individual variable ventilation promoted lung protection.
- This may be useful during prolonged ventilation when there is no respiratory drive.

Mechanical ventilation is routinely used in general anaesthesia or the intensive care setting. However, there is a considerable body of evidence that indicates that prolonged positive pressure ventilation can induce or worsen injury to the lung tissue through exaggerated mechanical stress, a condition termed ventilator-induced lung injury (VILI).[1–3] These adverse changes result from the monotonous, cyclic alveolar opening and closure that exerts shear stress forces and increases strain in lung tissue. This in turn promotes lung inflammation with a subsequent deterioration of gas exchange.[3,4]

Various modes of mechanical ventilation have been suggested to overcome the deleterious effects of mechanical ventilation. While there is increasing evidence for the beneficial effects of mechanical ventilation with low tidal volumes associated with positive end-expiratory pressure (PEEP) and regular alveolar recruitment manoeuvers,[5,6] these measures do not fully prevent VILI.[7,8] Therefore, new ventilation modalities have been introduced recently in an attempt to minimise lung injury.[9] One of these attempts is to mimic the physiological variability of spontaneous ventilation.[10,11] This so called 'noisy' or variable ventilation consists of lung insufflations with variable tidal volumes, respiration rates, or both. Experimental and clinical studies have shown that mechanical ventilation with some degree of variability (or 'noise') in the amplitude of individual breaths is beneficial, both for the gas exchange and for the mechanics of the respiratory system.[12–26] However, these variable ventilation patterns were generated on the basis of mathematical models,[12,13] rather than on the physiological spontaneous ventilation of a given individual.

Such variable ventilation can be applied by either assisting the patient's respiratory activity via the modality called neurally adjusted ventilation assist (NAVA),[27] or by using a novel approach based on the pre-recorded spontaneous ventilation pattern to be applied in a controlled ventilation mode. We therefore compared these two variable ventilation modalities with conventional pressure-controlled ventilation with and without regular alveolar recruitment through sighs in normal lungs ventilated for a prolonged period of time. We hypothesised that the application of a degree of physiological variability would provide lung protection, whilst guaranteeing the same gas exchange and preserving normal respiratory function.[28,29]

Methods

All experiments and procedures were conducted under approval from the Swiss animal welfare committee (Geneva Cantonal Veterinary Office, registration number GE61-14 and GE54-15) and concurred with EU directive 2010/63/EU, and results are reported in compliance with the ARRIVE guidelines. Fifty-one female and five male New-Zealand White rabbits, weighing 3.4 (0.1) kg, were involved in the study. All animals came from the University animal farm (Arare, Geneva, Switzerland), and were housed 2 days before the experiment at the laboratory facility of the University, in a pathogen-free environment. Six animals died before randomisation and completion of the experimental protocol, consequent to either severe hypoxaemia because of difficulties in tracheal intubation or to haemodynamic instability. Eleven rabbits served as pilot study animals to optimise the sedation and anaesthesia protocol, to verify the feasibility and consistency of the physiologically variable ventilation (PVV) and NAVA recordings, and to master the techniques for cytological and histological analysis. Hence, 39 animals were randomised based on a list generated by a random number generator in Excel.

Protocol groups

Rabbits were randomly assigned to one of the four protocol groups. Conventional pressure-controlled ventilation was applied to the animals in Group PC (n=10). Rabbits in Group PCS (n=10) received identical pressure-controlled ventilation with regular application of a lung inflation manoeuvre (sighs with peak airway pressure of 20 cm H_2O every 30 min). Ventilatory pressure level and cycle duration were identical to normal ventilation values during non-sigh periods). Animals in the other two groups underwent variable ventilation based either on the pre-recorded respiratory activity during spontaneous breathing (Group PVV, n=10), or the diaphragmatic activity detected by a NAVA catheter (Group NAVA, n=9).

Recording of spontaneous breathing

In animals assigned to the Group PVV, a lubricated nasogastric electrode was inserted to record the electrical activity of the diaphragm (Edi) (Maquet Critial Care, Solna Sweden), after premedication by i.m. injection of xylazine (5 mg kg^{-1}) and spraying the nostrils and the mouth with one push lidocaine 10% (Astra-Zenca®) to minimise sneezing. The Edi was recorded for 40 min (Supplementary Fig. S1). The PVV pattern was generated from these recordings using software to replay repeatedly this modality, taking into account ventilatory frequencies rates up to 55 bpm and an Edi higher than 2 μV. The characteristics of the PVV pattern are provided in Supplementary Table S1.

Anaesthesia and surgical preparation

Animals in all groups were sedated with an i.m. injection of xylazine (5 mg kg^{-1}) and a 22 G catheter was secured in a marginal ear vein. Anaesthesia was induced by i.v. injection of propofol (3 mg kg^{-1}) and maintained by a continuous infusion of propofol (15–20 mg kg^{-1} h^{-1}) and ketamine (5 mg kg^{-1} h^{-1}). All animals were intubated using a 3.0 mm cuffed tracheal tube. Mechanical ventilation was initiated in pressure-controlled mode using a paediatric respirator (Servo-i, Maquet Critical Care, Solna Sweden), with an FiO_2=30%, PEEP of 3 cm H_2O, and an inspiratory pressure of 6 cm H_2O above PEEP. Driving pressure (in group PC), ventilatory frequency, and NAVA level (in groups PVV and NAVA) were adjusted in order to maintain end-tidal CO_2 ($ETCO_2$) between 5.5% and 6%. The resulting tidal volume and ventilatory frequency values in these settings are detailed in Supplementary Table S1.

After ensuring proper depth of anaesthesia, muscle relaxation was induced by a continuous infusion of atracurium