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Regional Ventilation and Perfusion During Flow-Controlled Ventilation in Experimental Lung Injury: Assessment from Dual-Energy Computed Tomography

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Lung Injury, Dual Energy Computed Tomography, Flow Controlled Ventilation, Ventilated Gas Volume, Perfused Blood Volume, Ventilation/Perfusion Ratio

Abstract

Purpose: Flow-controlled ventilation (FCV) improves lung aeration and gas exchange but may raise intrathoracic pressure, potentially impeding pulmonary perfusion. This study explores radiographical image analysis to detect potential perturbations of regional ventilation-perfusion matching from application of FCV in experimental acute lung injury.

Methods: We compared FCV adjusted to the 1) minute volume (FCV-MV) and 2) capnography values (FCV-CO₂) of volume-controlled ventilation (VCV) at 1:1 inspiratory to expiratory (I:E) ratio in lavage (n=2) or oleic acid (n=9) induced porcine lung injury.

Transverse, juxtadiaphragmatic dual-energy computed tomography (DECT) images were acquired during uninterrupted mechanical ventilation. The ratio between ventilated gas volume (VGV) and perfused blood volume (PBV) was computed and used as surrogates to assess regional ventilation-perfusion matching.

Results: Nine (n=9) animals completed the protocol. Lung aeration increased during expiration in FCV, but the end-expiratory gas volume, mean airway pressure and gas exchange were similar to VCV 1:1. The VGV within the entire transverse section was 5.35 [4.62-8.15] mL in VCV 1:1, 5.45 [4.84-6.18] mL in FCV-MV and 5.78 [4.73-6.41] mL in FCV-CO₂. The corresponding PBV was 13.62 [12.09-19.01], 14.25 [13.28-20.79] and 17.31 [13.76-19.44] mL. The VGV to PBV ratio was 0.43 [0.29-0.49] in VCV 1:1, 0.32 [0.26-0.40] in FCV-MV and 0.31 [0.28-0.39] in FCV-CO₂. There were no differences between the modes in any of ten ventro-dorsal, horizontally orientated lung regions.

Conclusion: Using surrogate volumes of gas and blood computed from DECT images, regional ventilation-perfusion matching in FCV was not different from VCV with 1:1 I:E ratio in experimental acute lung injury.

Introduction

The Acute Respiratory Distress Syndrome (ARDS) is characterized by increased elastance with alveolar collapse and hypoxemia due to a heterogeneous lung injury with oedema and loss of surfactant production [1]. The abnormal elastance necessitates increased inspiratory pressures during mechanical ventilation and alveolar collapse is counteracted by application of a high positive end-expiratory pressure (PEEP). However, increased airway pressures infer stress on the lung tissue that may further aggravate the injury [2]. Flow-controlled ventilation (FCV) is a novel mode that may present advantages compared to conventional mechanical ventilation. By damping the expiratory flow, FCV limits the dissipation of energy to the pulmonary parenchyma which occurs with passive, rapid expiration [3]. In experimental ARDS models, FCV provides an increased intra-tidal aeration, associated with an increased number of “ideal” alveolar units and improved gas exchange [4-6]. However, the application of FCV has been shown to raise the mean airway pressure compared to conventional modes of ventilation [7]. An elevated intrathoracic pressure potentially impedes venous return, cardiac output (CO) and pulmonary perfusion, perturbing the ventilation-perfusion ratio in regions with lower perfusion pressure [8]. On the other hand, if FCV induces recruitment that mitigates the hypoxic vasoconstriction that comes with alveolar collapse, overall perfusion may increase and reconstitute the physiological matching to ventilation [9]. In summary, the effects of FCV on regional pulmonary perfusion remain unclear.

We could not find direct studies of physiological ventilation-perfusion ($\dot{V}/\dot{Q}$) matching during FCV in the literature covering experimental as well as clinical studies. Established methods for measuring $\dot{V}/\dot{Q}$ using radioactive or radiodense indicator substances are time consuming

and less useful to study short-time changes. Using radiographical surrogates, the aim of this study was to explore the analysis of dual-energy computed tomography (DECT) images to compare regional ventilation and perfusion between FCV and volume-controlled ventilation (VCV) in an experimental model of ARDS. Our hypothesis was that FCV, compared to VCV, would affect pulmonary perfusion and possibly the ratio between ventilation and perfusion.

Methods

The study was approved by the Regional Animal Ethics Committee in Uppsala on August 26, 2022 (Dnr 5.8.18-15019/2022) and conducted at the Hedenstierna Laboratory, Uppsala University, Sweden. The animals were handled in adherence with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Council of Europe No. 123, Strasbourg, 1985) and the study is reported according to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) Essential 10 guidelines [10].

Animals

Eleven healthy pigs (*Sus scrofa domesticus*, 9 male) of mixed Swedish, Hampshire and Yorkshire breed were included. They had free access to food and water before the experiment, and they were submitted to deep intravenous anaesthesia with muscle relaxation during the entire protocol. Acute lung injury (ALI) was induced by whole lung lavage with saline 30 mL/kg (n=2) or intravenously injected oleic acid (n=9) targeting a moderate injury, defined as normoxemia at a fraction of inspired oxygen (FiO₂) of 0.5. Anaesthetic procedures, instrumentation, data acquisition and the induction of lung injury are detailed in the supplementary appendix.

Protocol

All animals were included in this non-randomised, non-blinded study. After preparation, they were left to rest for one hour during VCV with inspiratory to expiratory (I:E) ratio 1:2, tidal volume (V_t) 6-8 mL/kg and respiratory rate (RR) adjusted to target normocapnia (approximate arterial partial carbon dioxide pressure; PaCO_2 5.3 kPa). Measurements started in baseline VCV mode with I:E ratio 1:1. Best positive end-expiratory pressure (PEEP) was individually defined according to the overdistension and collapse (OD-CL) method using Electric Impedance Tomography (EIT; ENLIGHT 1800; Timpel Medical SA, São Paulo, Brazil) [11]. The PEEP was increased to a point where dynamic compliance started to decrease from an observed maximum. It was then ramped back in steps of 2 cmH₂O to the point where the simultaneously lowest degree of collapse and overdistension was identified (Figure S1). After 15 minutes of stable uninterrupted ventilation, blood gases and respiratory mechanics data were collected. Next, FCV was applied using the Evone ventilator (Ventinova Medical BV, Eindhoven, The Netherlands). With this device, both inspiratory and expiratory flows are kept constant at a 1:1 I:E ratio. Tidal volume is adjusted by setting the driving pressure, while RR and the consequent minute ventilation (MV) are adjusted by varying the flow velocity [12]. We used the recommended Conventional Tube Adapter (CTA; Ventinova Medical BV, Eindhoven, The Netherlands), to allow for device specific pressure monitoring of tracheal pressure. Best PEEP was again titrated as described above. For the first FCV measurement (FCV-MV), flow and peak pressure were adjusted to maintain the same MV of the preceding VCV. After a period of steady ventilation of 15 minutes, data were collected. For the next FCV measurement (FCV-CO₂), TV was optimized for best dynamic compliance as described for FCV [13], and RR was titrated to maintain an end-tidal CO₂ (EtCO₂) as close as possible to the preceding EtCO₂ during VCV 1:1. The animals were

ventilated with the new settings for 15 minutes before a new set of data was collected. After the establishment of lung injury, titration of best PEEP and compliance in FCV-CO₂ as well as data acquisition were repeated as described above. Next, the ventilated animals were transported to the computed tomography (CT) laboratory where they were positioned supine on the CT table and allowed to rest for 30 minutes. The sequence of ventilation modes with PEEP set to the previously titrated “best” level was repeated with CT scans were performed immediately before the measurements. A final control VCV 1:1 set of measurements was added to evaluate the stability of the lung injury (Figure 1).

Figure 1. Protocol timeline

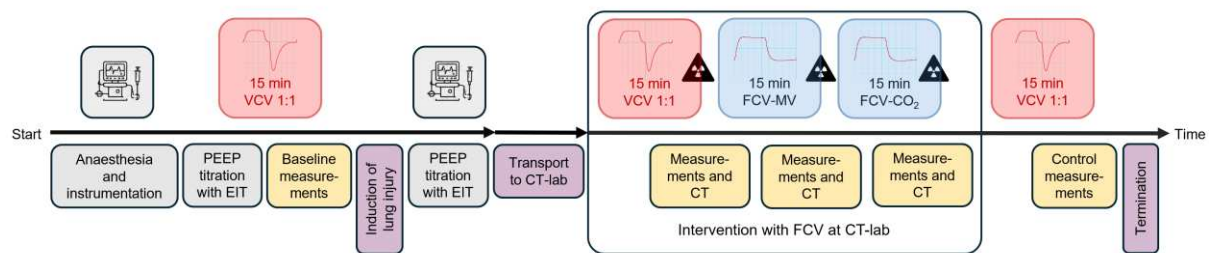


Figure 1. Protocol timeline with the intervention sequence outlined. PEEP – Positive end-expiratory pressure, EIT – Electrical impedance tomography, CT – computed tomography.

CT image analysis

Procedures and exposure parameters for the acquisition and reconstruction of dynamic, juxtadiaphragmatic dual-energy CT (DECT) and single-energy CT (SECT) images as well as details for the generation of iodine distribution images are described in the online supplementary appendix. Iodine distribution images were generated using the syngo.CT application (version VB20A, Siemens Healthineers, Erlangen, Germany) based on three-material decomposition of the 80 kVp and tin-filtered Sn140 kVp DECT images. The lung boundaries were manually outlined on the 80 kVp images, generating a binary mask applied

to all computations [14, 15]. All subsequent image processing and computation was non-blinded and performed using purpose-developed scripts in MATLAB (v2024b, MathWorks, Natick, MA, USA).

Applying a Hounsfield Unit (HU) interval from -1000 to 0, gas volumes were calculated from Sn140 kVp DECT and SECT images using the formula:

$$V_{gas} = \sum_{i=1}^n \left[V_{vox} \times \left(\frac{-HU}{1000} \right) \right]$$

where V_{gas} is the volume of gas, HU the attenuation in the single voxel and V_{vox} is the volume of the single voxel [16].

Applying a HU interval from 0 to 500, blood volume was calculated from the iodine distribution images using the custom formula:

$$V_{blood} = \sum_{i=1}^n \left[V_{vox} \times \left(\frac{HU}{HU_{ao}} \right) \right]$$

where V_{blood} is the volume of blood, HU the attenuation of the single voxel, and HU_{ao} the attenuation in a manually placed circular region of interest (ROI) in the aorta (Figure S2).

Outcome variables

As surrogates for physiological $\dot{V}/\dot{Q}$ matching, we used the ratio between radiographically derived ventilated gas volume (VGV) and perfused blood volume (PBV). For VGV, we calculated the difference in V_{gas} between the Sn140kVp DECT images acquired at peak inspiration and end-expiration during stable iodine attenuation in the aortic ROI (Figure S2) [17]. For PBV, we calculated the mean of V_{blood} from the peak inspiratory and expiratory DECT images [18]. Regional VGV and PBV were quantified within ten equal, horizontal,

ventro-dorsally distributed lung regions (Figure S3). With equal effective ventilation volumes, the aeration during expiration should be the only volumetric difference between the modes. To verify this, the area under the expiratory phase of the gas volume curve, calculated from the 100 kVp SECT images for better temporal resolution, was compared between the modes with the gas volume normalized at the start of inspiration. The most ventral and most dorsal lung sections were excluded from this analysis because their limited anatomical extent caused susceptibility to partial-volume effects and other computational artifacts.

Statistical analysis

Given the exploratory nature of the study, the number of individual animals was decided according to the Mead Resource Equation that allows for the determination of the sample size when the effect of a treatment is difficult to estimate a priori [19]. Data are expressed as median (IQR) due to the low number of individuals. The Wilcoxon signed-rank test was used for paired measurements. A p-value of < 0.05 was considered statistically significant. Correction for multiple paired comparisons was performed according to the Bonferroni-Holm method, with separate correction applied within each of two groups of variables: 1) respiratory, hemodynamic and blood gas variables; 2) radiologically derived variables. Statistical computations were made using R (v4.4.2, The R Foundation, Vienna, Austria).

Results

Two animals with oleic acid-induced injury were excluded, one due to pneumothorax and one due to pulmonary edema occluding the tracheal pressure monitoring tube, leaving nine (n=9) animals (8 male, weight 29.2-31.7 kg) for the complete analysis.

Induction of lung injury during ventilation in VCV 1:2 I:E ratio caused a decrease in median [IQR] PaO₂ from 17.0 [15.7-18.7] to 10.6 [9.4-13.4] kPa and PaO₂/FiO₂ (P/F) ratio from 56.7 [52.3-62.3] to 34.7 [31.2-40.8] kPa. Mean pulmonary artery pressure (MPAP) increased from 21 [18-24] to 36 [26-43] mmHg and dynamic compliance (C_{dyn}) decreased from 22 [19-29] to 15 [12-18] cmH₂O·L⁻¹.

During the intervention, there was no significant difference between VCV 1:1 and FCV-MV or FCV-CO₂ with respect to hemodynamics, gas exchange, respiratory mechanics or mean airway pressure (Table 1). The complete set of physiological data measured during the entire protocol appears in the supplementary appendix (Table S1).

Table 1. Median [IQR] hemodynamic, blood gas, and respiratory mechanics variables during the different ventilation modes.

Ventilation mode ^a :	VCV 1:1	FCV-MV	FCV-CO ₂
HR (min ⁻¹)	108 [87-134]	103 [88-125]	102 [87-131]
MAP (mmHg)	79 [72-97]	79 [73-94]	88 [72-98]
MPAP (mmHg)	26 [25-27]	27 [22-29]	25 [24-26]
CVP (mmHg)	10 [8-12]	10 [9-11]	10 [9-12]
PAOP (mmHg)	12 [9-12]	12 [10-12]	11 [10-12]
CO (L·min ⁻¹)	3.6 [3.3-5.4]	3.8 [3.2-5.9]	4.0 [3.2-5.4]
Shunt (%)	8.6 [6.0-14.0]	7.2 [6.5-16.3]	7.8 [4.7-15.0]
SpO ₂ (%)	97 [95-100]	96 [95-99]	98 [95-100]
PaO ₂ (kPa)	14.3 [12.3-16.6]	14.6 [12.8-16.7]	15.5 [12.7-17.0]
PaCO ₂ (kPa)	6.01 [5.1-7.07]	6.75 [5.34-7.55]	6.08 [5.25-6.99]
EtCO ₂ (kPa)	5.7 [5.2-7.7]	5.8 [5.4-7.3]	5.8 [5.2-7.4]
P _{Peak} (cmH ₂ O)	25 [22.5-26.5]	23 [20-25]	25 [22-29]

P _{Mean} (cmH ₂ O)	13.7 [11.5-15.3]	14.4 [13.0-16.6]	15.7 [13.4-17.0]
PEEP (cmH ₂ O)	9 [6-10]	8 [5-10]	8 [5-9]
V _t (mL)	240 [198-296]	234 [204-296]	243 [205-347]
RR (min ⁻¹)	33 [19-39]	36 [19.5-39]	37 [22-38.5]
MV (L·min ⁻¹)	7.9 [5.7-9.2]	7.7 [6.2-8.7]	7.9 [7.2-8.9]
Peak flow _{insp} (L·s ⁻¹)	0.27 [0.23-0.32]	0.24 [0.22-0.28]	0.29 [0.24-0.30]
Peak flow _{exp} (L·s ⁻¹)	-0.53 [-0.74-- 0.50]	-0.26 [-0.28-- 0.20]	-0.28 [-0.28-- 0.23]
C _{dyn} (L·cmH ₂ O ⁻¹)	16.4 [14.1-18.6]	15 [12.5-16.5]	15.0 [12.0-16.5]
C _{stat} (L·cmH ₂ O ⁻¹) ^b	21.0 [18.4-23.5]		
C _{corr} (L·cmH ₂ O ⁻¹) ^c		22.0 [19.1-23.1]	20.3 [18.1-22.0]

^a—Ventilation modes: VCV, volume-controlled ventilation, with I:E ratio 1:1, performed in the computed tomography (CT) laboratory after induction of ALI; FCV-MV, flow-controlled ventilation in the CT laboratory with minute ventilation matched to VCV; FCV-CO₂, flow-controlled ventilation in the CT laboratory with end-tidal carbon dioxide (EtCO₂) matched to VCV.

^b—C_{stat}, static respiratory system compliance, calculated only during VCV

^c—C_{corr}, corrected respiratory system compliance (see Appendix), calculated only during FCV.

Abbreviations: VCV, volume-controlled ventilation; FCV, flow-controlled ventilation; IQR, Inter Quartile Range; HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; CO, cardiac output; Shunt, intrapulmonary shunt fraction; SpO₂, peripheral oxygen saturation; P_aO₂, arterial partial pressure of oxygen; P_aCO₂, arterial partial pressure of carbon dioxide; EtCO₂, end-tidal carbon dioxide; P_{Peak}, peak airway pressure; P_{Mean}, mean airway pressure; PEEP, positive end-expiratory pressure; V_t, tidal volume; RR, respiratory rate; MV, minute ventilation; Peak flow_{insp}, peak inspiratory flow; Peak flow_{exp}, peak expiratory flow; C_{dyn}, dynamic respiratory system compliance; C_{stat}, static respiratory system compliance, C_{corr}, corrected respiratory system compliance.

The intra-tidal gas volume, computed from the SECT images, was higher during expiration in both FCV modes compared to VCV 1:1 but the end-expiratory volumes did not differ (Figure 2). A tidal breath with the higher expiratory gas volume is illustrated in an online

supplementary video with dynamic SECT acquisitions during VCV 1:1 and FCV-MV (Figure S4).

Figure 2. Gas volume over one normalized breath

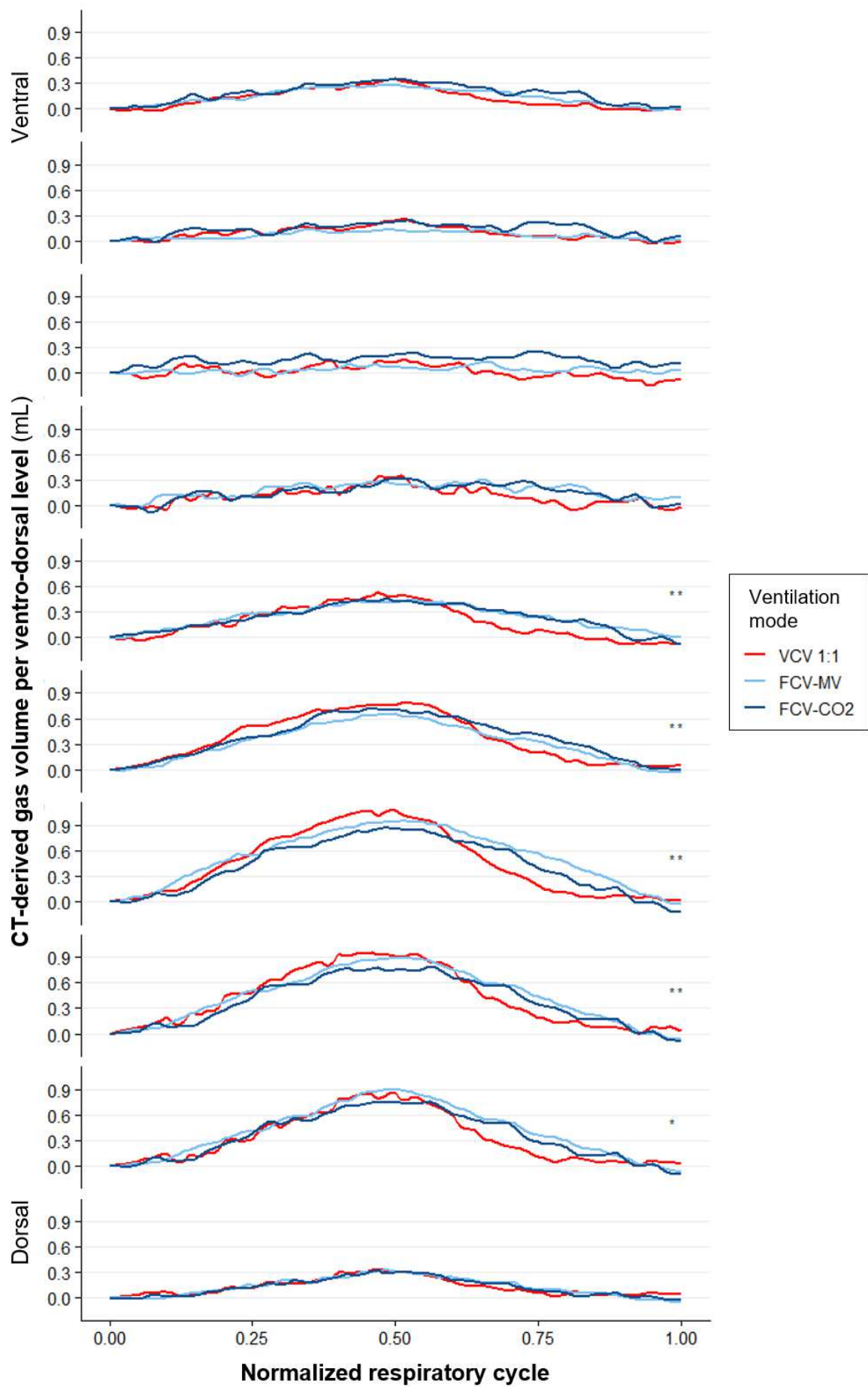


Figure 2. Average computed tomography derived gas volume profiles over the tidal excursion in each ventro-dorsal lung region, with the most dorsal region shown at the bottom. Gas volume curves were normalized to both respiratory-cycle duration (x-axis) and gas volume at the start of inspiration (y-axis), allowing direct comparison of the shape of expiratory gas-emptying pattern between ventilation modes independent of respiratory rate and absolute lung volume. Differences in expiratory emptying were quantified by comparing the area under the expiratory portion of the normalized curves (expiratory AUC) between the ventilation modes. The most ventral and most dorsal lung sections were excluded from the analysis because their limited anatomical extent increases susceptibility to partial-volume effects and other computational artifacts. *-Significant difference in expiratory AUC between VCV 1:1 and FCV-MV. **-Significant difference in expiratory AUC between VCV 1:1 and both FCV-MV and FCV-CO₂ respectively. For abbreviations regarding ventilation modes, please see methods section.

The analysis of VGV in the entire transverse DECT image yielded 5.35 [4.62-8.15] mL in VCV 1:1, 5.45 [4.84-6.18] mL in FCV-MV and 5.78 [4.73-6.41] mL in FCV-CO₂. Corresponding PBV was 13.62 [12.09-19.01], 14.25 [13.28-20.79] and 17.31 [13.76-19.44] mL. The VGV to PBV ratio was 0.43 [0.29-0.49] in VCV 1:1, 0.32 [0.26-0.40] in FCV-MV and 0.31 [0.28-0.39] in FCV-CO₂. The VGV, PBV and VGV to PBV ratio in the ventro-dorsal regions of the lung did not differ significantly between the FCV modes and VCV 1:1 (Figure 3).

Figure 3. VGV, PBV and VGV/PBV per region

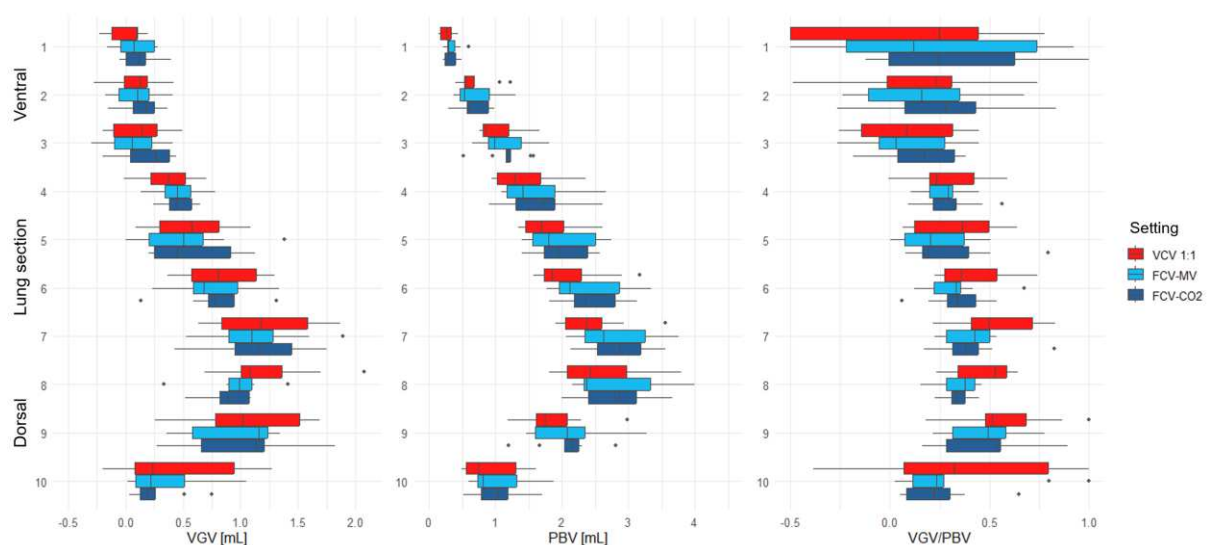


Figure 3. Horizontal boxplots of ventilated gas volume (VGV), perfused blood volume (PBV), and the VGV/PBV ratio across ventro-dorsal lung regions. No significant differences were observed between modes.

Discussion

In this study, using the ratio between VGV and PBV computed from DECT images as a surrogate, we aimed to explore possible changes in physiological $\dot{V}/\dot{Q}$ matching during FCV in porcine ALI. However, we did not observe any differences between FCV and conventional VCV with an I:E ratio of 1:1. We could not find other studies addressing this research question for comparison, but our findings may be scrutinized from different perspectives. Changes in pulmonary perfusion may have been localized outside the fixed juxtadiaphragmatic lung segment covered by the dynamic DECT exposure. Although we observed a higher degree of aeration during expiration in FCV, the mean airway pressure and the end-expiratory gas volume were not significantly different. It is possible that the intra-tidal volume effect did not affect pulmonary perfusion to a detectable degree with the relatively high RR used in our protocol.

Improved gas exchange with FCV has been reported in earlier studies comparing the Evone ventilator to both Pressure- and Volume-Controlled Ventilation in experimental lung injury [5, 6]. Indeed, we titrated the best PEEP guided by EIT, seeking a combination of minimal overdistension and collapse which should allow for optimal gas exchange, but FCV was not better than VCV 1:1 in our protocol. As we applied a more moderate degree of lung injury in our model, the potential for recruitment with ameliorated gas exchange could have been negligible. Also, the RR in the referenced studies was significantly lower in FCV as opposed to our study with V_t and RR adjusted to maintain MV and $EtCO_2$ respectively. In theory,

elevated RR may induce air trapping and hyperinflation that could affect gas exchange, but the image analysis did not suggest increased overdistension as the end-expiratory gas volume did not increase in FCV. Furthermore, air trapping is less likely in young individuals, and its absence agrees with CT data reported from another study of FCV with a reduction in non-aerated but no increase in overdistended lung tissue [13]. In summary, the physiological explanation for our finding of unchanged perfusion, ventilation and gas exchange with the application of FCV is yet to be definitively established.

Methodological aspects and limitations

Assessing the degree of deviation from normal physiological $\dot{V}/\dot{Q}$ matching is complex as both $\dot{V}$ and $\dot{Q}$ vary with lung structure and gravity. Averaged numbers, mostly derived from the multiple inert gas elimination technique (MIGET) [20] are relatively consistent, spanning from 0.8 to 1.0 in humans and from 0.8 to 1.1 in young pigs [21]. However, MIGET measurements do not provide spatial distribution of $\dot{V}/\dot{Q}$. Imaging techniques provide better regional discrimination, even if they are not suited for emergency diagnostics [22, 23]. We chose DECT for its excellent regional resolution and rapid image acquisition, combining estimation of VGV from Gattinoni's universally accepted formula for gas content [16] with a novel computation of voxel blood volume content, assuming proportionality with PBV [18]. Notwithstanding, the lack of temporal dimension reduces the VGV and PBV to surrogates without a scaled relation to $\dot{V}/\dot{Q}$ measured by standard methods.

Longitudinal movement of the lung during ventilation may induce artifacts when using images acquired at peak inspiration and expiration for computation. While computing VGV can be supported by the Cavalieri principle [24], the limited thickness of the reconstructed DECT images inferred large individual variations in the blood volume calculations. These

heterogeneous numbers limit the precision of the comparison between the ventilator modes even if the setup with the animals being their own control adds some strength to the analysis.

Several methods to control expiratory flow during mechanical ventilation have been studied, from add-on devices manipulating the expiration from conventional ventilators [25-28] to the purpose-designed Evone ventilator which controls inspiratory and expiratory flow in full [13, 29]. We chose VCV with 1:1 I:E ratio for comparison to FCV because we desired a constant inspiratory flow pattern and effective ventilation in both groups. However, several other studies have compared FCV to modes with an I:E ratio of 1:2. The artificial airway also differs between studies, from narrow tubes primarily designed for endotracheal surgical access [30] to adapters for conventional endotracheal tubes [31]. This variety of technical solutions restricted the number of studies we could refer to for comparison, and the validity of our results is limited to technical settings like ours.

We defined “best” PEEP by applying EIT, aiming for the lowest possible fractions of simultaneous overdistension and collapse [32]. This precludes comparison of our results to settings where the Evone is used according to the best practice as defined by the inventors. However, we titrated best PEEP once for each ventilation mode and then kept the PEEP constant during the measurements to reflect a clinical situation in which there is no expectation of short-term physiological changes [33].

Finally, the experimental ALI only models the early, exudative phase of ARDS and the findings in this study cannot be translated to the later, more complex trajectory of clinical ARDS, typically associated with further progress of inflammation and extended time on MV.

Conclusion: Using surrogate volumes of gas and blood computed from DECT images, regional ventilation-perfusion matching in FCV was not different from VCV with 1:1 I:E ratio in experimental acute lung injury.

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Statements and declarations

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Competing interests

All authors declare that they have no relevant financial or non-financial interests to disclose. The Evone® manufacturer had no role in the conception of the study, the data curation and analysis and did not pre-view the manuscript.

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Ethical approval

Ethical approval was issued by the Regional Animal Ethics Committee, Uppsala (Dnr 5.8.18-15019/2022).

Availability of data and material

The data set is available from the corresponding author on reasonable request.

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