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A Comparison of High-frequency Jet Ventilation and Synchronised Intermittent Mandatory Ventilation in Preterm Lambs

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Abstract

Purpose: Synchronised intermittent mandatory ventilation (SIMV) and high-frequency jet ventilation (HFJV) are accepted ventilatory strategies for treatment of respiratory distress syndrome (RDS) in preterm babies. We hypothesised that adequate oxygenation and ventilation would be achieved with SIMV and HFJV but that HFJV would be associated with less lung injury. Furthermore, we hypothesised that HFJV would have the least impact on pulmonary blood flow as mean airway pressure is likely to be lower during HFJV than during SIMV.

Methods: Preterm lambs of anaesthetised ewes were instrumented, intubated and delivered by caesarean section after intratracheal suction and instillation of surfactant. Each lamb was managed for 3 hours according to a predetermined algorithm for ventilatory support consistent with open lung ventilation. Pulmonary blood flow (PBF) was measured continuously and pulsatility index was calculated. Ventilatory parameters were recorded and arterial blood gases were measured at intervals. At postmortem, *in situ* pressure-volume deflation curves were recorded, and bronchoalveolar lavage fluid and lung tissue were obtained to assess inflammation.

Results: There were no differences in arterial oxygenation or partial pressure of carbon dioxide despite lower mean airway pressure during SIMV for most of the study. There were no consistent significant differences in end systolic and end diastolic PBF, lung injury data and static lung compliance.

Conclusions: SIMV and HFJV have comparable clinical efficacy and ventilator pressure requirements when applied with a targeted lung volume recruitment strategy.

Keywords: high-frequency jet ventilation, respiratory distress syndrome, pulmonary blood flow, lung injury, gas exchange

Introduction

The lungs of preterm infants are vulnerable to ventilation induced lung injury [1]. Preterm newborns often require invasive ventilatory support, which exposes them to positive intrathoracic pressures, the risk of lung injury from volutrauma and atelectotrauma and compromised cardiac output. Contemporary ventilatory strategies that are employed for the management of respiratory distress syndrome (RDS) in preterm babies include volume-targeted/guaranteed synchronised intermittent mandatory ventilation (SIMV) and high-frequency jet ventilation (HFJV).

The potential physiological advantages of HFJV over SIMV include: the mean airway pressure (P_{aw}) is relatively low during HFJV because less of the respiratory cycle is spent in inspiration; HFJV enhances mucociliary clearance by combining fast inspirations with relatively slow, passive exhalations (I:E ratio may be as low as 1:12); and the use of small tidal volume (V_T) breaths during HFJV at low frequencies, in combination with low inspiratory to expiratory ratios, make HFJV especially useful in patients with gas trapping. HFJV delivers high velocity and small V_T breaths that do not penetrate injured areas of lung with high resistance, allowing for maturation and healing [2].

Despite these features comparisons between HFJV and SIMV for the management of preterm infants with acute RDS in a clinical setting have not reported a consistent advantage of one strategy over the other [3-5]. Carlo et al (1990) found that the early use of HFJV did not prevent or substantially reduce mortality or morbidity rates associated with assisted ventilation [3]. Wiswell et al (1996) found HFJV resulted in significantly more adverse outcomes than conventional ventilation (CV) in the early management of premature infants with RDS [4]. Keszler et al (1997), however, found that the incidence of BPD at 36 weeks of postconceptional age was significantly lower in babies managed with HFJV compared to CV and that the babies receiving HFJV required less home oxygen [5]. Variation in study design, ventilator management and outcome measures between studies make it difficult to substantiate a clear benefit of one strategy over another. Perhaps the greatest limitation to these studies was failure to consistently pursue a protective lung ventilation approach which relies upon opening the lung and keeping it open to optimise ventilation and perfusion [6, 7]. When Keszler et al (1997) employed an optimal volume strategy in almost half their cohort of babies receiving HFJV they found that HFJV improved oxygenation, decreased the incidence of hypocapnia and reduced the risk of grade III-IV intraventricular haemorrhage (IVH) and/or periventricular leukomalacia (PVL) [5].

The results of the Keszler study suggest that HFJV may prove a suitable ventilator strategy for preterm babies with RDS but a direct and controlled comparison with SIMV has not been performed. Both SIMV and HFJV have unique features, which provide justification for their use in certain scenarios. A SIMV strategy delivers breaths of a similar size and at a similar frequency to spontaneous ventilation while high-frequency strategies deliver breaths smaller than dead space volume at frequencies varying from 3-20 Hz depending on the specific ventilator used. High-frequency jet ventilation offers potential for lung protective ventilation as the low tidal volumes reduce the risk of cyclic volutrauma [8-11]. Furthermore, the airway pressure waveform is attenuated along the airways during HFJV which may decrease the pressure and flow cost of ventilation induced lung injury [2].

The aim of this study was to compare HFJV with a moderate lung protective SIMV strategy in a preterm lamb model of RDS. We hypothesised that each strategy would facilitate acceptable oxygenation and ventilation, but that the low delivered tidal volumes of HFJV would result in less evidence of ventilation induced lung injury than a SIMV strategy. Furthermore, we hypothesised that compared to SIMV, HFJV would cause less reduction of pulmonary blood flow due to a proportionately greater duration of the cycle spent at the positive end-expiratory pressure with less impairment of venous return.

Materials and Methods

All animal procedures were approved by the University of Western Australia animal ethics committee, in accordance with guidelines of the National Health and Medical Research Council of Australia [12].

Animals, Instrumentation and Delivery

Twin-bearing date-mated merino ewes were anaesthetised at 128-130 d gestation (term \approx 150 d) with intramuscular xylazine (0.5 mg kg^{-1} , Troy Laboratories, N.S.W., Australia) and ketamine (20 mg kg^{-1} , Parnell Laboratories, N.S.W., Australia) and intubated (7.5 mm cuffed tracheal tube, Portex Ltd. England). Maternal anaesthesia was maintained with isoflurane in 100 % O_2 . The fetus was exteriorized via hysterotomy and a right lateral thoracotomy was performed. A flow probe (4R, Transonic Systems, Ithaca, NY) was positioned around the left pulmonary artery and a catheter was inserted into the main pulmonary artery [13]. The fetus was intubated orally (4.5 mm cuffed tracheal tube, Portex Ltd. England), lung fluid was suctioned and intra-tracheal surfactant (100 mg kg^{-1} , Abbott Laboratories, U.S.A.) was administered prior to delivery of the lamb. Unventilated controls (UVC; $n=6$) were euthanised (pentobarbitone 100 mg kg^{-1} i.v. Jurox, Australia) at delivery without instrumentation, suctioning or surfactant. Remaining lambs were randomized to one of two ventilation groups: synchronized intermittent mandatory ventilation (SIMV; $n=6$); or high-frequency jet ventilation (HFJV; $n=8$) as outlined below.

Ventilation

Instrumented lambs were dried and weighed. Lung volume was initially recruited by delivering 2 sustained inflations to $30 \text{ cmH}_2\text{O}$ (20 s and 10 s duration respectively) with an infant T-piece resuscitator (NeopuffTM, Fisher & Paykel Healthcare, Auckland, New Zealand), immediately before ventilation was commenced using the assigned ventilation strategy as detailed below. The initial FiO_2 was 0.4 for both groups.

Synchronised Intermittent Mandatory Ventilation

Initial settings for synchronised intermittent mandatory ventilation (SIMV) with volume guarantee (VG) included: respiratory rate 50 breaths/min; t_1 0.5 s; VG 5 mL/kg; positive end-expiratory pressure (PEEP) 7 cmH_2O ; and a peak inspiratory pressure limit ($\text{PIP}_{\text{limit}}$) of 30 cmH_2O (Babylog 8000+, Drägerwerk, Lubeck, Germany). After 5 min, the VG was increased to 7 mL/kg and $\text{PIP}_{\text{limit}}$ was increased to 40 cmH_2O . FiO_2 was

altered to target SpO₂ 88-94 %, V_T was altered to target PaCO₂ 45-55 mmHg and PEEP was altered according to the response of SpO₂ to changes in FiO₂ (Supplementary Figure 1A).

High-frequency Jet Ventilation

High-frequency jet ventilation (Life Pulse™, Bunnell Inc., Salt Lake City, U.S.A.) coupled to a pressure-limited time-cycled infant conventional ventilator (Babylog 8000+, Drägerwerk, Lubeck, Germany) was commenced with the following initial settings: respiratory rate 420 breaths/min (7 Hz); peak inspiratory pressure (PIP_{HFJV}) 40 cmH₂O; PEEP 8 cmH₂O; FiO₂ 0.4 and t₁ was fixed at 0.02 s. PIP_{HFJV} was adjusted to achieve permissive hypercapnia (PaCO₂ 45-55 mmHg) to a maximum of 40 cmH₂O. FiO₂ was altered to target SpO₂ 88-94 % and SIMV breaths were delivered according to the protocol algorithm (Supplementary Figure 1B) to target lung volume recruitment.

Postnatal care

Propofol (0.1 mg/kg/min; Norbrook Laboratories Ltd., Victoria, Australia) and remifentanyl (0.05 µg/kg/min; Abbott Laboratories, U.S.A.) were infused continuously through an umbilical vein for anaesthesia and analgesia. An umbilical arterial catheter was used for intermittent sampling to assess gas exchange and acid-base balance. Rectal temperature was monitored continuously and maintained between 38° and 39° C (normothermic for newborn lambs). Ventilator settings and physiological data were recorded at intervals. After final measurements were obtained, the FiO₂ was increased to 1.0 for 2 min after which the tracheal tube was occluded for 3 min to facilitate lung collapse prior to euthanasing the lamb (pentobarbitone 100 mg kg⁻¹ i.v. Jurox, Rutherford, Australia).

Physiological Analyses

Continuous measurements of pulmonary blood flow (PBF) were processed via calibrated pressure transducers (Maxxim Medical, Clearwater, U.S.A.). Data were amplified and digitally recorded (Powerlab 8SP, ADInstruments, N.S.W., Australia). Pulmonary waveform analysis was performed at regular time points as described previously [14] to quantify changes in pulmonary blood flow throughout the cardiac cycle. Pulsatility Index (PI), a measure of downstream resistance to blood flow, was calculated as (peak systolic flow – minimum flow after systolic peak)/mean peak systolic flow and averaged over five consecutive cardiac cycles.

Post-mortem

The lung was exposed by thoracotomy, and an *in situ* deflation pressure volume curve was obtained [15]. The right upper lung lobe was inflated fixed (30 cmH₂O) in formalin and samples of the right lower lobe were snap frozen for molecular analyses. Bronchoalveolar lavage (BAL) was performed on the left lung for cytology and protein analysis by the Lowry method [16, 17]. Differential cell counts were performed on cytopsin samples of the BAL fluid stained with Diff-Quik (Fronine Lab Supplies, N.S.W., Australia).

RNA was extracted from the left lung and reverse transcribed to cDNA (QuantiTect® Reverse Transcription Kit, Qiagen, U.S.A.). Expression of IL-1 β and IL-6 was measured by qRT-PCR [18] and normalized to 18S RNA [19] using the $2^{-\Delta\Delta CT}$ method [20].

Statistical Analyses

One-way analysis of variance was used to compare groups at specific time points while the effect of ventilator strategy on ventilator requirements and physiological changes over the duration of the study were determined using two-way repeated measure analysis of variance. Posthoc comparisons were performed using the Holm-Sidak method. Analyses were performed using SigmaStat (Version 3.5, Systat Software Incorporated, U.S.A.) with $p < 0.05$ considered statistically significant. Data are expressed as mean (SEM) unless stated.

Results

The gender distribution, birth weight, gestational age and arterial pH and $PaCO_2$ of the lambs in each group were not different (Supplementary Table 1).

Ventilation and Oxygenation

The $PaCO_2$ decreased from 101.2 (11.8) to 68.5 (6.2) mmHg and from 97.9 (20.4) to 50.6 (4.3) mmHg in the first 30 minutes of the study in the HFJV and SIMV groups respectively. There was no difference between the ventilated groups throughout the study (Figure 1A). The ΔP was also not different between the ventilated groups (Figure 1B). FiO_2 commenced at 0.4 in all ventilated groups. At 75 min FiO_2 was higher in the HFJV group (0.43 (0.06)) compared to the SIMV group (0.3 (0.07)) (Figure 1C). Despite a trend for increasing alveolar-arterial difference in both ventilated groups the partial pressure of oxygen ($AaDO_2$) was not different at any time point (Figure 1D). Paw was significantly lower in the SIMV group for the entire study, with the exception of the 10-minute time point (Figure 1E). At the end of the study the Paw was 15.9 (0.8) cmH₂O in the HFJV group and 12.4 (0.8) cmH₂O in the SIMV group.

Pulmonary Blood Flow

End systolic and end diastolic pulmonary blood flows were comparable until 150 min from which time HFJV lambs had lower flows (Supplementary Figure 2A and 2B respectively). Pulsatility Index was comparable for the duration of the study and was 1.35 (0.05) in the HFJV group and 1.11 (0.03) in the SIMV group at the end of the ventilation period (Supplementary Figure 2C).

Post-mortem

BAL fluid protein concentration and cell populations were similar between all groups (Table 1). The expression of IL-1 β and IL-6 were not different between groups (Supplementary Figure 3A and 3B). The lungs of the animals in the HFJV group consistently inflated to a greater volume than those in the SIMV group, as assessed by the deflation limb of the post-mortem pressure-volume curve. However, statistical significance was reached at the 10 minute time point only ($p = 0.048$) (Supplementary Figure 4).

Discussion

This study aimed to compare HFJV to a SIMV strategy that included moderate PEEP (7 cmH₂O) over a 3 hour ventilation study using a preterm lamb model of RDS. Gas exchange and pulmonary vascular resistance was similar for both groups though HFJV was associated with shunting of blood at the end of the ventilation period. Furthermore, there were no differences in the markers of lung injury.

Each lamb was managed identically immediately after delivery and then according to a predetermined ventilation strategy specific algorithm that was designed to be lung protective and consistent with the principles of the open lung approach [6, 7]. The initial sustained inflations were performed as a specific lung volume recruitment manoeuvre for all animals so the subsequent ventilation strategy followed a lung volume recruitment process and was less aggressive than it would have been if these initial sustained inflations had not been performed. In the SIMV group, the initial PEEP was chosen on the basis of previous observations in the preterm lamb model to maintain recruited lung and avoid over distension [21]. For the HFJV group we chose to use a combination of intermittent SIMV breaths and incrementing PEEP to recruit and stabilise alveoli. The maximum PIP_{HFJV} was set at 40 cmH₂O as we have previously successfully ventilated lambs without needing to exceed this limit [9]. The number of SIMV breaths was limited to 5 breaths/min during HFJV, in line with clinical recommendations, and our previous experience that this SIMV breath rate was sufficient to provide physiological benefit at the initiation of ventilation (unpublished data). The PIP_{SIMV} was kept 5 cmH₂O below PIP_{HFJV} as the physiological consequences of PIP_{SIMV} being set above or below PIP_{HFJV} are unknown. The former will cause the interruption of HFJV breaths for the duration of the SIMV breath and the latter is argued to promote the phenomenon of ‘HFJV-stacking’ such that the peak pressure in the central airways may be higher than either the preset PIP_{SIMV} or PIP_{HFJV}. Nonetheless, our prior experience is that HFJV stacking is clinically insignificant as peak pressures only 1-2 cmH₂O higher than the PIP_{SIMV} are observed when pressure is monitored at the airway opening. Further, we sought to avoid sustained peak inspiratory pressures > 40 cmH₂O as these are frequently associated with development of air-leak. Both the SIMV and the HFJV ventilation protocols aimed to minimise cyclic stretch within the lung using a permissive hypercapnia approach.

The comparison of ventilation strategies is a challenge as ventilator settings and displayed measurements vary between modalities. During SIMV and HFJV, *Paw* is determined by PIP, PEEP, respiratory frequency, and the *t_I:t_E* ratio [22]. During SIMV the fresh gas flow also impacts upon *Paw* and as PIP, ΔP and *Paw* are fully transmitted to the distal airways pressure measurements at the airway opening closely approximate alveolar

pressures [2]. During HFJV, however, the ΔP is attenuated in the distal airways and alveoli and the pressure monitored at the airway opening via the custom designed tracheal tube adaptor closely approximates the mean pressure at the distal tip of the tracheal tube [23].

One of the aims of this study was to compare the physiological responses to SIMV and HFJV in a standardised model of RDS. Oxygenation and ventilation variables were recorded to determine whether or not the different strategies achieved similar physiological outcomes. Oxygen requirements followed a similar trend between the groups with a gradual increase in FiO_2 and $AaDO_2$ over the 3 h study indicating progressive ventilation-perfusion mismatching, typical of naïve (non-steroid exposed) preterm lambs at 128 d gestation with moderately-severe hyaline membrane disease. Ventilation was also comparable between ventilated groups as the target $PaCO_2$ was achieved within 30 minutes.

There was a predictable initial increase in PBF in all groups with the transition from fetal to neonatal circulation as the pulmonary vasculature dilates. End systolic and diastolic pulmonary blood flow subsequently steadily became more negative over the remainder of the study in all groups. Given that the fall in PBF was mirrored by a steady increase in pulsatility index, particularly in the first 90 min after birth, these findings are most likely explained by an progressive increase in pulmonary vascular resistance resulting in the return of right to left shunting of blood through the ductus arteriosus [24].

The fall in end systolic and end diastolic pulmonary blood flow in the HFJV animals over the last 30 min of the study compared to the SIMV group was unexpected and is difficult to explain. We had expected the magnitude of change in PBF to mirror changes in Paw as it has been reported that increasing Paw decreases PBF and increases pulmonary vascular resistance during SIMV [25] and HFJV [9]. Despite higher Paw during HFJV, end systolic and diastolic PBF was not different between the 2 groups. Although the pulsatility index increased in the HFJV group over the last 30 min of the study, it was not significantly higher than the pulsatility index in the SIMV group and hence does not explain the late fall in PBF in the HFJV animals.

Given that we followed an algorithm for optimal ventilation with each strategy, and there were not marked differences in ventilator parameters it is not surprising that we did not find a difference in lung injury markers. Many different studies assess lung injury in response to mechanical ventilation in neonates and animals [26-29]. Comparisons of lung injury following HFOV and CV vary and demonstrate either little difference in the alveolar leakage and systemic inflammation in neonates [30], probable attenuation of early activation of

inflammation and clotting in preterm lambs during HFOV when compared to CV [31] and reduced pro-inflammatory cytokines in HFOV treated neonates compared to CV [32]. There are fewer studies comparing lung injury during HFJV but a comparison of HFJV and HFOV in rabbits showed a clear reduction in lung injury following HFJV [33]. The lack of difference in the markers of lung injury we chose to study suggests that the strategies were equivalent in their ability to produce inflammation in the lung.

Early recruitment of the functional residual capacity immediately after birth may facilitate early achievement of ventilation on the deflation limb of the pressure-volume curve. The delivery of a sustained inflation before commencing a particular ventilation strategy has consistently decreased the requirement for subsequent aggressive alveolar recruitment manoeuvres in both animal and human studies [34-36].

There are a number of limitations to this study. Although we aimed to compare two different ventilation strategies based on an open lung approach, the ventilation period was short which may have prevented a difference in lung injury markers becoming apparent. The changes in end systolic and end diastolic blood flow are also difficult to interpret in light of the short duration of the study. It is also important to acknowledge that surfactant was administered to the lambs immediately after delivery, which may not always be achieved in clinical practice. The lambs in our study were anaesthetised and underwent an invasive surgical procedure. The hemodynamic effects of anaesthesia combined with the physical impact of instrumentation on lung inflation may have had an impact on physiological outcomes. Nevertheless, these limitations were for the most part standard across each group and this model provides the first direct comparison of these two lung protective ventilation strategies in an animal model. Finally our assessment of lung injury was limited to examination of BAL fluid and two RNA markers. More comprehensive evaluation of lung injury was not undertaken given the lack of difference in these major markers of inflammation.

In conclusion, the open lung approach to SIMV and HFJV were suitable for respiratory management in the context of our model of RDS in preterm lambs. The lack of significant differences in end systolic and end diastolic PBF for the majority of the study, lung injury data and static lung compliance demonstrate that in the absence of airleaks, both SIMV and HFJV strategies can be employed in the clinical setting with a comparable pressure cost of ventilation.

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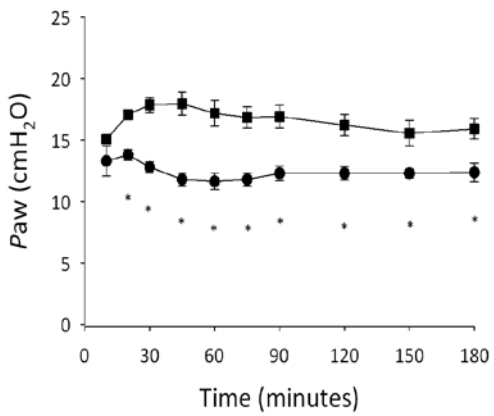
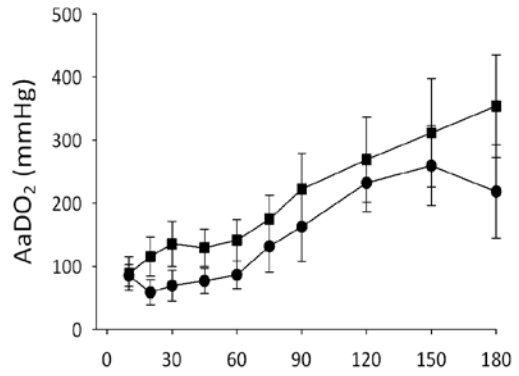
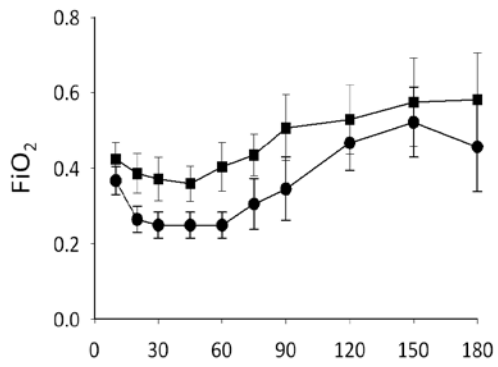
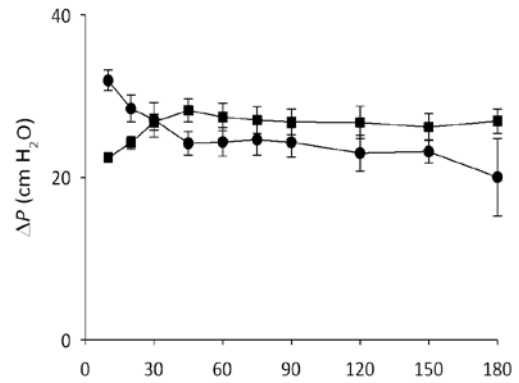
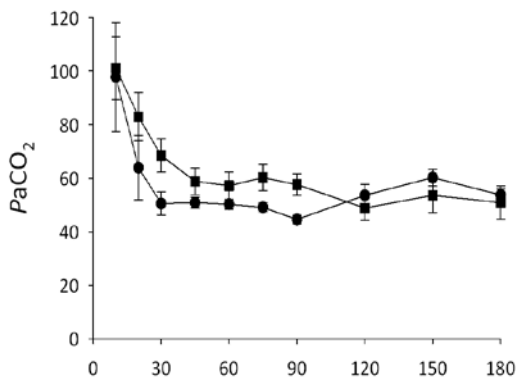
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Figure Legends

Figure 1 Ventilation and Oxygenation: **A:** Partial pressure of carbon dioxide in arterial blood (P_{aCO_2}), **B:** Airway pressure amplitude (ΔP) (cmH₂O), **C:** Fractional inspired oxygen concentration (FiO_2), **D:** Alveolar - arterial difference in the partial pressure of oxygen ($AaDO_2$) (mmHg), **E:** Mean airway pressure (P_{aw}). * $p < 0.05$ HFJV compared to SIMV. Closed circle = SIMV, closed square = HFJV.



Time (minutes)