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Limiting ventilator-associated lung injury in a preterm porcine neonatal model☆

Michaela Kollisch-Singule [a,*], Sumeet V. Jain [a], Joshua Satalin [a], Penny Andrews [b], Quinn Searles [a], Zhiyong Liu [a], Yan Zhou [a], Guirong Wang [a], Andreas H. Meier [a], Louis A. Gatto [a,c], Gary F. Nieman [a], Nader M. Habashi [b]

[a] Department of Surgery, SUNY Upstate Medical University, 750 E. Adams St., Syracuse, NY, 13210, USA
[b] Department of Trauma Critical Care Medicine, R Adams Cowley Shock Trauma Center, University of Maryland School of Medicine, 22 S. Greene St., Baltimore, MD, 21201, USA
[c] Department of Biological Sciences, SUNY Cortland, 22 Graham Ave, Cortland, NY, 13045, USA

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ABSTRACT

Purpose: Preterm infants are prone to respiratory distress syndrome (RDS), with severe cases requiring mechanical ventilation for support. However, there are no clear guidelines regarding the optimal ventilation strategy. We hypothesized that airway pressure release ventilation (APRV) would mitigate lung injury in a preterm porcine neonatal model.

Methods: Preterm piglets were delivered on gestational day 98 (85% of 115 day term), instrumented, and randomized to volume guarantee (VG; n = 10) with low tidal volumes (5.5 $cm^3\ kg^{-1}$) and PEEP 4 cmH_2O or APRV (n = 10) with initial ventilator settings: P_{High} 18 cmH_2O, P_{Low} 0 cmH_2O, T_{High} 1.30 s, T_{Low} 0.15 s. Ventilator setting changes were made in response to clinical parameters in both groups. Animals were monitored continuously for 24 hours.

Results: The mortality rates between the two groups were not significantly different ($p > 0.05$). The VG group had relatively increased oxygen requirements (F_iO_2 50% ± 9%) compared with the APRV group (F_iO_2 28% ± 5%; $p > 0.05$) and a decrease in PaO_2/FiO_2 ratio (VG 162 ± 33 mmHg; APRV 251 ± 45 mmHg; $p < 0.05$). The compliance of the VG group (0.51 ± 0.07 $L \cdot cmH_2O^{-1}$) was significantly less than the APRV group (0.90 ± 0.06 $L \cdot cmH_2O^{-1}$; $p < 0.05$).

Conclusion: This study demonstrates that APRV improves oxygenation and compliance as compared with VG. This preliminary work suggests further study into the clinical uses of APRV in the neonate is warranted.

Level of Evidence: Not Applicable (Basic Science Animal Study)

With research and improvements in clinical care, survival of preterm infants has increased over the last two decades, as have the diseases associated with prematurity [1]. In particular, pulmonary disorders are the leading cause of morbidity in newborn infants [2] and responsible for more than 50% of deaths in very preterm infants [3]. Preterm infants are particularly prone to respiratory distress syndrome (RDS) because of surfactant deficiency [4]. The absence of surfactant predisposes the infant to ventilator-induced lung injury (VILI) secondary to repetitive alveolar collapse and expansion. The combination of RDS and VILI results in the more severe respiratory disease bronchopulmonary dysplasia (BPD) [5]. With an increase in survival of preterm neonates, the incidence of BPD has been increasing over the last two decades with the incidence of BPD varying inversely with the age and weight of the neonate [1]. The long-term consequences of BPD include chronic lung disease, pulmonary hypertension, increased susceptibility to respiratory infections and higher mortality [5].

Treatment of RDS includes prenatal steroids, exogenous surfactant replacement, mechanical ventilation and lung transplant [4]. Despite the use of exogenous surfactant administration [6], BPD remains the most common chronic respiratory disease in infants [1,7]. Incomplete knowledge of mechanical ventilation and lung interactions lead to VILI and is a key mechanism of BPD since surfactant alone is not sufficient to maintain alveolar stability. In order to prevent BPD and the associated complications, it is important to prevent VILI by optimizing mechanical ventilation strategies to improve and sustain alveolar recruitment and prevent derecruitment. Our group has shown that the preemptive application of airway pressure release ventilation (APRV) minimizes VILI and protects the lung from developing acute respiratory distress syndrome (ARDS) in mechanically ventilated adults at risk of developing

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* Corresponding author at: SUNY Upstate Medical University, 750 E. Adams Street, Syracuse, NY, 13210. Tel.: +1 315 464 6311; fax: +1 315 464 6237.
E-mail addresses: KolliscM@upstate.edu (M. Kollisch-Singule), JainSu@upstate.edu (S.V. Jain), SatalinJ@upstate.edu (J. Satalin), plandrews@intensivecareonline.com (P. Andrews), SearlesQ@upstate.edu (Q. Searles), LiuZh@upstate.edu (Z. Liu), ZhouYa@upstate.edu (Y. Zhou), WangG@upstate.edu (G. Wang), MeierAn@upstate.edu (A.H. Meier), Louis.Gatto@cortland.edu (L.A. Gatto), NiemanG@upstate.edu (G.F. Nieman), nmh@xmxmail.com (N.M. Habashi).

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lung injury [8]. APRV sustains the plateau pressure over a prolonged time allowing maximal alveolar recruitment with a brief expiratory phase to minimize alveolar derecruitment [9]. However, because of limited evidence supporting its use in infants, APRV is currently used primarily as a rescue ventilation mode, after the lung has been severely damaged (i.e. already developed BPD) [10]. Since a primary component of ARDS in the adult is surfactant deficiency, similar to RDS, we hypothesize that preemptive application of APRV to the preterm piglet with RDS should also prevent VILI. The results of this study might then be translated to human infants to hopefully reduce the incidence of VILI and thereby, the incidence and severity of BPD.

1. Materials and methods

All experiments were performed in accordance with National Institute of Health guidelines in the use of laboratory animals and approved by the SUNY Upstate Medical University Institutional Animal Care and Use Committee.

1.1. Cesarean section and preterm piglets

Cesarean section was planned on two pregnant Yorkshire sows on gestation day 98 (85% of 115 day term, comparable to a human fetus delivered at 25 weeks) [11]. Prior to cesarean section, the sow was premedicated with a ketamine/xylazine mixture (90 mg/mL/10 mg/mL) at a dose of 0.1 mg/kg of ketamine. Under sterile conditions, a tracheostomy was performed, following which a surgical plane of anesthesia was maintained with 2% isoflurane. Inhalational anesthetic was used to facilitate rapid recovery of the piglets from the effects of maternal anesthesia. The sow hemodynamics and respiratory status were monitored continuously and were provided intravenous hydration in addition to respiratory support. Piglets were removed individually and instrumented immediately after delivery since they do not spontaneously breathe at this age. Any additional piglets in the litter after the $n = 10$ per group was achieved served as a Control group ($n = 6$), had a baseline ABG drawn and were euthanized with intravenous sodium pentobarbital (150 mg/kg) injected through the umbilical vein and necropsy performed. After all the piglets were delivered, maternal blood was obtained and the sow euthanized with intravenous sodium pentobarbital (150 mg/kg).

1.2. Piglet instrumentation

Upon the delivery of a piglet, the airway was suctioned out and the piglet was weighed and placed on a heating mat under a heating lamp. 1% lidocaine was injected subcutaneously into the neck and a tracheostomy performed with a 2.5 Fr endotracheal tube. Piglets were immediately connected to a ventilator (Dräger Infinity C500 ventilator, Lübeck, Germany) with volume guarantee settings (as described under *Ventilation Settings*). An umbilical artery catheter (3.5F Argyle™, Covidien, MA, USA) was placed to be used for blood pressure monitoring and arterial blood gases, and an umbilical vein catheter (3.5F Argyle™, Covidien, MA, USA) for fluid administration. An esophageal catheter was passed and secured to decompress the stomach. Following instrumentation, the piglets were placed in a neonatal isolette (Dräger Babytherm 8010, Lübeck, Germany) with temperatures adjusted to maintain piglet temperature at 38.5 ± 0.5 °C.

1.3. Piglet resuscitation and intensive care

Each piglet received a single prophylactic dose of antibiotic, cefazolin (50 mg/kg/dose), administered via the UVC. Maternal plasma was administered (5 mL/kg, IV) after placement of the UVC to provide passive immunity and compensate for the absence of colostrum. Each piglet was provided hourly fentanyl (2 μg/kg/h) and midazolam (6 μg/kg/h) titrated to maintain a continuous plane of anesthesia. Parenteral nutrition (Baxter Clinimix E2.75/10) was provided continuously at a rate of 4 mL/kg/h, beginning immediately after placement of the UVC. Boluses with Lactated Ringer's (10 mL/kg) or albumin (10 mL/kg) were provided as necessary to maintain a goal MAP of 30-35 mmHg. Vasopressors (norepinephrine, vasopressin, epinephrine, dobutamine) were available if any piglets became unresponsive to fluid resuscitation. Piglets at the chosen gestational age rarely spontaneously breathe [12], however any piglet demonstrating evidence of spontaneous breathing received rocuronium (10 μg/kg/min) in order to standardize the piglets.

Blood pressure, pulse and oxygen saturation were monitored continuously (Dräger Infinity Delta XL, Lübeck, Germany) with hourly recordings. Compliance was calculated as $\Delta V/\Delta P = V_t/(\text{Pplat-PEEP})$. At baseline and every 4 hours, arterial blood gases were measured (Cobas 221 blood gas analyzer, Roche Diagnostics, Indianapolis, IN). The bladder was decompressed manually every 12 hours. The piglets were repositioned every 4 hours from one side to the other to avoid dependent edema.

1.4. Ventilation settings

All piglets were randomized a priori and labeled according to the order of delivery. The veterinarian delivering the piglets was blinded to treatment strategy during delivery and did not participate in the ventilation protocol. Upon receiving a tracheostomy and being connected to the ventilator, all animals were started on VG with V_t of 5.5 $cm^3 \cdot kg^{-1}$, inspiratory time of 0.3 s, respiratory rate of 40 bpm, PEEP 4 cmH_2O and F_iO_2 50%.

Piglets in the VG group were maintained on the same settings. Respiratory rate was titrated according to P_aCO_2 (goal of 45–55 mmHg) and PEEP and F_iO_2 was titrated according to downward trends in P_aO_2, SpO2 (goal SpO_2 88%–94%), and respiratory system compliance. If F_iO_2 requirements were increasing in response to decreasing P_aO_2 or SpO_2, PEEP was also incrementally increased (to a maximum of 7 cmH_2O).

Piglets in the APRV group were transitioned from VG to the following initial settings: P_{High} set to the plateau pressure established in VG for a time (T_{High}) of 1.3 s, set to occupy approximately 90% of the ventilator cycle [13]. The expiratory time (T_{Low}) was initially set at 0.15 s with a release pressure (P_{Low}) of 0 cmH_2O [14]. The peak expiratory flow (PEF) is defined as the greatest absolute flow rate during the release from P_{High}. The T_{Low} was adjusted so that the ratio between the end of the expiratory flow (EEF) and PEF (EEF/PEF) was 75% [13]. F_iO_2 was set at 50% and ventilator settings titrated according to decrements in P_aO_2,SpO_2 or respiratory system compliance. Changes to T_{High} and P_{High} were also made accordingly to maintain P_aCO_2 at a goal of 45–55 mmHg.

1.5. Necropsy

After 24 hours, the experimental protocol was terminated, animals euthanized with an overdose of sodium pentobarbital (150 mg/kg) and necropsy performed. Lungs were inflated with air to 20 cmH_2O using stepwise increases in PEEP to standardize lung volume and grossly photographed. The right lower lobe was tied off and sectioned for histological assessment. The mass of the right middle lobe was recorded at necropsy and again after 48 hours of desiccation to establish a wet–dry weight. Any animals with an early mortality (<24 hours) had an early necropsy performed and remained a part of the study to establish mortality. Only the animals that survived the duration of the study were compared in the final assessment for all other data outside of mortality.

1.6. Bronchoalveolar lavage fluid (BALF) and lung tissue

The left lung was lavaged to obtain 3 mL of BALF using three aliquots of 2 mL normal saline, and the BALF spun at 3500 × rpm at 4 °C for 10 min, and then the pellets were mounted on a slide by cytospin centrifuge at 1000 rpm for 3 min. Analysis of cell population in the BALF was performed as described previously [15]. The supernatant was

Table 1
Hemodynamics and respiratory parameters at 0, 12, and 24 hours after birth in volume guarantee (VG) and airway pressure release ventilation (APRV). Reported *p*-values are after RM ANOVA. * = $p < 0.05$ VG vs APRV after post hoc Tukey's test for differences between groups at individual time points.

	Group	0 h	12 h	24 h	*P*-value
Heart Rate (Beats · Minute^{-1})	VG	107.1 ± 6.6	113.2 ± 12.2	120.3 ± 10.2	$p = 0.4470$
	APRV	119.0 ± 10.3	153.8 ± 19.6	170.8 ± 22.7	
Mean arterial pressure (mmHg)	VG	39.0 ± 3.1	34.8 ± 0.9	31.9 ± 1.7	$p = 0.0395$
	APRV	36.3 ± 1.8	41.8 ± 3.3*	38.8 ± 2.4*	
SpO_2 (%)	VG	98.0 ± 1.2	98.9 ± 0.7	94.3 ± 2.9	$p = 0.3267$
	APRV	99.8 ± 0.3	99.3 ± 0.3	99.5 ± 0.5	
F_iO_2 (%)	VG	0.5 ± 0.0	0.4 ± 0.0	0.5 ± 0.1	$p = 0.0609$
	APRV	0.5 ± 0.0	0.3 ± 0.1	0.3 ± 0.0	
Plateau pressure (cmH_2O)	VG	18.1 ± 1.5	17.6 ± 1.5	17.9 ± 2.3	$p = 0.5620$
	APRV	17.8 ± 1.2	17.3 ± 0.9	15.5 ± 0.3	
Driving pressure (cmH_2O)	VG	15.3 ± 1.2	12.8 ± 1.6	12.7 ± 2.2	$p = 0.8789$
	APRV	15.2 ± 2.2	13.8 ± 0.7	12.2 ± 0.2	
Tidal Volume (cc · kg^{-1})	VG	5.6 ± 0.2	5.8 ± 0.1	5.7 ± 0.1	$p = 0.0002$
	APRV	5.8 ± 0.0	11.4 ± 0.5*	11.0 ± 0.8*	
Compliance (L · cmH_2O^{-1})	VG	0.38 ± 0.03	0.51 ± 0.08	0.51 ± 0.07	$p = 0.0051$
	APRV	0.34 ± 0.07	0.84 ± 0.08*	0.90 ± 0.06*	
pH	VG	7.41 ± 0.05	7.39 ± 0.05	7.36 ± 0.04	$p = 0.3599$
	APRV	7.46 ± 0.04	7.45 ± 0.04	7.41 ± 0.03	
P_aO_2/FiO_2 (mmHg)	VG	228 ± 40	203 ± 15	162 ± 33	$p = 0.0149$
	APRV	284 ± 70*	281 ± 19*	251 ± 45	
Cumulative volume infused (mL · kg^{-1})	VG	18.1 ± 2.0	90.0 ± 4.8	146.9 ± 4.3	$p = 0.9432$
	APRV	19.9 ± 5.7	90.3 ± 11.8	146.0 ± 9.2	

used for total protein and other molecular analysis. Total protein concentration was determined by microBCA method and phospholipid concentrations were assessed using an in vitro phospholipids C assay kit (Wako Diagnostics, Richmond, VA) as described previously [16]. The data from the above analyses were compared to determine the degree of alveolar edema and quantitative microscopic analysis of BALF cellularity was also performed.

1.7. Statistical analysis

Data are reported as mean ± SEM. Repeated measures ANOVA was used to compare differences within and between treatment groups for continuous parameters and post hoc Tukey's tests if significance was found in the group effect. Kaplan–Meier curve was performed to assess for differences in mortality with a log-rank test. For BALF cellularity, total protein, phospholipid and wet–dry weights involving comparisons among Control, APRV and VG, univariate ANOVA was used. *P*-values <0.05 were considered significant. Analyses were performed using JMP (version 5.1.1, Cary, NC).

2. Results

The two litters consisted of 14 and 13 piglets, respectively. From the first litter, four each were randomly assigned to VG or APRV. From the second litter, six each were randomly assigned to VG or APRV, to reach a total of 10 piglets each. The average piglet mass was similar between groups (VG 771 ± 49 g; APRV 762 ± 78 g; $p > 0.05$) with a range of 484–1140 g. The APRV group had six early mortalities (as defined by mortality earlier than the 24 hour study period) as compared with VG with three early mortalities ($p > 0.05$). The average time to mortality was similar between groups (7.7 ± 1.5 hours in VG; 7.5 ± 1.4 hours in APRV; $p > 0.05$). Every piglet that survived past the first 11 hours survived the duration of the study and none of these piglets required vasopressor support. The VG piglets (n = 7) and the APRV piglets (n = 4) that survived the duration of the study were compared for the remainder of the results.

2.1. Pulmonary data

The P_aO_2/F_iO_2 ratio immediately at birth, as obtained from the Control animals, was 60.0 ± 11.2. The P_aO_2/F_iO_2 ratio demonstrated an immediate rise after tracheostomy was performed and all animals connected to their respective ventilator settings at an F_iO_2 of 50%, with a P_aO_2/F_iO_2 ratio of 228 ± 40 mmHg in the VG group and 284 ± 70 mmHg in the APRV group (Table 1). Over time, the F_iO_2 was weaned down from 50% to 28% ± 5% at 24 hours in the APRV group. Weaning of the F_iO_2 was attempted in the VG group, but by the end of the study, the F_iO_2 in the VG group was greater than the APRV group at 50% ± 9% ($p > 0.05$; Fig. 1A). Consistent with the increased oxygen requirements in the VG group, there was a significant decline in the P_aO_2/F_iO_2 ratio to 162 ± 33 by the end of the study, whereas the P_aO_2/F_iO_2 ratio remained constant in the APRV group (final P_aO_2/F_iO_2 ratio 251 ± 45 mmHg; $p < 0.05$; 1B). The lung compliance in the APRV group increased over time to be significantly greater than that of the VG group by the end of the study ($p < 0.05$; 1C). The tidal volumes were significantly lower in the VG group (5.7 ± 0.1 mL·kg^{-1}) when compared to the APRV group (11.0 ± 0.8 mL·kg^{-1}; $p < 0.05$), consistent with the findings of previous studies [17,18]. Despite the greater tidal volumes in the APRV group, the plateau pressure between the two groups was similar ($p > 0.05$; Fig. 1D) as well as the driving pressure ($p > 0.05$; Table 1).

2.2. Hemodynamics

Piglets were provided maintenance hydration with Clinimix parenteral nutrition and additional hydration was provided as needed to maintain a goal MAP of 35 mmHg and in response to tachycardia and lactic acidosis. The heart rate was therefore similar between groups ($p > 0.05$; Table 1), as was the cumulative volume of fluids administered over the 24-hour period between VG (146.9 ± 4.3 mL·kg^{-1}) and APRV (146.0 ± 9.2 mL·kg^{-1}; $p > 0.05$; Table 1), however the MAP was significantly greater in the APRV group as compared with VG ($p < 0.05$; Table 1).

2.3. Gross pathology

The lung wet–dry weight was not significantly different between the VG group (8.1 ± 0.6) and APRV group (6.0 ± 1.1; $p > 0.05$), although there was a trend toward less edema with APRV. Chest X-rays were performed at 2, 12 and 24 hours after baseline measurements in the piglets. An inspiratory hold was performed for the VG group. The VG group generally demonstrated reduced lung volume with a greater incidence of basilar collapse as compared with the APRV group (Fig. 2).

On gross examination, the APRV group tended to demonstrate fully inflated lungs, but two had concomitant evidence of pleural effusion and atelectasis. The VG group demonstrated heterogeneous lung injury.

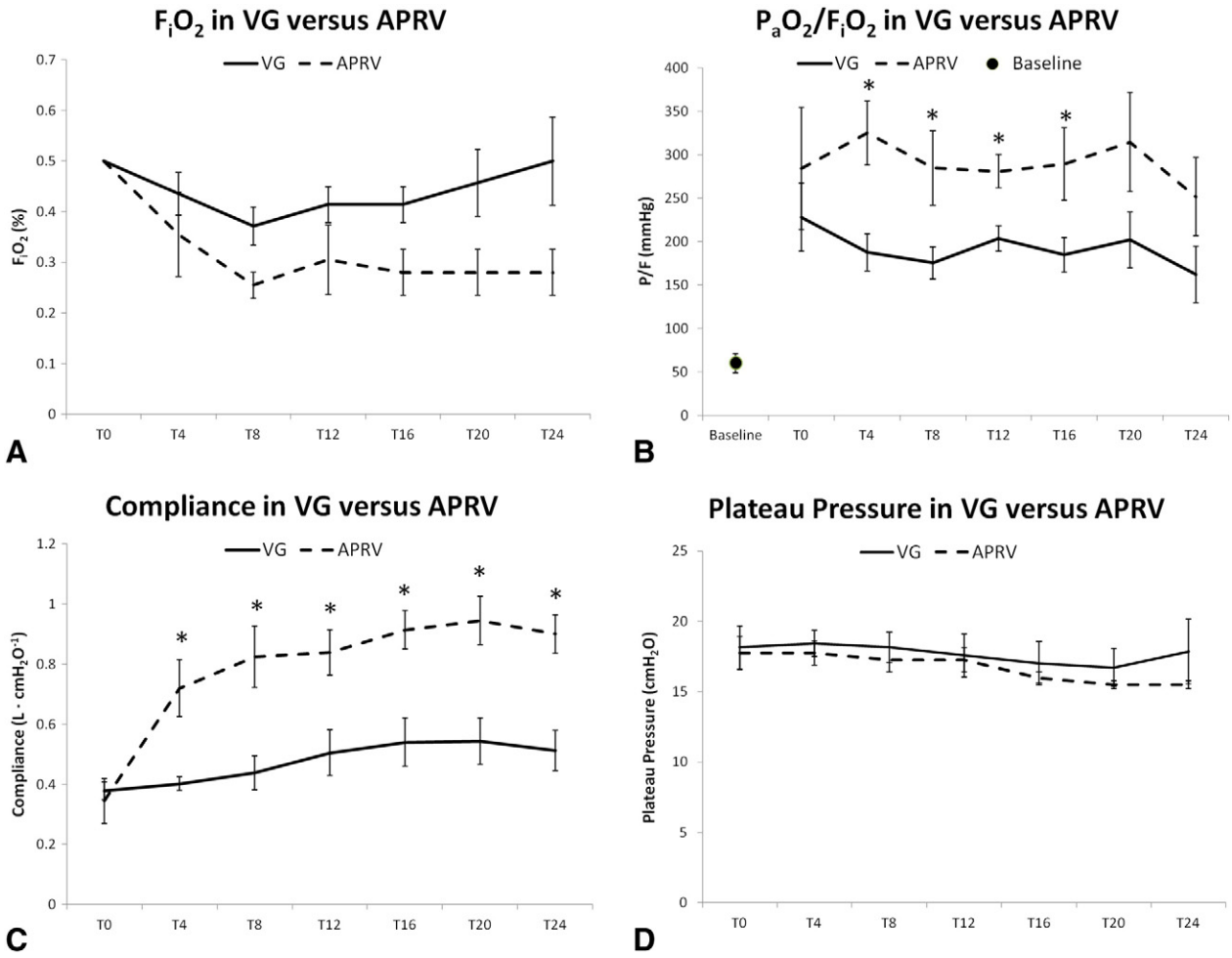

Fig. 1. Comparison of volume guarantee (VG – black solid line) and airway pressure release ventilation (APRV – black dashed line) over the course of the 24-hour study with regard to (A) F_iO_2, (B) P_aO_2/F_iO_2, (C) Compliance and (D) Plateau Pressure. * = $p < 0.05$ between groups.

One animal had pink, healthy, well-inflated lungs whereas the remainder had varying degrees of atelectasis. Three animals demonstrated a combination of pleural effusion and foamy airway edema.

2.4. Bronchoalveolar lavage fluid protein & quantitative histology

The cellularity of the BALF was significantly decreased in the control animals (52 ± 2 cells/hpf) as compared with VG (102 ± 9 cells/hpf) and APRV (87 ± 8 cells/hpf) (Fig. 3; $p < 0.05$) with a significant difference between the cellularity between the two experimental groups. Consistent with the increase in cellularity, there was a significant difference in the total protein concentration in the BALF among the three groups (Control 275 ± 87 μg/mL; VG 1054 ± 249 μg/mL; APRV 708 ± 84 μg/mL; $p < 0.05$). The phospholipid concentration in the Control BALF and APRV BALF were similar (Control 48.5 ± 7 μg/mL; APRV 48.5 ± 6 μg/mL; $p > 0.05$) but significantly less than VG (82 ± 9 μg/mL; $p < 0.05$).

3. Discussion

With the use of antenatal steroids and exogenous surfactant administration, there have been significant improvements in the outcomes associated with RDS, so that many infants no longer require endotracheal intubation, instead receiving continuous positive airway pressure CPAP for respiratory support [2,3]. Still, despite these lung protective strategies, the morbidity and mortality associated with RDS remain unacceptably high [2]. For those infants that do require endotracheal intubation and mechanical ventilation, there have been few studies investigating ventilation modes. This is partially because of the difficulty in studying a fairly low incidence disease, but also because of the concern for potentially injuring the lungs without additional study. APRV, for instance, is not used routinely in the NICU because of a lack of research demonstrating efficacy, but is instead viewed as a rescue strategy. Given the reluctance to test ventilator strategies on very low birth weight infants, a reliable preterm animal model is necessary.

Previous preterm piglet studies involving mechanical ventilation born at a similar gestational age as in this study (approximately 98 days), used study endpoints of 6 hours [19] and 8 hours after delivery [12]. These studies demonstrate the feasibility of a porcine model in testing ventilation treatment strategies for preterm neonates, but lack the longevity to have clinical relevance. Thus, in our experiment we extended the study duration to 24 hours and provided continuous hemodynamic monitoring and resuscitation, in accordance with standard NICU care.

In a similar preterm porcine model by Arrindell et al. [20], piglets were ventilated with APRV or VG for 24 hours, however at a later gestational age of 102 days (equivalent to a 28-week human infant). Our findings of improved aeration on chest radiographs and reduction in gross lung atelectasis in the APRV group are similar to the findings of Arrindell et al [20]. Piglets in that study [20] also required a lower F_iO_2 and had a significant improvement in oxygenation (measured by oxygenation index), also similar to the findings in the current study. Thus, Arrindell et al. [20] conclude that APRV may be considered a safe mode in the neonate, while recognizing that this age group tends to

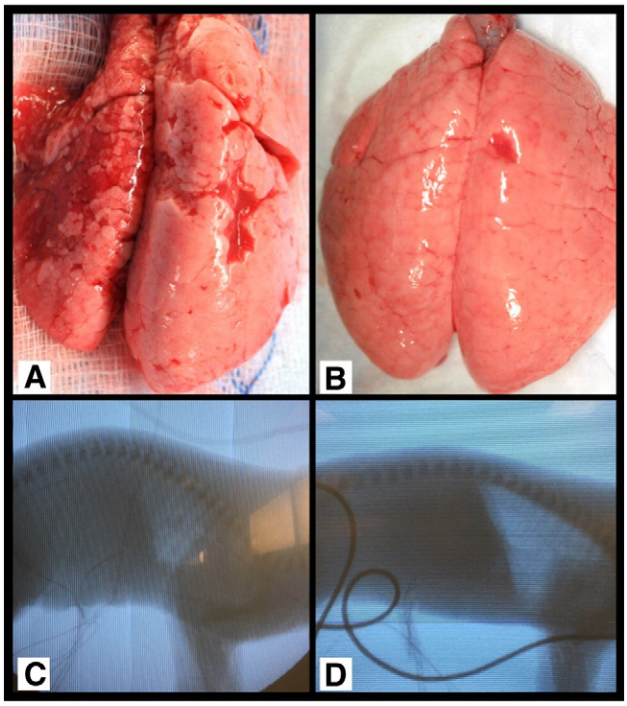

Fig. 2. Gross lung pictures comparing (A) volume guarantee with (B) airway pressure release ventilation demonstrating increased heterogeneity and atelectasis in the VG group. Lungs were inflated with air to the same airway pressure (20 cmH_2O) to standardize lung volume in these photos. Corresponding chest radiographs similarly demonstrate (C) atelectasis in volume guarantee and (D) recruitment in airway pressure release ventilation.

have functional surfactant and may not require invasive positive pressure ventilation. This study, therefore, serves as an extension of the Arrindell et al. [20] work demonstrating similar results when comparing APRV to VG in a preterm piglet model birthed at gestation day 98 (functionally equivalent to a human infant born three weeks earlier).

The pathophysiology of BPD includes a combination of overinflation and atelectasis [21]. This regional inhomogeneity is also well described in ARDS [22,23] with a delivered tidal volume or pressure preferentially distributing to the most compliant inflated regions while leaving the remaining atelectatic regions collapsed [24]. The premise behind a low tidal volume guarantee strategy (VG) is to minimize the volume that the healthy area of the lung needs to accommodate to prevent overdistension. However, if the available lung surface area is too small to support even a lower tidal volume, then undue tissue strain and VILI may still occur [24–27]. Consistent with previous work, the APRV group in this study resulted in significantly larger tidal volumes than the VG group [17,18]. Previous adult animal models of ARDS have demonstrated that APRV reduces alveolar heterogeneity [28], and improves alveolar recruitment [14], thus allowing these larger tidal volumes to be distributed across a larger set of open, homogenous alveoli, thereby reducing alveolar microstrain [14]. This is corroborated by the similar driving pressures between the APRV and VG groups despite the differing tidal volumes, leading to the demonstrably increased compliance in the APRV group. These data served as the premise behind our hypothesis that APRV could be a useful ventilation strategy in RDS, since both RDS and ARDS have similar pathogenic mechanisms involving surfactant deficiency [18,29] and regional inhomogeneity [1,22] combined with ventilator-induced lung injury [5,30].

Several previous animal models, including lamb, [31,32] baboon [33,34] and pig, [19,20] have also demonstrated the impact of mechanical ventilation strategy on the clinical trajectory of preterm infants born with respiratory distress syndrome. In studies of preterm baboons, low tidal volumes led to increased lung injury when combined with low PEEP, whereas high frequency ventilation, also with small tidal volumes, but maintaining higher mean airway pressures reduced lung injury [33,34]. Thus, this study supports the notion that low tidal volumes do not necessarily provide a benefit if lung recruitment is sacrificed [30]. Although the importance of PEEP has been advocated in clinical use [29] in order to maintain lung recruitment and stability [35], this recommendation is theoretical in that there is little direct evidence given the difficulty in studying this patient population with a low prevalence and multiple comorbidities [36]. Despite the perceived importance of maintaining adequate mean airway pressures, the nonconventional ventilation modes that target higher mean airway pressures, such as high frequency ventilation and APRV, tend to be considered rescue ventilation modes, rather than effective primary modes of ventilation [10,29,37]. In this current study, we demonstrate that APRV can be used as a primary mode of ventilation in neonatal piglets at risk of respiratory distress syndrome. In conclusion, the APRV group in this study had a significant improvement in compliance and improvement in

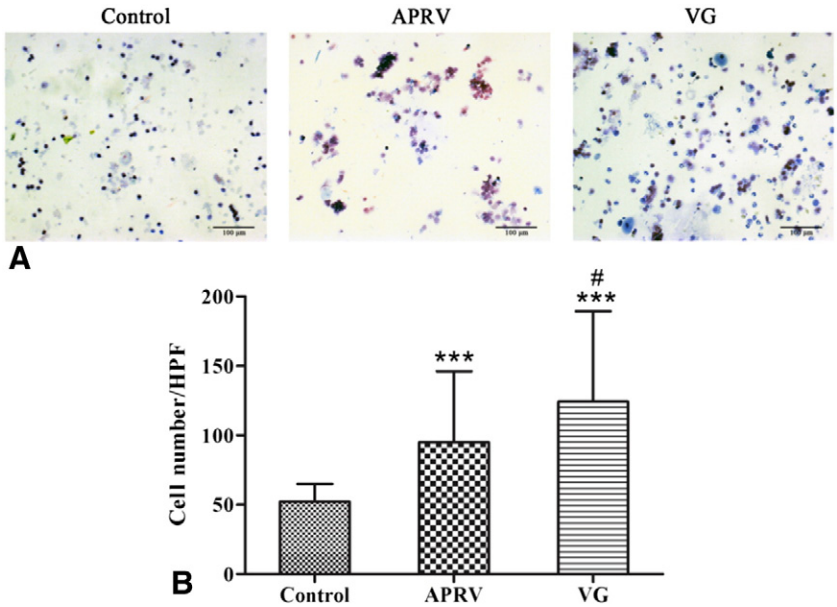

Fig. 3. Photomicrographs of BALF cellularity in the Control, airway pressure release ventilation (APRV) and volume guarantee (VG) groups (A) and quantitative assessment of cellularity (B). *** = $p < 0.05$ vs Control. # = $p < 0.05$ VG vs APRV.

oxygenation (based on P_aO_2/F_iO_2), with a relative reduction in oxygen requirements. This suggests that APRV mitigated the degree of lung injury and may reduce the incidence of BPD, the late morbidity of RDS. Furthermore, the APRV group may have reduced VILI, as indicated by protein and phospholipid concentrations in the BALF [38]. This was demonstrated in a robust, high-fidelity model of preterm infant RDS. Combined, these data suggest that APRV may be a useful modality in the treatment of preterm neonates with RDS in need of mechanical ventilation.

3.1. Study limitations

The greatest limitation of this study was the 24-hour mortality rate of 55%. In the previously mentioned study of preterm piglets birthed at a gestational age of 102 days [20], all the experimental animals survived the 24 hour duration of the study, however piglets with a mass <600 g were excluded and animals at this age have increased hemodynamic stability with spontaneous breathing [12]. In a study of preterm piglets born at 97 days [12], the survival by the 8 hour endpoint reached 83% as compared with 75% at 8 hours in the current study. By 11 hours in the current study, the survival dropped to 45%, however all animals that survived to 11 hours survived the duration of the 24 hour study suggesting that the first 12 hours are the most tenuous. Thus the early mortality rates in this study, although unfortunate from a scientific perspective, is the clinical reality in animals delivered at gestation day 98. A compounded limitation of this study is the low power, as a result of the mortality rate, which may have contributed to the lack of statistical significance at individual time points and in certain parameters, such as F_iO_2.

Disclosures

Dräger Medical provided the ventilators, monitors and neonatal beds used in this study but had no involvement in the conceptualization, design, funding or implementation of the study. The manuscript was prepared and revised without any input from Dräger Medical. GFN, NMH and PLA have presented and received honoraria and travel reimbursement at events sponsored by Dräger Medical outside of the submitted work. MKS has received travel reimbursement at events sponsored by Dräger Medical. MKS, GFN, NMH, PLA and SVJ have lectured for Intensive Care Online (ICON). NMH holds patents and is the founder of ICON, and PLA is employed by ICON.

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