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Lung Protective Ventilation (ARDSNet) versus APRV: Ventilatory Management in a Combined Model of Acute Lung and Brain Injury

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No conflicts of interest are declared.

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Abstract

Background—Concomitant lung/brain traumatic injury, results in significant morbidity and mortality. Lung protective ventilation (ARDSNet) has become the standard for managing acute respiratory distress syndrome (ARDS); however, the resulting permissive hypercapnea may compound traumatic brain injury (TBI). Airway pressure release ventilation (APRV) offers an alternative strategy for management of this patient population. APRV was hypothesized to retard the progression of acute lung/brain injury to a greater degree than ARDSNet in a swine model.

Methods—Yorkshire swine were randomized to ARDSNet, APRV, or sham. Ventilatory settings and pulmonary parameters, vitals, blood gases, quantitative histopathology, and cerebral microdialysis were compared between groups using chi-square, Fisher's exact, Student's t-test, Wilcoxon rank-sum, and mixed effects repeated measures modeling.

Results—22 swine (17 male, 5 female), weighing 25±6.0kg, were randomized to APRV (n=9), ARDSNet (n=12), or sham (n=1). PaO_2/FiO_2 (P/F) ratio dropped significantly while intracranial pressure increased significantly for all three groups immediately following lung and brain injury. Over time, peak inspiratory pressure, mean airway pressure, and P/F ratio significantly increased, while total respiratory rate significantly decreased within the APRV group compared to the ARDSNet group. Histopathology did not show significant differences between groups in overall brain or lung tissue injury; however, cerebral microdialysis trends suggested increased ischemia within the APRV group compared to ARDSNet over time.

Conclusion—Previous studies have not evaluated the effects of APRV in this population. While our macroscopic parameters and histopathology did not observe a significant difference between groups, microdialysis data suggest a trend toward increased cerebral ischemia associated with APRV over time. Additional and future studies should focus on extending the time interval for observation to further delineate differences between groups.

Level of Evidence—II

Study Type—Therapeutic

Keywords

lung protective ventilation (ARDSNet); airway pressure release ventilation (APRV); combined lung and brain injury swine model; acute respiratory distress syndrome (ARDS); traumatic brain injury (TBI)

Background

The annual incidence and 60-day mortality of acute respiratory distress syndrome (ARDS) within the United States is 190,000 and 26%, respectively (1-3). Trauma is one of the most common causes of ARDS (1). Based upon the Acute Respiratory Distress Syndrome Network (ARDSNet) protocol, standard treatment for these patients involves invasive mechanical ventilation utilizing low tidal volume ventilation (6-8 mL/kg ideal body weight) (4).

Over one million Americans suffer traumatic brain injury (TBI) each year resulting in 80-90,000 permanently disabled individuals and 50,000 deaths (5, 6). The prevalence of ARDS among Americans with TBI is 21.2% (7). Additionally, 20-25% of patients with isolated TBI will go on to develop ARDS (8, 9). Invasive mechanical ventilatory management of these patients is complicated. Currently, the brain trauma foundation recommends achieving normal arterial partial pressure of O_2 and low normal arterial partial pressure of CO_2 to maintain intracranial pressure (ICP) below 20 mmHg and cerebral perfusion pressure (CPP) above 60 mmHg (10-13). While ARDSNet is ideal for managing ARDS, permissive hypercapnea results in increased cerebral perfusion leading to elevated ICP and cerebral ischemia, further compounding TBI (9, 14, 15).

Airway pressure release ventilation (APRV) was originally described in the late 1980's to address VILI associated with conventional, pressure-controlled ventilation (16, 17). The mechanics behind APRV simulate continuous positive airway pressure (Phigh) along with short, intermittent bursts of lower pressure (Plow). It accomplishes this by utilizing an inversed inspiration to expiration (I:E; Thigh:Tlow) ratio thus enhancing recruitment and oxygenation while reducing atelectrauma (17, 18). However, as a means to reduce patient:ventilator mismatch by allowing spontaneous breaths, it may cause large tidal volume shifts, thus potentially contributing to volutrauma (17). That said, spontaneous breathing and reduced Thigh periods may assist with hypercapnea. Presently, it is used mainly as a rescue therapy for patients with ARDS, but it has not been formerly evaluated in patients with concomitant lung and brain injury. Furthermore, a concomitant lung and brain injury swine model does not exist evaluating APRV. Thus, the purpose of this pilot study was to develop a simultaneous ARDS/TBI model in swine to evaluate the effects of APRV on injury progression compared with ARDSNet. We hypothesized that APRV would retard the progression of acute brain and lung injury to a greater degree than ARDSNet.

Methods

Animals

The Animal Care and Use Committee within our University's Department of Comparative Medicine approved this pilot study. Healthy, male and female, Yorkshire swine were used.

Anesthesia and Surgical Preparation

Animals were fasted preoperatively. Premedication consisted of intramuscular10-20mg/kg ketamine. Induction consisted of intravenous 1-4cc push of 5mg/kg ketamine and 0.2-1.0mg/kg midazolam. Animals were placed on a heating pad and intubated using a 5.5-6.5 endotracheal tube. Continuous anesthesia consisted of intravenous 5mg/kg/hr ketamine and 0.2-1.0mg/kg/hr midazolam. Intermittent intravenous pushes of 0.2-0.9mg/kg morphine were administered as needed for analgesia. Maintenance fluids consisted of Lactated ringer's solution, at 5cc/kg/hr.

Surgical Instrumentation

While prone, a midline, sagittal skin incision was performed along the dorsal surface of the head. Skin flaps were retracted to expose the underlying skull. Three burr holes were then

created. The first burr hole (6.3mm diameter) was placed approximately 10 mm right/lateral of midline and 10 mm posterior to the coronal suture overlying the right parietal lobe. A CMA 20 Elite (14mm shaft length, 10mm membrane length, 20,000 Dalton porosity) cerebral microdialysis probe (CMA, A Harvard Apparatus Company, Holliston, MA, USA) was placed through this opening and directly into cerebral tissue. A second burr hole (2.71mm diameter) was placed approximately 10 mm right/lateral of midline and 10 mm anterior to the coronal suture overlying the right frontal lobe. An Integra Neurosciences Camino intracranial pressure-temperature monitoring system (110-4BT catheter and camino advanced monitor; Integra Neurosciences, Plainsboro, NJ, USA) was placed through this opening. Finally, a third burr hole (6.3mm diameter) was placed approximately 10 mm left/lateral of midline and 10 mm anterior to the coronal suture overlying the left frontal lobe. A balloon-tipped catheter (5cc, 10Fr Foley) was placed through this opening.

Animals were then placed supine in preparation for vascular cutdowns. The right common carotid artery, right internal jugular vein, and right femoral vein were cannulated using a 7fr, 5cm cordis, a 7fr, 5cm cordis, and an 8fr, 23cm cordis, respectively (Cordis Corporation, Johnson and Johnson, Fremont, CA, USA).

Treatment groups

Registered respiratory therapists performed ventilatory management. All animals were initially placed on pressure support (pressure support=5-10cm H_2O, peep=5cm H_2O, and FiO2=50%) using a Hamilton Medical G5 (Hamilton Medical, Bonaduz, Switzerland) prior to randomization to ARDSNet, APRV, or sham.

The ARDSNet group was managed according to the ARDSNet protocol (19). This included utilization of low tidal volume ventilation (6-8 cc/kg). Additionally, FiO_2 and peep were adjusted to maintain PaO_2 and SpO_2 between 55-80 mmHg and 88-95%, respectively, while maintaining plateau pressures less than 30 mmHg. The APRV group was initially started on P_{high}<25cm H_2O, P_{low}=0 cm H_2O, T_{high}=4.0seconds, and T_{low}=0.40-0.55seconds. P_{high}, T_{high}, T_{low}, and FiO_2 were adjusted to minimize lung derecruitment, limit airway pressures, optimize the efficiency of CO2 clearance, and minimize dead space ventilation (20, 21). Additionally, animals were allowed to spontaneously breathe while on APRV.

Finally, one sham group was incorporated, and consisted of one animal initially placed on pressure support utilizing the above-mentioned settings, subjected to lung and brain injury, and then immediately euthanized. This group served as a standard comparison for the two experimental groups (i.e., APRV and ARDSNet).

Lung and Brain Injury

Following randomization, lung injury was induced by injecting 0.1N Hydrochloric acid (4cc/kg, pH=1.41) down the endotracheal tube (22, 23). This method has been previously described as creating a model in animals that most closely parallels ARDS in humans by inducing lung inflammation, edema, hemorrhage, and variable lung region aeration. One hour and thirty minutes following hydrochloric acid administration, our lung injury model was validated by achieving a PaO_2/FiO_2 (P/F) ratio of less than 200mmHg (i.e., ARDS criteria) for all three groups (i.e., sham, APRV, and ARDSNet) (24). Brain injury

(intracranial hypertension) was subsequently induced by inflating the intracranially placed, balloon-tipped catheter with saline at a rate of 1cc/min to achieve an intracranial pressure between 30-40mmHg (3-5cc) (25-27). This model has previously been validated by Purins, et.al. and described as providing consistent/reproducible intracranial hypertension that allows one the ability to determine the exact volume of brain tissue displaced. Thirty minutes following induction of intracranial hypertension, our brain injury model was validated by achieving an ICP between 30-40mmHg for all three groups (i.e., sham, APRV, and ARDSNet).

Physiologic Measurements

Ventilator settings, vitals, and lab measurements (i.e., blood gases, I-stat Blood Analysis System, Heska, Model MN 300, Abbott Point of Care Inc., Abbott Park, IL, USA) were recorded at baseline (pre-randomization and pre-injury), 30 minutes following lung and brain injury, and then every hour thereafter for a total of 6.5hr following lung and brain injury. Cerebral microdialysis samples were collected at similar intervals using sterile, cerebral nervous system perfusion fluid (M Dialysis Inc, North Chelmsford, MA, USA) and a CMA 107 microdialysis pump (M Dialysis Inc, North Chelmsford, MA, USA) at a flow rate of 0.3uL/min. Samples were then stored in an −80 Celsius fridge until subsequent analysis for pyruvate, lactate, glucose, and glycerol (M Dialysis Inc, North Chelmsford, MA, USA) using a CMA 600 microdialysis analyzer (M Dialysis Inc, North Chelmsford, MA, USA) (28).

Necropsy

Following each experiment, animals were euthanized using 150mg/kg Pentobarbitol (29). The brain and right lung were subsequently harvested, preserved in formalin, and submitted to pathology for gross and histopathologic evaluation.

Quantitative Histology

Lung and brain specimens were weighed, measured, and inspected. Routine hematoxylin and eosin stained sections were reviewed. Brain lesions were cataloged and sections of hippocampus were examined for perkinje cells injury, hemorrhage, necrosis and glial reactive changes. Slides of lung were assessed for alveolar hemorrhage, vessel thrombi, degree of congestion, and parenchymal disruption, and quantitatively scored for the extent of alveolar and/or interstitial acute inflammation by measuring alveolar space neutrophils (score 0 = none, score 1 = 1-5 cells/hpf, score 2 = >5 cells/hpf); interstitial neutrophils (score 0 = none, score 1 = 1-5 cells/hpf, score 2 = >5 cells/hpf); hyaline membranes (score 0 = none, score 1 = 1/hpf, score 2 = >1/hpf); alveolar protein debris (score 0 = none, score 1 = 1/hpf, score 2 = >1/hpf); and alveolar septal thickening (score 0 = <2x, score 1 = 2x-4x, score 2 = >4x) (30). The values were then scored and averaged [Total Score (weighted) = (20 x alveolar neutrophils) + (14 x interstitial space neutrophils) + (7 x hyaline membranes) + (7 x airspace proteinaceous debris) + (2 x alveolar septal thickening)]. Pathologists were blinded to ventilatory mode randomization.

Statistical Analysis

Categorical data were analyzed using either chi-square or Fisher's exact test. Continuous data were analyzed using either Student's t-test or Wilcoxon rank-sum. Interaction between group and time were tested using a mixed effects repeated measure model. The between-subject factor was treated as the fixed effect while the within-subject factor was treated as the random effect. Error between the subjects was assumed to be correlated and was modeled using either an unstructured or diagonal-constant variance-covariance matrix, depending on the underlying structure of the Hessian matrix. Normality and heterodasticity was checked using multivariable log-normal. When appropriate a stabilizing transformation was applied to the data (e.g., logarithm). Cumulative sum residual plots were used to assess model goodness-of-fit (31). Analysis was performed using SAS Version 9.3© (Cary, NC, USA) programming software. Statistical significance was defined as a P-value of less than 0.05.

Results

Twenty-two pigs (17 male, 5 female), weighing 25±6.0kg, were used for this pilot study. Prior to randomization and injury, mean static compliance, P/F ratio, ICP, and CPP were 30±6.7, 445±88, 15±5.5, and 95±21, respectively (Table 1). Animals were subsequently randomized to APRV (n=9), ARDSNet (n=12) or sham (n=1). Prior to lung and brain injury, animals randomized to APRV were noted to have significantly greater $PaCO_2$ (p=0.052) and arterial concentrations of bicarbonate (p=0.040) compared to animals randomized to ARDSNet (not represented in tables).

Ventilator settings and pulmonary mechanics, and vitals are compared between APRV and ARDSNet following lung and brain injury in Table 2. Static compliance [APRV (p<0.001) and ARDSNet (p<0.001)], P/F ratio [APRV (p<0.001) and ARDSNet (p<0.001)], and CPP [APRV (p<0.001) and ARDSNet (p=0.023)] dropped significantly while ICP [APRV (p=0.008) and ARDSNet (p<0.001)] increased significantly immediately following lung and brain injury (additionally, our sham group experienced a decline in P/F ratio from a baseline of 474 to a nadir of 122 and an incline in ICP from a baseline of 16 to a peak of 38; not represented in tables). Over time, PIP, mean airway pressure, and P/F ratio significantly increased, while total respiratory rate significantly decreased within the APRV group compared to the ARDSNet group. Static compliance significantly increased within the ARDSNet group compared to the APRV group over time.

Arterial and venous blood gases are compared between the two groups following lung and brain injury in Table 3. Over time, $PvCO_2$ within the cerebral runoff significantly decreased within the APRV group compared to the ARDSNet group.

Cerebral microdialysis biomarkers following lung and brain injury are presented in Table 4 and stratified by ventilator mode setting. A noticeable trend can be appreciated as time progressed (i.e., glucose and pyruvate decreased while lactate, glycerol, and the lactate/pyruvate ratio increased). The progression of these changes appears to be more dramatic for APRV compared to ARDSNet (i.e., lactate significantly increases within the APRV group compared to the ARDSNet group, and the decrease in pyruvate approaches significance).

On necropsy, brain (APRV=84±4.9g, ARDSNet=82±7.1g; p=0.79) and lung (APRV=322±65g, ARDSNet=348±69g; p=0.54) specimens were similar in weight (sham=80g and 366g, respectively). On histopathology, brain sections did not demonstrate ischemic related changes for assessment or comparison between groups. Quantitative histopathology scoring for the lung is provided in Table 5 and stratified by ventilator mode setting. A significant difference between the two groups was not observed.

A difference was not observed between ventilator mode groups regarding volume of resuscitative fluids utilized (i.e., APRV=1061±494, ARDSNet=1118±321; p=0.76 (Not represented in tables). A difference was not observed between ventilator mode groups regarding incidence of mortality prior to reaching our final measurement time point [APRV=3(33%) versus ARDSNet=3(25%); p=1.00] (Not represented in Tables). Additionally, elapsed time from lung and brain injury to death did not significantly differ between groups (APRV=295±159 versus ARDSNet=324±129minutes; p=0.54) (Not represented in Tables).

Discussion

The main findings of our pilot study demonstrated that physiologic parameters [i.e., ventilator settings and pulmonary mechanics (excluding PIP, mean airway pressure, total respiratory rate, static compliance, and P/F ratio), vitals, and arterial and venous blood gases] and histopathology did not significantly differ between APRV and ARDSNet groups. However, cerebral microdialysis indicated a trend towards increased cerebral ischemia in APRV compared to ARDSNet treated animals over time.

Previous studies evaluating APRV in swine models with ARDS have observed a protective and even preventative effect regarding disease progression following insult. Albert, et. al., prospectively evaluated 22 pigs (low tidal volume=6, HFOV=5, APRV=6, and recruitment and decremental positive-end expiratory pressure titration=5), head-to-head for a six-hour period following lung injury (32). While although none of the arms were significantly better than low tidal volume ventilation, the authors observed that APRV was superior to low tidal volume ventilation regarding oxygenation and ventilation efficacy, and reduced inflammation. The authors go on to suggest that APRV's enhanced efficacy is most likely attributable to the inherent spontaneous breaths, which improve lung recruitment and assist with aeration of dependent lung tissue, reduce over-distension, and minimize mechanical breaths. Guldner, et. al., prospectively evaluated 12 pigs with lung injury using APRV with different levels of spontaneous breathing (0%, greater than 0-30%, greater than 30-60%, and greater than 60%) in a crossover design (33). The authors observed that greater levels of spontaneous breathing was associated with improved oxygenation, decreased mean transpulmonary pressure, decreased nonaerated lung tissue, and decreased lung stress and strain. Similarly, we observed an increase in PaO_2, and a decrease in PaCO2 and minute ventilation for APRV compared to ARDSNet over time (not significant). However, mean airway pressure significantly increased within the APRV group compared to the ARDSNet group over time. This may be explained by the use of increasingly greater P_{high}'s over an extended period of time (T_{high}) within the APRV group. Additionally, we observation that as P_{high} exceeded 13-15mmHg, ventilator dyssynchrony ensued, and a forced expiratory

maneuver occurred along with cessation of spontaneous breathing (as denoted by a significant drop in respiratory rate over time among the APRV group). To our knowledge, this observation has not been previously reported, and may have been related to a compounded increase in intracranial hypertension. Additionally, the extended P_{high} phase combined with the observed forced expiratory maneuver may explain the lesser SvO_2 (right femoral vein) within the APRV group compared to the ARDSNet group at each time point (not significant).

Furthermore, spontaneous breaths that did occur could cause marked variability in transpulmonary pressure and tidal volume. A case report and summary on tidal volume variability during APRV, comments on the additional use of pressure support to assist with spontaneous breaths (34). The authors report that, while although the objective in ARDS patients is to maintain tidal volumes between 6-8 mL/kg, spontaneous breaths assisted by pressure support and occurring during the P_{high} phase of ventilation, have the potential of exceeding 9-11 mL/kg.

Our results may also be explained by the interaction between concomitant lung and brain injury at the molecular level. Previous studies have described a “double hit” model whereby TBI stimulates a cascade of events resulting in upregulation of cytokines that are released into the circulation and create a systemic inflammatory environment (9). This process sets up other organ systems to vulnerability, injury, and failure (e.g., VILI). Additionally, sympathetic storm, commonly associated with TBI, intermittently increases systemic intravascular pressure resulting in damaged endothelium and increased vascular permeability. Within the pulmonary tissue, this causes intravascular proteins to leak out of the capillaries and into the interstitial space. Thus, the downstream effects of the TBI may have negated the protecting and preventing benefits of APRV regarding progression of lung injury.

Furthermore, animals treated with APRV in our study, were significantly more likely to have increased $PaCO_2$ and bicarbonate (right common carotid), but normal pH (right common carotid) [i.e., chronic obstructive lung disease (COPD)] prior to lung and brain injury. Veeravagu, et. al., recently performed a retrospective review of over 190,000 hospital admissions for TBI with and without ARDS using the United States, Nationwide Inpatient Sample database (35). Using multivariate stepwise regression analysis, the authors observed that COPD was an independent predictor of ARDS. This may explain the dramatic difference in initial P/F ratios observed immediately following lung and brain injury between groups. Conversely, Roy, et. al., prospectively evaluated 12 pigs (APRV=4, low tidal volume=3, and sham=5), head-to-head for a 48-hour period following lung and intestinal injury (i.e., “two-hit”) (20). The authors observed that introduction of APRV immediately following injury resulted in decreased lung permeability, edema, and surfactant degradation; ultimately, preventing the development of ARDS. While prevention of ARDS was not apparent between either group in our study, both groups observed an improvement in P/F ratio over time and the rate of improvement was significantly increased for APRV compared to ARDSNet.

Using cerebral microdialysis, our study observed a trend towards increased ischemia within the APRV group compared to the ARDSNet group. Our results may be explained by the elevated mean airway pressure attributable to the prolonged Phigh phase and forced expiratory maneuver previously mentioned. This would have increased intrathoracic pressure resulting in decreased venous return. This, in turn, would increase cerebral venous congestion, ICP, and ischemia. A decrease in venous return would also result in a decrease in cardiac output and CPP. Thus, resulting in the decreased SvO2 observed within the APRV group compared to ARDSNet.

Conversely, Kreyer, et. al., using a crossover design, prospectively evaluated the effects of spontaneous breathing during APRV on cerebral and spinal cord perfusion in 12 pigs with lung injury (APRV with spontaneous breathing, APRV without spontaneous breathing and high tidal volume, and APRV without spontaneous breathing and low tidal volume) (36). The authors observed an increase in both systemic and regional cerebral and spinal cord blood flow with spontaneous breathing compared to APRV without spontaneous breathing and high tidal volume. However, this association is most likely attributable to the differences in tidal volumes used, as a similar difference in blood flow was not observed when comparing APRV with spontaneous breathing to APRV without spontaneous breathing and low tidal volume. Thus, the improved cerebral circulation is likely secondary to a reduction in intrathoracic pressure, which reduces cerebral venous congestion, and improves venous return, cardiac output, and CPP.

Limitations

Our pilot study is strengthened by the head-to-head, randomized comparison of two study groups, and the addition of cerebral microdialysis and quantitative histopathologic analysis. However, may be limited by a lack of blinding. While the quantitative histopathologic analysis of our study was blinded, other components were not. This may have contributed to selection bias regarding ventilatory management within each group. We attempted to minimize this bias by instructing respiratory therapists to strictly adhere to ventilatory mode guidelines while optimizing care. The small number of animals evaluated also limits our study. This was a pilot study, and thus a formal power analysis was not completed; however, many previous studies evaluating concomitant ARDS/TBI utilized fewer animal numbers and/or were limited by crossover design (26, 36-38). While crossover designs minimize the number of animals used, washout periods would not reverse the pulmonary or cerebral damage caused by the preceding ventilatory mode. Thus, results would be predicated upon the order of ventilatory modes analyzed. Additionally, as previously mentioned, six animals died prematurely (APRV=3, ARDSNet=3) due to the critical severity of our model. Thus, for those animals, missing variables were present for the time periods following their death. We accounted for those missing variables by utilizing a mixed effects repeated measures model. Another limitation of our study was the short duration of evaluation following lung and brain injury (i.e., 6.5 hours). Previous studies comparing APRV and low tidal volume ventilation strategies within lung injury models over an extended duration (i.e., 48 hours) observed that it took approximately six hours before physiologic parameters began to significantly differ between groups (20, 21). This might explain our lack of significant

findings between the three groups (i.e., sham, APRV, and ARDSNet) regarding quantitative histopathology for both lung and brain tissue.

Conclusion

Previous studies have not evaluated the effects of APRV in a concomitant ARDS/TBI swine model setting. Based upon the results of our pilot study, we reject our hypothesis. While our macroscopic parameters and histopathology did not observe a significant difference between groups, microdialysis data suggest a trend toward increased cerebral ischemia associated with APRV over time. Additional and future studies should focus on extending the time interval for observation to further delineate differences between groups.

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Table 1

Baseline (Pre-Injury and Pre-Randomization) Characteristics on Pressure Support (N=22)

Measured Characteristics	Mean ± SD
Demographics	
Gender (male) – n (%)	17 (77%)
Weight (kg)	25 ± 6.0
Ventilator Settings and Pulmonary Mechanics (Pressure Support)	
FiO_2	0.46 ± 0.096
Peak Inspiratory Pressure	18 ± 3.2
Mean Airway Pressure	8.05 ± 1.8
Peep	5.3 ± 0.88
Total Respiratory Rate	24 ± 6.3
Exhaled Tidal Volume	237 ± 50
Minute Ventilation	5.4 ± 1.6
Static Compliance	30 ± 6.7
P/F Ratio	445 ± 88
Vitals	
Heart Rate (bpm)	106 ± 22
Mean Arterial Pressure	114 ± 24
Oxygen Saturation	98 ± 2.7
End Tidal CO_2	43 ± 7.4
Temperature	39 ± 0.96
Central Venous Pressure	9.5 ± 3.5
Intracranial Pressure	15 ± 5.5
Cerebral Perfusion Pressure	95 ± 21
Right Common Carotid Artery Blood Gas	
pH	7.4 ± 0.040
$PaCO_2$	47 ± 6.8
PaO_2	208 ± 68
Bicarbonate	28 ± 3.9
SaO_2	99 ± 1.05
Potassium	3.3 ± 0.49
Right Femoral Vein Blood Gas (Positioned Within IVC Proximal to Right Atrium)	
$PvCO_2$	49 ± 8.2
PvO_2	47 ± 11
SvO_2	76 ± 12
Lactate	2.4 ± 2.04
Right Internal Jugular Vein Blood Gas (Measuring Cerebral Runoff)	
pH	7.3 ± 0.048

Measured Characteristics	Mean ± SD
$PvCO_2$	58 ± 9.3
PvO_2	39 ± 13
Bicarbonate	29 ± 4.9
SvO_2	59 ± 17
Potassium	3.3 ± 0.50
Cerebral Microdialysis Biomarkers	
Glucose	1.1 ± 0.80
Lactate	3.9 ± 4.6
Glycerol	115 ± 142
Pyruvate	237 ± 451
Lactate/Pyruvate	22 ± 11

APRV=airway pressure release ventilation. ARDSNet=acute respiratory distress syndrome network. IVC=inferior vena cava. Kg=kilograms. bpm=beats per minute. P/F ratio=PaO_2/FiO_2 ratio. SD=standard deviation.

Table 2

Ventilator Settings and Pulmonary Mechanics, and Vitals Following Lung and Brain Injury

Variables	30 min (Mean±SD)	1.5hr (Mean±SD)	2.5hr (Mean±SD)	3.5hr (Mean±SD)	4.5hr (Mean±SD)	5.5hr (Mean±SD)	6.5hr (Mean±SD)	P-Value†
Ventilator Settings and Pulmonary Mechanics								
FiO_2 APRV ARDSNet	0.53±0.25 0.50±0.13	0.5±0.24 0.5±0.17	0.52±0.21 0.46±0.14	0.56±0.23 0.41±0.08	0.60±0.21 0.42±0.07	0.58±0.22 0.41±0.06	0.55±0.23 0.47±0.14	0.33
PIP APRV ARDSNet	16.5±2.7 29.3±5.0	18.7±6.2 29.2±4.5	21.6±6.3 29.5±4.7	22.6±5.1 28.2±2.0	22.4±5.4 28.0±3.2	22.2±5.0 27.7±3.8	21.2±6.1 27.7±3.5	0.042
Mean Airway Press APRV ARDSNet	10.2±2.3 14.8±2.6	11.7±4.2 15.2±3.0	14.8±6.5 14.7±3.8	15.3±4.7 13.1±2.1	14.8±4.5 13.3±1.8	15.6±5.2 12.5±2.9	14.8±5.7 12.8±2.9	0.018£
Set RR APRV ARDSNet	16.8±9.0 30.4±4.5	19.3±8.9 31.7±4.3	19.8±10.0 32.5±6.5	23.0±10.7 31.3±5.0	23.0±8.6 30.8±4.8	22.2±7.7 30.8±4.8	18.8±7.1 30.8±5.4	0.41
Total RR APRV ARDSNet	47.8±14.3 32.0±6.4	37.4±10.9 32.9±5.1	33.9±12.6 33.1±6.6	29.1±11.7 32.2±5.4	27.7±9.1 32.2±5.4	30.7±14.6 32.1±5.6	27.3±9.4 33.2±5.0	0.0005
Exh Tidal Vol APRV ARDSNet	155±28 180±38	161±33 177±41	166±40 171±33	172±52 164±34	171±50 166±32	176±55 167±35	161±53 161±34	0.074
MV APRV ARDSNet	5.2±1.3 5.8±1.8	4.7±1.2 5.8±1.7	4.5±1.3 5.7±1.3	4.1±1.4 5.3±1.2	4.0±1.0 5.3±1.3	4.4±1.3 5.3±1.4	4.0±0.5 5.2±0.9	0.28£
Static Comp APRV ARDSNet	11.7±1.1 10.9±4.7	13.4±3.0 11.6±5.0	11.8±2.9 9.4±2.6	11.8±2.8 9.6±2.9	11.5±3.6 9.7±2.6	11.3±2.5 11.4±6.2	10.9±2.9 12.3±7.7	0.037£
P/F Ratio APRV ARDSNet	165±66 181±52	182±58 194±68	178±71 190±81	168±68 216±75	161±70 213±74	206±105 211±71	197±76 196±78	0.038
Vitals								
HR (bpm) APRV ARDSNet	116±54 112±34	100±33 120±45	108±42 128±44	124±56 115±17	115±51 115±14	103±36 125±18	103±38 125±18	0.37
MAP APRV ARDSNet	105±14 109±19	101±12 108±17	98±21 104±22	107±19 106±22	105±29 101±25	102±33 101±23	99±31 94±26	0.17
O_2 Saturation APRV ARDSNet	91±6 94±3	92±3 94±4	92±4 93±4	91±2 94±4	92±2 94±4	93±2 94±5	93±2 95±5	0.94
End Tidal CO_2 APRV ARDSNet	53±9 44±6	48±9 45±8	48±8 46±8	52±12 45±7	47±11 44±6	41±5 45±8	43±7 45±7	0.37
Temperature APRV ARDSNet	39.1±1.1 38.9±1.2	38.8±1.1 39.0±1.2	39.0±1.2 39.2±1.2	39.2±1.4 39.1±1.1	39.1±1.2 39.2±1.2	38.9±1.0 39.3±1.1	39.0±1.0 39.2±1.0	0.89
CVP APRV ARDSNet	8.6±7.4 9.8±5.0	11.0±6.7 9.1±4.6	11.6±6.3 10.0±3.9	10.6±5.9 11.0±3.6	11.0±5.5 10.3±4.3	10.3±5.3 10.9±4.6	10.5±5.7 10.3±4.3	0.39
ICP APRV ARDSNet	40±19 31±6	33±3 30±6	34±2 30±5	35±4 33±7	33±4 31±5	32±3 31±6	31±2 29±6	0.77

Variables	30 min (Mean±SD)	1.5hr (Mean±SD)	2.5hr (Mean±SD)	3.5hr (Mean±SD)	4.5hr (Mean±SD)	5.5hr (Mean±SD)	6.5hr (Mean±SD)	P-Value[†]
Ventilator Settings and Pulmonary Mechanics								
CPP	65±14	68±14	64±22	72±20	72±29	70±33	69±31	0.081
APRV	78±21	77±19	74±23	74±23	70±24	71±23	65±24	
ARDSNet								

[†]Interaction between group (ARDSNet versus APRV) and time were tested using a mixed effects repeated measure model. Normality and heterodasticity was checked using multivariable log-normal; $p<0.05$.

[£]When appropriate a stabilizing transformation was applied to the data (e.g., logarithm). APRV=airway pressure release ventilation. ARDSNet=acute respiratory distress syndrome network. CPP=cerebral perfusion pressure. CVP=central venous pressure. Exh Tidal Vol=exhaled tidal volume. HR=heart rate. ICP=intracranial pressure. MAP=mean arterial pressure. MV=minute ventilation. P/F ratio=PaO_2/FiO_2 ratio. PIP=peak inspiratory pressure. RR=respiratory rate. SD=standard deviation. Static Comp=static compliance.

Table 3

Arterial and Venous Blood Gases Following Lung and Brain Injury

Variables	30 min (Mean±SD)	1.5hr (Mean±SD)	2.5hr (Mean±SD)	3.5hr (Mean±SD)	4.5hr (Mean±SD)	5.5hr (Mean±SD)	6.5hr (Mean±SD)	P-Value†
Right Common Carotid Artery Blood Gas								
pH	7.24±0.08	7.28±0.06	7.27±0.09	7.25±0.10	7.28±0.07	7.31±0.08	7.30±0.07	0.78
APRV	7.27±0.07	7.28±0.07	7.29±0.08	7.30±0.09	7.30±0.07	7.29±0.08	7.29±0.10	
ARDS Net								
$PaCO_2$	66.1±19.1	61.6±7.7	61.1±8.8	63.4±7.4	59.3±10.3	53.3±6.8	54.7±5.5	0.62
APRV	55.9±10.6	55.0±12.0	53.7±10.6	52.2±8.0	53.4±6.7	54.2±9.6	56.2±8.1	
ARDS Net								
PaO_2	77±21	80.2±8.3	80.7±7.2	83.3±13.7	86.1±13.7	106.0±34.1	97.8±20.5	0.15£
APRV	86±17	90.1±27.6	80.6±15.3	84.9±17.5	86.6±17.9	83.6±15.2	84.2±15.3	
ARDS Net								
Bicarbonate	27.8±3.8	28.4±3.0	28.0±3.9	28.3±3.7	27.7±4.3	27.2±4.4	27.2±4.8	0.46
APRV	25.6±3.9	25.9±4.1	25.5±3.6	25.5±3.6	26.2±3.7	26.4±4.2	26.7±3.7	
ARDS Net								
SaO_2	89±8	93±4	93±3	93±3	94±3	96±3	96±3	0.27
APRV	94±4	94±3	93±3	94±4	94±4	94±4	93±4	
ARDS Net								
Potassium	3.5±0.5	3.8±0.6	3.9±0.7	4.2±0.9	4.3±1.2	4.3±1.5	4.3±1.3	0.93
APRV	3.7±0.5	4.0±0.6	4.2±0.7	4.0±0.6	4.2±0.6	4.2±0.6	4.3±0.8	
ARDS Net								
Right Femoral Vein Blood Gas (Positioned Within IVC Proximal to Right Atrium)								
$PvCO_2$	71.5±17.9	68.4±7.0	71.7±12.6	64.4±14.6	67.0±8.4	60.5±12.1	64.0±11.0	0.15
APRV	61.5±9.6	59.4±11.3	58.5±14.4	58.1±10.2	57.3±8.5	58.8±10.2	62.8±13.96	
ARDS Net								
PvO_2	40.9±6.1	41.4±6.0	40.6±7.4	43.6±7.7	42.7±9.0	39.0±7.5	39.7±6.7	0.69
APRV	43.3±7.6	41.7±6.6	40.9±6.7	42.9±6.8	44.7±3.6	44.6±5.0	44.2±7.2	
ARDS Net								
SvO_2	62±10	65±8	61±14	65±12	64±15	60±18	61±16	0.67
APRV	66±9	66±11	65±14	61±24	72±7	71±10	69±13	
ARDS Net								
Lactate	1.45±0.56	1.32±0.38	1.43±0.57	1.29±0.62	1.62±0.80	1.26±0.35	1.22±0.37	0.23£
APRV	2.45±1.65	2.37±1.85	2.44±2.06	1.90±1.18	1.84±1.36	1.90±1.26	2.02±1.29	
ARDS Net								
Right Internal Jugular Vein Blood Gas (Measuring Cerebral Runoff)								
pH	7.20±0.07	7.21±0.09	7.22±0.10	7.21±0.11	7.23±0.07	7.26±0.08	7.25±0.09	0.28
APRV	7.20±0.07	7.22±0.06	7.21±0.09	7.23±0.09	7.23±0.08	7.22±0.11	7.22±0.09	
ARDS Net								
$PvCO_2$	81.4±16.3	74.3±7.3	67.1±10.9	74.7±10.1	69.1±6.1	61.8±5.8	61.5±5.8	0.0195£
APRV	68.5±8.0	69.6±12.7	69.8±12.4	68.4±11.0	67.0±7.1	71.8±17.6	70.7±10.3	
ARDS Net								
PvO_2	42.2±5.7	44.1±7.4	45.0±7.3	47.7±3.3	46.9±2.7	45.8±5.2	46.2±8.3	0.13£
APRV	42.8±6.0	39.6±7.9	36.7±10.9	39.6±10.6	37.7±7.0	38.7±4.0	42.1±3.5	
ARDS Net								
Bicarbonate	31.8±2.7	30.0±5.4	28.7±7.4	29.4±4.1	29.3±4.2	28.7±6.1	27.0±5.5	0.22
APRV	27.4±4.2	28.8±4.5	28.0±3.6	28.9±4.4	28.8±6.1	28.9±3.5	28.3±3.2	
ARDS Net								
SvO_2	63±9	66±9	69±8	74±5	72±6	73±9	71±14	0.26
APRV	63±11	60±13	54±18	60±13	58±12	60±12	65±8	
ARDS Net								
Potassium	3.78±0.52	3.8±0.5	3.7±0.7	4.2±1.1	4.4±1.2	4.3±1.0	4.1±1.2	0.15£
APRV	3.76±0.52	4.1±0.6	4.4±0.9	4.3±0.7	4.2±0.8	4.5±0.8	4.5±2.7	

Variables	30 min (Mean±SD)	1.5hr (Mean±SD)	2.5hr (Mean±SD)	3.5hr (Mean±SD)	4.5hr (Mean±SD)	5.5hr (Mean±SD)	6.5hr (Mean±SD)	P-Value†
Right Common Carotid Artery Blood Gas								
ARDS Net								

† Interaction between group (ARDSNet versus APRV) and time were tested using a mixed effects repeated measure model. Normality and heterodasticity was checked using multivariable log-normal; $p<0.05$.

£ When appropriate a stabilizing transformation was applied to the data (e.g., logarithm). APRV=airway pressure release ventilation. ARDSNet=acute respiratory distress syndrome network. IVC=inferior vena cava. SD=standard deviation.

Table 4

Cerebral Microdialysis Biomarkers Following Lung and Brain Injury

Variables	30 min (Mean±SD)	1.5hr (Mean±SD)	2.5hr (Mean±SD)	3.5hr (Mean±SD)	4.5hr (Mean±SD)	5.5hr (Mean±SD)	6.5hr (Mean±SD)	P-Value†
Glucose¥ APRV ARDSNet	1.8±1.2 1.4±1.3	0.84±0.65 1.8±1.5	0.23±0.071 2.4±1.1	TSTD 3.9±0.20	TSTD 4.3±1.1	TSTD 2.4±0.10	TSTD 2.2±0.66	---
Lactate APRV ARDSNet	4.5±2.0 5.1±1.8	5.6±2.9 4.7±2.9	6.9±1.9 8.0±6.0	6.5±1.4 7.9±6.2	6.2±0.60 3.8±2.9	6.5±1.1 4.6±2.9	6.6±1.2 7.8±5.3	0.013£
Glycerol¥ APRV ARDSNet	80±41 154±139	63±26 123±96	102±118 143±86	156±254 175±84	185±292 113±140	355±454 111±134	262±403 209±197	---
Pyruvate APRV ARDSNet	136±67 164±45	130±70 107±35	102±110 300±283	147±148 95±52	126±153 106±73	68±38 142±99	96±56 191±186	0.051£
Lactate/Pyruvate APRV ARDSNet	35±10 30±9.0	58±44 39±17	174±132 41±21	106±82 105±130	145±115 66±81	124±69 68±83	93±52 83±105	0.16£

Continuous data were analyzed using either Student's t-test or Wilcoxon rank-sum depending upon the normalcy of distribution.

† Interaction between group (ARDSNet versus APRV) and time were tested using a mixed effects repeated measure model. Normality and heterodasticity was checked using multivariable log-normal; $p<0.05$.

£ When appropriate a stabilizing transformation was applied to the data (e.g., logarithm).

¥ Insufficient data to compute likelihood function. APRV=airway pressure release ventilation. ARDSNet=acute respiratory distress syndrome network. SD=standard deviation. TSTD=too small to determine.

Table 5

Lung Quantitative Histopathology

Variables	Sham Mean	APRV Mean±SD	ARDSNet Mean±SD	P-Value
Alveolar Neutrophils	0.10	1.8 ± 0.17	1.8 ± 0.14	0.86
Interstitial Space Neutrophils	1.1	1.7 ± 0.11	1.7 ± 0.083	0.72
Hyaline Membranes	0.0	0.58 ± 0.12	0.57 ± 0.17	0.91
Airspace Proteinaceous Debris	0.10	0.20 ± 0.35	0.050 ± 0.14	0.30
Alveolar Septal Thickening	0.40	0.60 ± 0.12	0.64 ± 0.0996	0.47
Total Score*	19	66 ± 3.99	65 ± 2.2	0.44

Continuous data were analyzed using either Student's t-test or Wilcoxon rank-sum depending upon the normalcy of distribution.

P-Value relates to the comparison between APRV and ARDSNet.

APRV=airway pressure release ventilation. ARDSNet=acute respiratory distress syndrome network.

* Total Score (weighted)=(20 x alveolar neutrophils) + (14 x interstitial space neutrophils) + (7 x hyaline membranes) + (7 x airspace proteinaceous debris) + (2 x alveolar septal thickening)