VENTILATOR „CHIRANA AURA V“ IN TWO MODELS OF NEONATAL ACUTE LUNG INJURY – A PILOT STUDY

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Abstract

In severe respiratory insufficiency, neonatal and pediatric patients should be ventilated artificially by a ventilator. Aim of this experimental study was to evaluate whether the newly developed ventilator Chirana Aura V may effectively ventilate the lungs of animals with two different models of acute lung injury: acute respiratory distress syndrome (ARDS) induced by repetitive saline lavage and meconium aspiration syndrome (MAS) induced by intra-tracheal instillation of neonatal meconium.

The experiments were performed on 10 adult rabbits (New Zealand white). In ARDS group (n=5), the lungs were repetitively lavaged with saline (30 ml/kg) until partial pressure of oxygen (PaO₂) in arterial blood was under 26.7 kPa at inspiratory fraction of oxygen FiO₂=1.0. In MAS group (n=5), animals were instilled 4 ml/kg of suspension of human meconium (25 mg/ml). When the model of acute lung injury was developed, animals were ventilated for additional 2 hours with pressure control ventilation (PCV) regime by ventilator Chirana Aura V. Ventilatory parameters, blood gases, acid-base balance, end-tidal CO₂, O₂ saturation of hemoglobin, oxygenation indexes, ventilation efficiency index, dynamic lung compliance, and right-to-left pulmonary shunts were measured and calculated in regular time intervals. In both experimental groups, used ventilatory settings provided acceptable gas exchange within the period of observation. Thus, the results indicate that ventilator Chirana Aura V might be suitable for ventilation of animal models of acute lung injury. However, further pre-clinical investigation is needed before its use may be recommended in neonatal and/or pediatric patients with acute lung injury.

Key words: acute respiratory distress syndrome, meconium aspiration syndrome, respiratory insufficiency, mechanical ventilation, pressure control ventilation

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a life-threatening situation, which may originate as a consequence of various diseases. It is characterized by diffuse alveolar injury due to inflammation, lung edema and ventilation-perfusion mismatch, finally leading to worsened lung compliance and hypoxemia (1-3). The so called Berlin Definition has recently considered 3 categories of ARDS according to the severity of hypoxemia: mild (with PaO₂/FiO₂ 26.7-40 kPa), moderate (PaO₂/FiO₂ 13.3-26.7 kPa) and severe (PaO₂/FiO₂ less than 13.3 kPa) (4).

In an acute phase of ARDS, injury of alveolar epithelial and endothelial cells occurs, with subsequent leak of proteinaceous liquid into the alveoli. Detachment of alveolar cells type I leads not only to lung edema formation, but loss of barrier function predisposes to higher risk of bacteraemia and sepsis. Damage of pneumocytes type II worsens the synthesis and metabolism of pulmonary surfactant, what results in higher surface tension in the alveoli and their subsequent collapse. Histopathologically, diffuse alveolar injury with massive infiltration of neutrophils, alveolar hemorrhage and generation of hyaline membranes may be found. Due to on-going inflammation, increased production of pro-inflammatory substances, such as cytokines (IL-1beta, IL-6, IL-8, TNFalpha), proteases, reactive oxygen spe-

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cies, or matrix-metalloproteinases further deteriorate the lung tissue damage. Acute phase is followed by fibroproliferative phase, with fibrosis, neovascularization and recovery (1-3).

Similar pathological changes may be observed also in meconium aspiration syndrome (MAS). However, respiratory insufficiency is caused by perinatal aspiration of the first stools of the newborn – meconium. Aspirated meconium causes airway obstruction, with finding of hypoxemia, hypercarbia and acidosis in the laboratory investigation. In addition, due to a content of highly deleterious substances, such as gastrointestinal enzymes including phospholipase A₂, bilirubin, cholesterol, free fatty acids etc., movement of meconium distally into the alveolar compartment causes surfactant dysfunction, neutrophil-derived inflammation, pulmonary vaso- and bronchoconstriction, and lung edema (5).

In the treatment of both ARDS and MAS, artificial ventilation and various pharmacological medicaments including exogenous surfactant, pulmonary vasodilators and anti-inflammatory agents are used (1-3, 5). Considering the injury of lung parenchyma and surfactant dysfunction, „small-volume“ ventilation strategies are preferred, with tidal volumes around 6 ml/kg b.w. and appropriate end-expiratory pressure (PEEP). However, up to now there is no consensus on tidal volumes, frequency of ventilation, or ventilatory pressures in various types of artificial ventilation (1, 6-9).

Goal of this pilot study was to evaluate whether the newly developed ventilator Chirana Aura V may be perspective used also for ventilation of the neonatal and pediatric patients. For this purpose, experimental models of two most frequent causes of neonatal respiratory insufficiency (ARDS and MAS) were prepared. Changes in ventilatory parameters, blood gases and indexes of gas exchange were monitored within 2 hours of pressure control ventilation (PCV) regime after experimental induction of these models to detect whether this type of ventilator may keep the adequate gas exchange in animals with the body weight and tidal volumes corresponding to those in the newborns.

METHODS

Design of experiments was approved by the local Ethics Committee of Jessenius Faculty of Medicine and National Veterinary Board.

Adult rabbits (New Zealand white) of 2.9 ± 0.3 kg body weight (b.w.) were anesthetized with intramuscular ketamine (20 mg/kg b.w.; Narketan, Vétoquinol, UK) and xylazine (5 mg/kg b.w.; Xylarium, Riemser, Germany), followed by intravenous infusion of ketamine (20 mg/kg/h). Tracheotomy was performed and catheters were inserted into a femoral artery and right atrium for sampling the blood, and into a femoral vein to administer anesthetics. Animals were then paralyzed with pipecuronium bromide (0.3 mg/kg b.w./30 min; Arduan, Gedeon Richter, Hungary) and subjected to a PCV mode by ventilator Chirana Aura V (Chirana, Slovakia).

Model of acute respiratory distress syndrome (ARDS)

From the beginning of the study, all animals were ventilated with a frequency of 40/min, fraction of inspired oxygen (FiO₂) of 1.0, inspiration time (Ti) 45%, peak inspiratory pressure (P_{pc}) of about 1.6 kPa to keep a tidal volume (V_T) between 6-9 ml/kg b.w. and positive end-expiratory pressure (PEEP) of 0.5 kPa.

After 15 min of stabilization, respiratory parameters were recorded and blood gases were analyzed by combined hematology analyzer (RapidLab 348, Siemens, Germany). Then, rabbit lungs were repetitively lavaged with saline (0.9% NaCl, 37 °C, 30 ml/kg), so that saline was administered by syringe homogenously into right and left lungs during positioning of the animal and immediately suctioned by a suction device. After 2 min of stabilization, the lavage procedure was repeated. Lavage was performed 10-12 times, until PaO₂ decreases to <20 kPa in FiO₂ 1.0 in 2 measurements at 5 and 15 min after the lavage. From the moment of full-filled criteria of respiratory insufficiency (i.e. induction of ARDS), animals were ven-

tilated for additional 2 hours of PCV with subsequent settings: frequency 40/min, FiO_2 1.0, PEEP 0.5 kPa, Ppc 1.8-2.3 kPa according to the actual value of expired CO_2 and blood gases. Blood gases and respiratory parameters were recorded at 0.5, 1, and 2 hours after creating the model of ARDS. At the end of experiments, animals were sacrificed by an overdose of anesthetics.

Model of meconium aspiration syndrome (MAS)

Materials: Meconium was collected from healthy term neonates, lyophilized and stored at -20°C . Before use, meconium was suspended in 0.9% NaCl at a concentration of 25 mg/ml.

At the beginning of the study, all animals were ventilated with a frequency of 40/min, FiO_2 0.21, Ti 45%, peak inspiratory pressure (Ppc) of about 1.6 kPa to keep a tidal volume (V_T) between 6-9 ml/kg b.w. and minimum positive end-expiratory pressure (PEEP) of 0.1 kPa at this stage of experiment.

After 15 min of stabilization, respiratory parameters were recorded and blood gases were analyzed (RapidLab 348, Siemens, Germany). Then, rabbits were intratracheally administered 4 ml/kg b.w. of meconium suspension (25 mg/ml). From this moment on, animals were ventilated with PCV mode using FiO_2 1.0, PEEP 0.5 kPa and Ppc 2.1-2.4 kPa according to the actual value of expired CO_2 and blood gases. From the moment of full-filled criteria of respiratory insufficiency (i.e. induction of MAS), animals were ventilated for additional 2 hours with the mentioned ventilator settings. Blood gases and respiratory parameters were recorded at 0.5, 1, and 2 hours after creating the model of MAS. At the end of experiments, animals were sacrificed by an overdose of anesthetics.

Measurement and calculation of parameters

Ventilatory parameters, such as Ppc, V_T , Paw (airway pressure), PEEP, mean pressure (MAP), MV (minute ventilation), ventilation frequency (f), fraction of inspired oxygen (FiO_2), and expired CO_2 were continuously measured and displayed on the screen of ventilator. Partial pressures of O_2 , CO_2 , pH, and saturation of hemoglobin by oxygen (SatO_2) in the arterial and mixed venous blood were measured by combined analyzer (RapidLab 348, Siemens, Germany).

Cdyn (dynamic lung compliance) was expressed as a ratio between V_T and airway pressure gradient (Paw-PEEP). Oxygenation index (OI) was calculated as: $\text{OI} = [(\text{MAP} \times \text{FiO}_2) \times 100] / \text{PaO}_2$. Index $\text{PaO}_2/\text{FiO}_2$ was calculated as $[(\text{PaO}_2/\text{FiO}_2) \times 100]$. Ventilation efficiency index (VEI) was calculated as: $\text{VEI} = 3800 / [(\text{Paw} - \text{PEEP}) \times \text{ventilation frequency} \times \text{PaCO}_2]$.

Right-to-left pulmonary shunts (RLS) were calculated by a computer program using the Fick equation: $(\text{CcO}_2 - \text{CaO}_2) / (\text{CcO}_2 - \text{CvO}_2) \times 100$, where CcO_2 , CaO_2 and CvO_2 are concentrations of oxygen in pulmonary capillaries, arterial and mixed blood. CcO_2 was calculated by using P_AO_2 (alveolar partial pressure of oxygen) from the equation: $\text{P}_A\text{O}_2 = (\text{PB} - \text{PH}_2\text{O}) \times (\text{FiO}_2 - \text{PaCO}_2) \times [\text{FiO}_2 + (1 - \text{FiO}_2)/\text{R}]$, where PB is barometric pressure and PH_2O the pressure of water vapour. Respiratory exchange ratio (R) was assumed to be 0.8 and the current value of hemoglobin necessary for calculating the oxygen concentration in the blood was measured by combined analyzer (RapidLab 348, Siemens, Germany).

Statistics

For data analysis, statistical package SYSTAT for Windows was used. Within-group differences were evaluated by Wilcoxon test. A value of $P < 0.05$ was considered statistically significant. Data are expressed as means $\pm$ SEM.

RESULTS

Repetitive lung lavage with saline in the ARDS group and intratracheal instillation of meconium suspension in the MAS group caused significant decrease in Cdyn, PaO_2 , $\text{PaO}_2/\text{FiO}_2$, SatO_2 , arterial pH, and VEI and increase in OI and RLS in comparison with initial values (all $P < 0.05$, Tables 1 and 2).

In the ARDS group, early after induction of ARDS model values of PaCO₂ and expired CO₂ were significantly higher than initial values (both $P<0.05$), then gradually lowered to acceptable values (Table 1).

According to the on-going worsening the lung functions, ventilatory parameters (particularly the ventilatory pressures) were changed, if necessary, to supply adequate gas exchange (Tables 1 and 2). Ppc firstly increased non-significantly vs. initial values ($P=0.066$ for comparison After ARDS/After MAS vs. Before ARDS/Before MAS), later significantly in the ARDS group ($P=0.042$ for comparison 30 min vs. Before ARDS), while in the MAS group increase in Ppc in 30 min vs. initial values was borderly non-significant ($P=0.059$). In the MAS group, significant increases in Paw, MAP and PEEP vs. initial values were observed, as well (Tables 1 and 2).

Table 1. Ventilatory parameters, blood gases and indexes of gas exchange in the ARDS group.

	Before ARDS	After ARDS	30 min	1 hour	2 hours
V _T (ml/kg)	7.65±0.71	7.11±0.94	7.38±0.81	8.29±1.02	8.54±0.47
f/min	40.0±0.0	40.0±0.0	40.00±0.0	41.3±1.3	41.3±1.3
Ppc (kPa)	1.56±0.04	1.82±0.08	1.90±0.06*	2.08±0.08	2.15±0.09
PEEP (kPa)	0.50±0.00	0.50±0.00	0.50±0.00	0.50±0.00	0.50±0.00
Paw (kPa)	2.20±0.08	2.30±0.15	2.44±0.12	2.68±0.12	2.80±0.17
MAP (kPa)	1.20±0.00	1.22±0.04	1.28±0.04	1.33±0.03	1.38±0.05
MV (l/min)	0.88±0.07	0.82±0.09	0.86±0.08	0.98±0.06	1.13±0.10
pHa	7.40±0.03	7.01±0.03*	7.15±0.05	7.17±0.05	7.17±0.02
PaCO ₂ (kPa)	5.80±0.80	9.33±1.06*	8.04±0.73	8.14±1.24	6.80±0.51
Expir CO ₂ (%)	2.70±0.18	5.24±0.81*	5.14±0.71	4.63±0.24	4.15±0.33
PaO ₂ (kPa)	67.29±6.11	17.80±2.62*	14.21±1.04	12.56±0.93	11.77±1.37
FiO ₂ (%)	100±0	100±0	100±0	100±0	100±0
PaO ₂ /FiO ₂	67.29±6.11	17.80±2.62*	14.21±1.04	12.56±0.93	11.77±1.37
OI	1.86±0.22	7.45±1.05*	9.20±0.71	10.67±0.54	12.06±1.15
SatO ₂ (%)	99.84±0.04	96.64±0.88*	95.64±0.82	94.73±0.84	92.70±2.31
RLS (%)	5.78±1.39	32.7±6.88*	33.08±5.45	30.46±3.41	26.94±3.67
VEI	8.07±1.13	5.91±0.28*	6.18±0.40	5.59±0.81	6.06±0.54
Cdyn (ml/kPa)	14.34±0.80	11.87±0.52*	11.45±0.58	11.33±0.61	11.32±0.57

Abbreviations: V_T: tidal volume, f/min: frequency of ventilation/min, Ppc: peak inspiratory pressure, PEEP: positive end-expiratory pressure, Paw: airway pressure, MAP: mean airway pressure, MV: minute ventilation, pHa: arterial pH, PaCO₂: arterial partial pressure of carbon dioxide, Expir CO₂: expired CO₂, PaO₂: partial pressure of oxygen, FiO₂: fraction of inspired oxygen, OI: oxygenation index, SatO₂: saturation of hemoglobin by oxygen, RLS: right-to-left pulmonary shunts, VEI: ventilation efficiency index, Cdyn: dynamic lung compliance. * $P<0.05$ for comparison with initial values (Before ARDS). Data are expressed as means±SEM.

Table 2. Ventilatory parameters, blood gases and indexes of gas exchange in the MAS group.

	Before MAS	After MAS	30 min	1 hour	2 hours
V _T (ml/kg)	8.90±0.31	8.78±0.57	9.85±0.43	8.42±0.81	8.79±1.02
f/min	40.0±0.0	40.0±0.0	40.0±0.0	42.5±2.5	40.0±0.0
P _{pc} (kPa)	1.60±0.06	2.14±0.16	2.35±0.05	2.30±0.08	2.43±0.07
PEEP (kPa)	0.10±0.00	0.50±0.00*	0.50±0.00	0.50±0.00	0.50±0.00
P _{aw} (kPa)	1.94±0.13	2.86±0.02*	2.88±0.08	2.90±0.11	2.97±0.12
MAP (kPa)	0.86±0.04	1.40±0.00*	1.43±0.03	1.38±0.05	1.43±0.03
MV (l/min)	0.94±0.09	1.04±0.05	1.10±0.06	1.05±0.16	1.00±0.12
pH _a	7.44±0.01	7.27±0.04*	7.24±0.06	7.17±0.03	7.06±0.03
PaCO ₂ (kPa)	6.06±0.28	6.57±0.76	6.28±0.55	5.88±0.37	5.60±0.67
Expir CO ₂ (%)	3.44±0.40	4.14±0.39	3.38±0.50	3.83±0.30	3.57±0.33
PaO ₂ (kPa)	9.99±0.78	7.68±0.32*	8.00±0.33	7.22±0.65	7.74±0.14
FiO ₂ (%)	21±0	40±0*	40±0	40±0	41.7±1.7
PaO ₂ /FiO ₂	47.57±3.70	19.21±0.81	19.20±0.83	18.04±1.63	18.62±0.75
OI	1.84±0.14	7.34±0.32*	7.16±0.30	7.78±0.62	7.41±0.20
SatO ₂ (%)	94.82±0.94	86.74±1.74*	86.20±1.06	78.18±3.24	77.33±2.65
RLS (%)	6.83±2.05	18.52±1.50*	18.5±81.57	21.93±3.44	18.02±1.13
VEI	8.71±0.49	6.48±0.77*	6.57±0.70	6.47±0.40	7.04±0.60
C _{dyn} (ml/kPa)	13.96±0.27	10.50±0.48*	10.91±0.37	9.95±1.07	10.38±1.38

Abbreviations: V_T: tidal volume, f/min: frequency of ventilation/min, P_{pc}: peak inspiratory pressure, PEEP: positive end-expiratory pressure, P_{aw}: airway pressure, MAP: mean airway pressure, MV: minute ventilation, pH_a: arterial pH, PaCO₂: arterial partial pressure of carbon dioxide, Expir CO₂: expired CO₂, PaO₂: partial pressure of oxygen, FiO₂: fraction of inspired oxygen, OI: oxygenation index, SatO₂: saturation of hemoglobin by oxygen, RLS: right-to-left pulmonary shunts, VEI: ventilation efficiency index, C_{dyn}: dynamic lung compliance. *P<0.05 for comparison with initial values (Before MAS). Data are expressed as means±SEM.

DISCUSSION

Acute respiratory distress syndrome (ARDS) and meconium aspiration syndrome (MAS) are syndromes characterized by severe lung injury, which cause acute hypoxemia requiring high concentrations of oxygen and high levels of positive end-expiratory pressure. Clinically, the mentioned syndromes are represented by severe ventilation-perfusion mismatch that leads to significant respiratory hypoxemic failure (1-3).

Respiratory support practice in the neonatal intensive care continues to evolve rapidly. New modalities and techniques have become available for infant with respiratory insufficiency over the past decade (10-12). However, mechanical ventilation can induce lung injury, particularly in premature and diseased lungs. There is increasing evidence that high peak inspiratory pressures and repetitive end-expiratory collapse are major determinants of lung injury (13). Ventilatory strategies that limit high inflation pressures and prevent end-expiratory collapse have been designed as lung-protective mechanical ventilation (14, 15).

Conventional mechanical ventilation is referred as a form of assisted ventilation in which the delivered gas volumes approach physiological tidal volumes, and the patterns of breathing attempt to mimic physiological breathing (12). During pressure-limited time-cycled ventilation mode, peak inspiratory pressure is set and, during inspiration, gas is delivered to achieve the target pressure (16).

In this study, pressure control ventilation (PCV) was used for ventilation of animals with experimentally-induced acute lung injury. As recently published, volume-controlled ventilation (VCV) is superior to PCV in several aspects (17). However, VCV and PCV are not different ventilatory modes, but are different control variables within a mode. VCV offers the safety of a pre-set tidal volume and minute ventilation but requires the clinician to appropriately set the inspiratory flow, flow waveform, and inspiratory time. During VCV, airway pressure increases in response to reduced compliance, increased resistance, or active exhalation and may increase the risk of ventilator-induced lung injury. PCV, by design, limits the maximum airway pressure delivered to the lung, but may result in variable tidal and minute volume. During PCV the clinician should titrate the inspiratory pressure to the measured tidal volume, but the inspiratory flow and flow waveform are determined by the ventilator as it attempts to maintain a square inspiratory pressure profile (18). Thus, advantage of PCV is a lower peak airway pressure, but disadvantage is that tidal volume delivery increases and decreases with changes of patient's compliance (18, 19).

Intensive care ventilator Chirana Aura V (Chirana, Slovakia) is a modern device for artificial ventilation of lungs. It was designed for adults, children and infants from 500 g b.w. Chirana Aura V has many advantages for ventilation of patients. It ensures minute ventilation from 0.1 l/min, with respiratory rates 4-180/minute and tidal volumes 3-2000 ml. Inspiration-to-expiration (I:E) ratio for mandatory breaths can be set in the range of 1:4-4:1 and PEEP in a range of 0 to 25 Pa x 100. In addition to pressure control ventilation, Chirana Aura V ventilator provides many other ventilation modes, such as volume control assisted (or synchronized intermittent mandatory ventilation, SIMV-in) conventional mechanical ventilation (CMV), support regimes, such as pressure support (PS), airway pressure release ventilation (APRV, or BIPAP), 2-level ventilation+PS, multi-level ventilation (MLV), continuous positive airway pressure (CPAP) etc.), and has some advanced features, e.g. Sigh (deep breath), or Leakage, spontaneous CPAP, apnoea ventilation automatically embedded in each mode or non-invasive ventilation (NIV) suitable for non-invasive pressure modes, etc.

In this pilot study, a basic ventilator mode PCV was used. Despite serious decrease in lung compliance and worsened gas exchange observed within 30 min after induction of the models of ARDS and MAS, we were able to keep relatively stable values of C_{dyn}, gradually lowering arterial partial pressure CO₂ and expired CO₂ and rather acceptable oxygenation within 2 hours of observation. Importantly, animals survived the period of observation without administration of any treatment, which may potentially improve the lung functions. In addition, PCV ventilation was well-tolerated by all animals, i.e. no serious hypotension or other cardiovascular changes were observed.

Considering our preliminary results, ventilator Chirana Aura V can be used for ventilation of laboratory animals with acute lung injury. However, further pre-clinical investigation is warranted, including testing of appropriate ventilator settings and potential side effects, before the use of new ventilator may be recommended for neonatal and/or pediatric patients.

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