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An Experimental Study in an Induced Lung Injury Model in Sheep to Test a Novel Compression Ventilator

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Abstract

BACKGROUND/AIMS: In a critical care setting, a simple, non-complex but reliable mechanical ventilator would serve as a candidate device in saving human life and qualified medical resources. In this study, we aimed to evaluate the efficacy, safety and reliability of a novel simple mechanical ventilator (ASC-1) developed for ventilation in an induced lung injury model and to compare the normal physiologic lung condition with an induced pathologic lung condition in sheep.

MATERIALS AND METHODS: A sheep ventilation model was established in three female sheep which were anesthetized and intubated. Sheep A was ventilated with a conventional mechanical ventilator, Sheep B was ventilated with ASC-1 accordingly to the protective ventilation protocols. The lung injury model was induced with saline lavage in Sheep C. Following this, the animal was ventilated with ASC-1. At the end of 12 hours, the sheep were euthanized under anesthesia. The vital signs and changes in their arterial blood gas (ABG) were recorded.

RESULTS: The biopsies collected from lungs were examined histologically. The injury and ventilation status of the lungs were examined radiographically. During the ventilation, all sheep maintained stable fluid-electrolyte balance and ABG, and no catastrophic events occurred in any of the sheep. The respiratory parameters of Sheep A were stabilized easily with an intensive care unit ventilator. Additionally, the parameters of Sheep B and Sheep C were also stabilized with the ASC-1 ventilator, at least clinically. The histological findings of the tissues were comparable between the three sheep.

CONCLUSION: As a safe, reliable, low-cost ventilator, the ASC-1 ventilator may be a good alternative to be used in critical respiratory care per se, resulting in no further lung damage, especially in pandemic conditions where shortages of ventilators may be problematic.

Keywords: Critical care, mechanical ventilation, animal model, sheep, lung injury

INTRODUCTION

Mechanical ventilation is one of the most common interventions implemented in critical respiratory care. More than half of the patients in the intensive care unit (ICU) are ventilated within the first 24 hours after ICU admission. These patients are comprised of individuals who have acute respiratory failure, compromised lung function, difficulty in breathing, or failure to protect their airway.[1] There are multiple modes of mechanical ventilation support which provide air to the patient based on pressure, flow and volume. In spite of being lifesaving, mechanical

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ventilation can be associated with life threatening complications, including air leaks and pneumonia.[2]

In the era of the coronavirus disease-2019 (COVID-19) outbreak, each medical facility is concerned about shortages of mechanical ventilator supplies. Stockpiling these sophisticated, expensive intensive care ventilators during pre-pandemic periods is not a feasible solution. Even well-developed countries which have an adequate number of commercial, technical and industrial resources for these medical devices are confronted with these limitations in the fight against COVID-19.[3] Therefore, an adequate number of affordable, easy-to-use, safe and efficient ventilators are urgently needed in ICUs.

Commonly used to provide positive pressure ventilation in the treatment of the respiratory failure, bag valve masks (BVMs) are hand-held, low-cost, easily attainable and simple medical devices. However, this successful system has certain shortcomings, resulting in several complications during ventilation. Manual ventilation of the intubated patients requires the physical effort of the operator as well as the operator's full attention on the procedure.[4] Moreover, it is challenging to verify whether the precise volume of air is being delivered during ventilation since the delivered volume depends on the method of squeezing. Additionally, the tidal volumes typically delivered using adult BVMs are often higher than the recommended volumes for lung protective ventilation protocols.[5] Unfortunately, healthcare professionals tend to cause hyperventilation when using the current BVM devices, which could have detrimental effects on the respiratory and cardiovascular physiology.[6] Therefore, overcoming the shortcomings of these of BVMs with the assistance of an alternative affordable device can provide opportunities in facilitating respiratory care.

One of BVM compression ventilators, the ASC-1, is a novel low-cost simple mechanical ventilator which is manufactured for ventilatory support and offers a favorable alternative when a conventional ICU ventilator is not available for intervention on respiratory failure patients. It also allows the clinician to control the tidal volume, the inspiratory pressure, the respiratory rate and the inspiratory/expiratory (I/E) ratio and to support positive end expiratory pressure (PEEP) and peak airway pressure monitoring, by integrating the filtration and plumbing with filters and suitable breathing systems (Figure 1). In the present observational experimental study, we aimed to evaluate the efficacy, safety and reliability of this novel ventilator (ASC-1), which was developed for mechanical ventilation, in an induced lung injury model, and to compare the normal physiologic lung condition with an induced pathologic lung condition in sheep.

MATERIALS AND METHODS

Animals

The study protocol was approved by the Committee of the Near East University for the Animal Care and Use (approval number: 2020/116, date: 20.05.2020). Patient approval has not been obtained as it is performed on animals. All protocols were in accordance with the National Laboratory Animals Care Guidelines. Three female sheep (*Ovis aries*) weighing between 50-65 kg were supplied by Near East University Havva Hanım Practice and Research Farm. Before the procedures, the sheep were examined by a veterinarian physically and all laboratory testing was performed. The selection criteria of the sheep were their comparable lung sizes to an adult human lung and comparable respiratory physiology to human respiratory physiology.[7]

One day before the experiment, the sheep were transferred from the farm and maintained in the Faculty of Veterinary Medicine of Near East University, in livestock pens with free access to food and water in a covered area at 20-22 °C and 12:12 light/dark cycle. The animals fasted for 10 hours before the study but they were allowed to drink water.

Anesthesia Protocol

The sheep were sedated with an intravascular (IV) injection of diazepam (0.5 mg/kg) and ketamine (8 mg/kg). After being properly sedated, the animals were weighed, placed on an operating table, and monitored with pulse oximetry and electrocardiography. Under Ultrasonography-guided, a jugular venous line was inserted and a 4 mg/kg bolus of propofol was administered in order to facilitate intubation using a cuffed endotracheal tube with 8 mm internal diameter. After intubation, a gastric tube was inserted with the aim of preventing ruminal tympany which would result in increased intraabdominal pressure, and hence raise some ventilation problems and regurgitation.[8] The carotid artery was cannulated for blood pressure measurements and arterial blood gas (ABG) sampling. Sedation was maintained with 12 mg/kg/h propofol

Figure 1. An image of the ASC-1 ventilator with a description of its settings.

and 4 mcg/kg/h ketamine infusions[9] and 0.15 mg/kg rocuronium boluses were administered IV; therefore, the dependence on the ventilators was facilitated and asynchronous breathing was prevented.

Study Protocol

The sheep were randomly allocated for the mechanical ventilation either with a standard ICU ventilator (Maquet Servo S, Getinge, Sweeden) or with a ventilation using a new simple compression ventilator integrated with a manual BVM, namely the ASC-1, or to ventilation using the ASC-1 ventilator following a moderate lung injury established by a saline-lavage application. According to this allocation, the sheep were labeled as Sheep A, Sheep B and Sheep C, respectively. In order to standardize the positions of the sheep and to prevent any positional bias on the findings related with the ventilation, all three sheep were placed on their right sides after anesthesia and kept in this position throughout the study.

To establish a modified lung injury model in Sheep C, a saline-lavage technique was applied according to the literature.[10] Briefly, 1 liter of warm isotonic saline solution was instilled in 200 mL portions into the lungs within 1 hour and then removed by aspiration in order to prevent a sudden derangement of vitals. The resulting hypoxemia was assessed by an arterial partial pressure of O_2 (PaO_2)/fraction of inspired oxygen (FiO_2) ratio (P/F) under 200 mmHg pressure. The lavage was repeated until this targeted hypoxemia (P/F between 100-200 mmHg) was obtained. The injury and ventilation status of the lungs were radiographically monitored by an X-ray device (Mobilett Mira Max Siemens, Erlangen, Germany) at the 30th minute after anesthesia and after the establishment of the lung injury.

To maintain the fluid-electrolyte balance and to supply all metabolic needs, 5% dextrose and Lactated Ringer infusions, and electrolyte replacements with the sodium bicarbonate, potassium chloride, and calcium gluconate or magnesium sulphate were applied, when needed.

At the 12th hour of the experiment, the study was ended by euthanizing the animals with a high dose xylazine and ketamine injection. The euthanized animals were dissected, and both lungs of the three sheep were surgically harvested for histological examinations.

Histological Evaluation

Both lungs were fixed in 10% neutral-buffered formalin solution. The pneumonectomy specimens were collected and processed at the Pathology Laboratory in the Faculty of Medicine of the Near East University. Approximately 3 mm-thick tissue samples were resected from each group, and twenty blocks were sampled from different regions of both lungs. The samples were routinely embedded in the paraffin blocks. These blocks containing the resected materials were serially sectioned at an average thickness of 3-4 µm and the sections were stained with hematoxylin-eosin and examined under a light microscopy. Two histologic slides (4 fields in each) were evaluated from each block. The following criteria were evaluated for histopathological evaluation: atelectatic changes, the presence of perivascular and peribronchial edema, the hyaline membranes and thrombi, the interstitial inflammatory infiltrate, the fibrosis and the necrosis.

Statistical Analysis

The sheep's vital signs and blood gas changes were monitored throughout the study in order to observe the effects of the novel BVM ventilator (ASC-1) and its reliability and safety for ventilation in a normal lung and an injured lung and these findings were compared with the findings from the conventional mechanical ventilator supported sheep. The injury and ventilation status of the lungs were radiographically displayed. The histological evaluation of the lungs focused on any detrimental effects of the new ventilator and the extent of any perivascular and peribronchial iatrogenic injury of the mechanical ventilation.

RESULTS

The chest X-rays of Sheep A and Sheep B are presented in Figure 2. Respiratory findings of lung injury were observed in Sheep B (Figure 2b) in comparison with Sheep A (Figure 2a). Both of the sheep's chest X-ray densities were increased.

Sheep A weighed 55 kg. Following anesthesia induction and endotracheal intubation, Sheep A was connected to a conventional ICU ventilator under a pressure-controlled ventilation mode in accordance with protective mechanical ventilation protocols (FiO_2 of 0.4, tidal volume of 6 mL per kg of predicted body weight, respiration rate of 15-20/min, PEEP of 6 cmH_2O, and inspiratory pressure of 20 cmH_2O at a target plateau lower than 30 cmH_2O). After a stabilization period of 40 minutes, the ABG showed a normal profile at pH: 7.43, pCO_2: 34 mmHg, pO_2: 350 mmHg, lactate concentration: 11 mg/dL, and base excess (BE):-1.7 with normal electrolyte levels. At the end of the study protocol, the euthanized Sheep A showed optimal ABG findings with only slight alterations in their ventilatory parameters according to the outcomes of the hourly follow-ups of gases. A histological analysis of the lungs revealed an interstitial infiltration of inflammatory cells in addition to diffuse lymphoid follicles and focal congestions in the alveolar walls of Sheep A (Figure 3).

Sheep B weighed 50 kg. Following the anesthesia induction and endotracheal intubation, Sheep B was connected to the ASC-1 ventilator with settings at 20 breaths/min, 6 lt/min of oxygen, 6 cmH_2O of PEEP under 26 cmH_2O inspiratory pressure, targeting an optimal blood gas change. After a stabilization period of 40 minutes, the ABG analysis revealed hypokalemia (2.8 mmol/lt K^+) and other electrolytes within the normal range (139 mmol/lt Na^+, 113 mmol/lt Cl^-, 1.24 mmol/lt ionized Ca^{+2}) at pH=7.48, pCO_2=24 mmHg, pO_2=92 mmHg, lactate=6 mg/dL and BE=-5.5 mEq/L. A bolus of 250 mL electrolyte solution mixed with

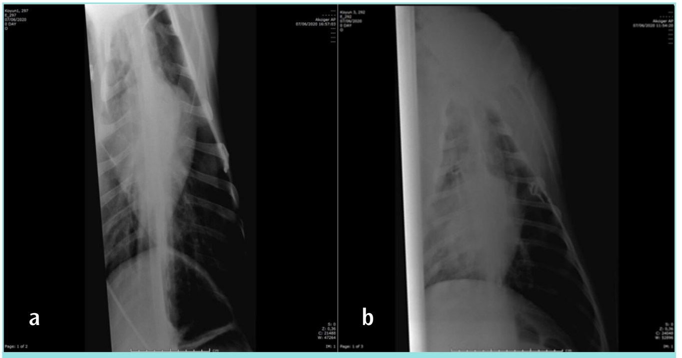

Figure 2. The chest X-rays of the lungs of the sheep under mechanical ventilation. The radiographies of the lungs were obtained after 30 minutes of ventilation with a conventional mechanical ventilator in Sheep A (a) and the novel ventilator (ASC-1) in Sheep B (b).

20 mmol/lt potassium was infused into Sheep B within 30 min, and the respiratory rate was shifted to 15/min and the inspiratory pressure to 24 cmH_2O under 10 lt/min of oxygen. Following these changes, the blood gases after 30 minutes of ventilation were measured at pH=7.27, pCO_2=54 mmHg, pO_2=360 mmHg, lactate=14 mg/dL, BE=-7.5 mEq/L, K^+=3.9 mmol/lt, Na^+=145 mmol/lt, and ionized Ca^{+2}=1.25 mmol/lt. Fluid infusion was sustained at a rate of 250 mL/hr. Then, the parameters were arranged according to the respiratory rate=24/min, oxygen=5 lt/min, inspiratory pressure=28 cmH_2O and PEEP=8 cmH_2O. After one hour, the blood gases were optimal at pH=7.38, pCO_2=46 mmHg, pO_2=208 mmHg, and lactate=12 mmol/lt. Thereafter, the ventilation was sustained with only slight alterations detected in the ventilation parameters at the 12^{th} hour of the procedure in Sheep B. A histological evaluation of the lungs of Sheep B displayed a focal infiltration of inflammatory cells to the interstitial area and congestion of alveolar walls with a mild inflammatory cell infiltration together with patchy, scarce atelectatic and emphysematous foci (Figure 4).

Sheep C weighed 65 kg. Following anesthesia and endotracheal intubation, the animal was kept stable under vital monitoring with ventilation using an anesthesia machine (eternity AM852, Beijing, China). The baseline ventilation parameters were measured as FiO_2=0.5, PEEP=6 cmH_2O, tidal volume=400 mL/min and a respiration rate of 18/min (resulting in a dynamic compliance of 85 mL/cmH_2O and a resistance of 7 cmH_2O/ml/sec). ABG analysis showed pH=7.44, pCO_2=35.2 mmHg, pO_2=300 mmHg, lactate=13 mg/dL and BE=-2.1 mEq/L, with a resultant P/F ratio of 600 mmHg. The values at 1.5 hour from injury induction (described in the methods section) were as follows: FiO_2=0.5, PEEP=6 cmH_2O, tidal volume=380 mL/min, respiratory rate=14/min yielding a dynamic compliance of 31 mL/cmH_2O and a resistance of 18 cmH_2O/mL/sec. The gas exchange values were pH=7.29, pCO_2=47 mmHg, pO_2=85 mmHg, lactate=11 mg/dL and BE=-5 mEq/L. The resultant P/F ratio determined after the induction of the lung injury was 170. Therefore, Sheep C was transferred to the ASC-1 BVM compression ventilator and the parameters were set as 8 lt/min oxygen, a respiration rate of 16/min, PEEP at 10 cmH_2O and an inspiration pressure of 24 cmH_2O. Within 1 hour of ventilation by the ASC-1 ventilator, the ABG values were measured as pH=7.21, pCO_2=50 mmHg and pO_2=68 mmHg. Therefore, the fresh gas rate was increased to 12 lt/min, PEEP=12 cmH_2O, inspiration pressure to 30 cmH_2O, respiratory rate to 25/min, thus an optimal gas exchange was obtained at pH=7.21, pCO_2=56 mmHg and pO_2=86.5 mmHg. At the end of the 12 hour-period, the sheep was euthanized. The histological findings were focal interstitial inflammatory cell infiltration with alveolar congestion, the atelectatic and emphysematous fields observed in micrographs (Figure 5).

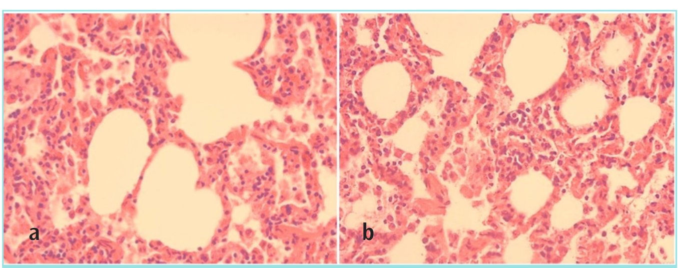

Figure 3. The histological micrographs of the specimens from the right lung (a) and the left lung (b) of Sheep A showing the intensive inflammatory cells (hematoxylin-eosin, x400).

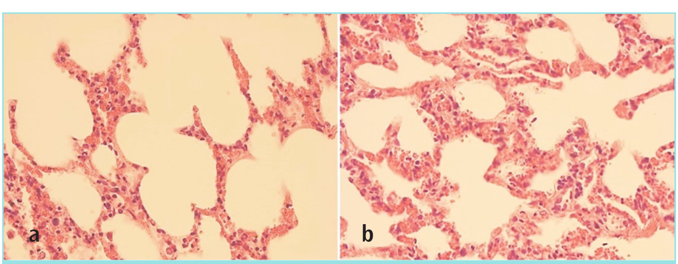

Figure 4. The histological micrographs of the specimens from the right lung (a) and the left lung (b) of Sheep B. (a) In the alveolar wall of the right lung, a vascular congestion and a few inflammatory cells were observed. (b) In the left lung, a vascular congestion and mild inflammatory infiltrates were observed in the emphysematous alveolar wall (hematoxylin-eosin, x400).

There were no differences between the histological findings of Sheep B and Sheep C with regards to the intensity of the inflammatory cell infiltration ratio, or the diffuseness of emphysema and atelectasis.

DISCUSSION

While BVMs are accredited as simple and useful medical devices which are very efficient in supporting the ventilation of patients with respiratory failure,[11] it is appreciated that even an automated BVM cannot replace a conventional ICU ventilator due to their clinical robustness. Mechanical ventilators are also reliable and safe devices which provide precise control over a large number of respiratory parameters; however, they are expensive and take considerable time to manufacture. In addition, in order to operate their system, qualified expertise is also needed. On the other hand, BVM ventilators can monitor a limited number of breathing parameters, and although they are less reliable, they are more cost-effective, easier to operate and even in low resource conditions, their production can be achieved in a short time. In the present experimental study, we evaluated the efficacy, safety and reliability of a novel BVM ventilator (ASC-1) developed for mechanical ventilation in an induced lung injury model and compared normal physiologic lung conditions with altered pathologic lung conditions in sheep. As expected, stabilizing the respiratory parameters of Sheep A was uncomplicated with an ICU ventilator, and stabilizing those of Sheep B and Sheep C's conditions was also achieved successfully with an ASC-1 ventilator, at least clinically.

The indications for using a BVM are hypercapnic respiratory failure, hypoxic respiratory failure, apnea, an altered mental status with

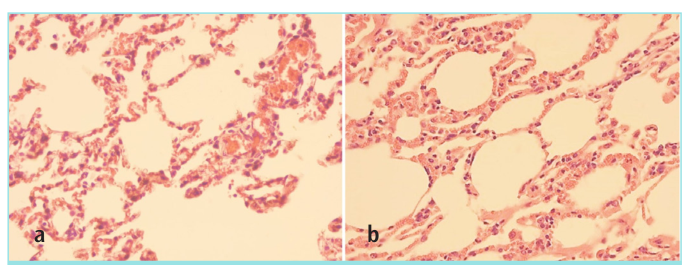

Figure 5. The histological micrographs of the specimens from the right lung (a) and the left lung (b) of Sheep C. (a) In the alveolar wall of the right lung, a vascular congestion and a few inflammatory cells were observed. (b) In the left lung, a vascular congestion and mild inflammatory infiltrates were observed in the emphysematous alveolar wall (hematoxylin-eosin, x400).

the inability to protect the airway, as well as for those patients who are undergoing anesthesia for elective surgical procedures. The contraindications are total upper airway obstruction and an increased risk of aspiration after paralysis and induction.[12] In the present animal model, a lung injury was induced in the lungs of a sheep in order to mimic a respiratory failure in a human. BVM ventilation can be aided by the use of a PEEP valve attached and titrated from 5 to 15 cmH_2O in order to improve oxygenation prior to intubation in patients who are unable to be appropriately pre-oxygenated with standard therapy. Therefore, we kept a PEEP of 6 cmH_2O on the ASC-1 as this pressure can open the lower esophageal sphincter and cause gastric insufflation and vomiting.[12]

Poor manual ventilation performance may depend on failures in delivering the quality of ventilation and a misunderstanding of the patient specific requirements. Unsafe manual ventilation may be alleviated by training reinforcement or accessory safety devices.[13,14] The ventilator used in this study, the ASC-1, is a simple mechanical ventilator into which a manual BVM can be incorporated. The appropriate ventilation may be indicated by electronic vital sign monitoring, the patient's chest rise, their skin color,[13] resistance on bag squeeze according to the patient lung pathology, CO_2 monitoring, and a flashing light on the BVM for rate of breath delivery.[15] Therefore, we compared the histopathological changes in the lung tissue samples of three sheep in order to determine the safety and reliability of the ASC-1 ventilator. The histologic examination of these samples showed a vascular congestion and emphysematous pattern in Sheep B and C's lungs; probably due to the higher driving pressures needed for ventilation with the ASC-1 ventilator. This suggests that even a sheep with an injured lung may be oxygenated by using this device. However, more advanced *in vivo* studies with larger samples are needed to understand how to use this device for the safe and protective ventilation of the lungs.

Study Limitations

Although there are several limitations to the present study including its very small number of experimental animals, this pilot study may facilitate the understanding that these types of simple ventilators can be easy-to-use and safe for ventilation. Even if mechanical ventilators are available, BVM devices may be readily used in emergency rooms and ambulances, as well as in clinics in low/middle-income countries where these devices may be the only option for the patients and clinicians until a mechanical ventilator is available.

CONCLUSION

It may be concluded that these ventilators, including the ASC-1, can be used for a limited period of time for the ventilation of patients with respiratory failure, particularly for the triage of patients where limited resources are available in terms of caregivers and devices, especially in pandemic-like conditions. We are aware of the small number of subjects in this study but this was an experimental pilot study which we consider may be a pioneer for more advanced studies on the exact safety and efficacy of ASC-1 ventilators in critical respiratory care.

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MAIN POINTS

- The recent global COVID-19 pandemic revealed how desperate conditions can result in great pressure due to uncountable patients being in need of mechanical respiratory support in times of shortages of resources or the unavailability of these devices. We now know that an adequate number of affordable, easy-to-use, safe and efficient ventilators are urgently needed in critical respiratory care settings.
- Bag-valve-mask (BVM) compression ventilators can be an alternative in such conditions, since they are low-cost and simple. In the present experimental study, we evaluated the efficacy, safety and reliability of a novel BVM ventilator (the ASC-1), which was developed for mechanical ventilation, in an induced lung injury model and compared the normal physiologic lung conditions with pathologically altered lung conditions in sheep.
- The injury and ventilation status of the lungs of the sheep were examined radiographically and biopsies collected from the lungs were examined histologically. Resulting in no further injury, it may be concluded that BVM compression ventilators can be used for a limited period of time for the ventilation of patients with respiratory failure, particularly for the triage of patients where limited resources are available in terms of caregivers and devices, especially in pandemic-like conditions.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Committee of the Near East University for the Animal Care and Use (approval number: 2020/116, date: 20.05.2020).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H.G., G.E., Ç.G., Concept: A.H.G., T.Ö., Design: T.Ö., G.E., Ö.T., G.M., Data Collection and/or Processing: A.H.G., Ç.G., H.Ö., Ö.T., G.M., Analysis and/or Interpretation: A.H.G., G.E., Ç.G., Ö.T., G.M., Literature Search: A.H.G., G.E., Writing: A.H.G., T.Ö., G.E., H.Ö.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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