Preclinical evaluation of a low-cost mechanical ventilator

Evaluación preclínica de un ventilador mecánico de bajo costo

Randall Chacón-Cerdas[1], Adrián Quesada-Martínez[2], Aníbal Ruíz-Barquero[3], Roberto Estrada-McDermott[4]

Chacón-Cerdas, R; Quesada-Martínez, A; Ruíz-Barquero, A; Estrada-McDermott, R. Preclinical evaluation of a low-cost mechanical ventilator. *Tecnología en Marcha*. Vol. 37, Nº especial. 30 Aniversario del Centro de Investigación en Biotecnología. Noviembre, 2024. Pág. 200-214.

https://doi.org/10.18845/tm.v37i9.7624

1 Biotechnology Research Center, Costa Rica Institute of Technology, Costa Rica.
rchacon@itcr.ac.cr
https://orcid.org/0000-0002-5364-4649

2 School of Material Science and Engineering, Costa Rica Institute of Technology, Costa Rica.
adquesada@itcr.ac.cr
https://orcid.org/0000-0002-5975-4195

3 School of Electronic Engineering. Costa Rica Institute of Technology, Costa Rica.
aniruiz@itcr.ac.cr
https://orcid.org/0000-0003-1300-3887

4 Large Animal Hospital, National University of Costa Rica, Costa Rica.
roberto.estrada.mcdermott@una.cr
https://orcid.org/0000-0002-1739-1461

Keywords

Oxygen saturation; respiratory rate; COVID-19; acute lung injury.

Abstract

The COVID-19 pandemic caused by the SARS-CoV-2 virus placed the global health systems in crisis due to the shortage of materials, devices, and emergency ventilation equipment for the Intensive Care Units (ICU). Low-cost ventilator designs emerged as a necessary option for many countries seeking to ameliorate the impact and demands for respiratory equipment. At the Costa Rica Institute of Technology (ITCR), a prototype mechanical ventilator (TEC-Ventilator) was developed with the following features: the capability to achieve a tidal volume of 250 to 800 mL with controlled increments of 50 mL, a respiratory rate of 10 to 30 breaths/min, a variable *Inspiration:Expiration* ratio from 1:1 to 1:5, and a fraction of inspired oxygen (FiO_2) of 21-70%. The safety and effectiveness of the device were evaluated in a preclinical study with eight pigs induced with acute lung injury, seven of which met the conditions for ventilator performance evaluation. Its performance was compared to that of a commercial ventilator used as a control by analyzing the statistical variation of parameters such as O_2 SAT, pO_2, pCO_2, pH, HCO_3^-, base excess, mean arterial pressure (MAP), respiratory rate (RESP), and heart rate (HR). It was found that the TEC ventilator provided stability of parameters equivalent to the commercial control. Additionally, the TEC ventilator did not cause complications and effectively managed respiratory failure in 100% of the evaluated subjects.

Palabras clave

Saturación de oxígeno; frecuencia respiratoria; COVID-19; lesión pulmonar aguda.

Resumen

La pandemia de COVID-19 provocada por la infección del virus SARS-CoV-2 colocó en crisis los sistemas de salud del mundo debido a la escasez de materiales, dispositivos y equipos de ventilación de emergencia para las unidades de cuidados intensivos (UCI). El diseño de dispositivos de ventilación de bajo costo surgió como una opción necesaria para los países con recursos limitados para satisfacer las demandas críticas de equipos respiratorios. En el Instituto Tecnológico de Costa Rica (ITCR) se desarrolló un prototipo de ventilador mecánico (TEC-Ventilador) que reunió las siguientes características: capacidad de 250-800 mL de ventilación con incrementos controlados de 50 mL, frecuencia respiratoria de 10 a 30 respiraciones/min, relación *Inspiración:Espiración* variable de 1:1 a 1:5, y una fracción inspirada de oxígeno (FiO_2) de 21-70%. Se evaluó la seguridad y efectividad del dispositivo en un estudio preclínico con ocho cerdos inducidos con una lesión pulmonar aguda, de los cuales siete reunieron las condiciones para la evaluación del desempeño del ventilador. Se comparó su rendimiento con el de un ventilador comercial control mediante el análisis estadístico de la variación de los parámetros de O_2 SAT, pO_2, pCO_2, pH, HCO_3^-, exceso de base, presión arterial media (PAM), frecuencia respiratoria (RESP) y frecuencia cardíaca (HR); encontrándose que el ventilador TEC proporcionó estabilidad de parámetros equivalentes comparado con el control comercial. Se encontró además que el ventilador TEC no causó complicaciones y manejó eficazmente la insuficiencia respiratoria en el 100% de los sujetos evaluados.

Introduction

The COVID-19 pandemic caused by SARS-CoV-2 has been one of the most relevant health emergencies in the modern era [1]. As of September 2022, 613,942,561 million people were officially reported as infected, causing more than 6.52 million cumulative deaths [2].

Health systems worldwide were compromised by the scarcity of resources to deal with infections distributed in waves due to virus variants that circulate almost immediately among symptomatic and asymptomatic patients [3]. One of the main limitations was the ICUs (Intensive Care Units) capacities, since they must add numerous COVID-19 patients to the routine cases they already treat. Statistics indicate that 14-17% of COVID-19 patients have required ICU care [1].

In response to infrastructure, supplies, and equipment challenges, some governments opened new hospitals, and others modified them to expand their capacity to attend to these patients. They also required ventilators, personal protective equipment, and diverse medical materials [4]. With limited equipment and the associated cost of commercial ventilators, local open-source projects arose to modify and manufacture this type of device to complement the demand [5], [6]. These devices must meet international safety and effectiveness requirements to ensure that their operation is stable and that their use in patients leads to more benefits than associated complications, characteristics generally defined as the minimum acceptable clinical standards [7]. Their ventilation range and versatile configuration classify them as equipment to treat severe cases in the ICU (Full featured) [5]. Although the global vaccination and the coordinated actions of the national health system have managed to control this pandemic, these types of equipment will always be necessary to deal with potential outbreaks or even new respiratory emergencies.

This preclinical study evaluates the safety and effectiveness of a low-cost mechanical ventilator designed and assembled at the Costa Rica Institute of Technology (TEC-ventilator or TEC-V) and tested in pigs with induced acute lung injury.

Methodology

Ventilator. The ventilation mechanism was based on an *Ambu* bag-type manual resuscitator [8]. It features two metal springs connected to a plastic syringe head that pushes the *Ambu* bag around and simulates breathing. The adapted tubes allow oxygen transport through the system and the patient's intubation by matching with routine accessories. The electronics and electrical parts include solenoid valves, power sources, a touchscreen, and flow sensors (Figure 1).

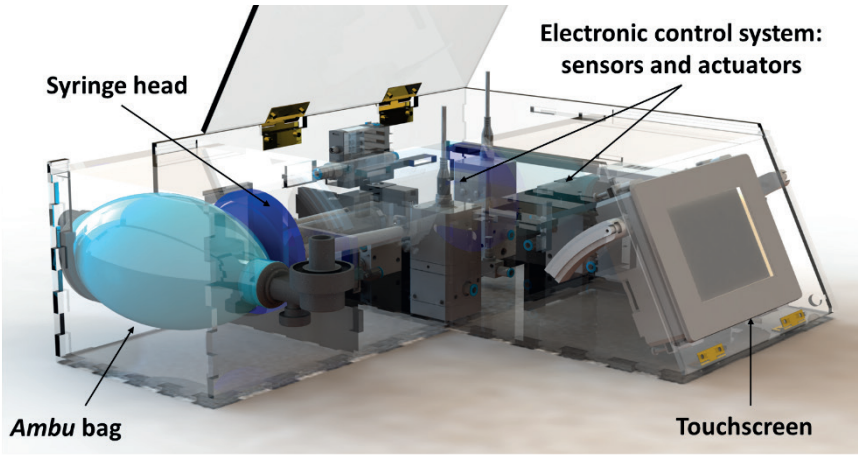

Figure 1. Isometric frontal view of the TEC-Ventilator.

The device provides the following specifications: variable breathing rate from 10 to 30 breaths per minute, tidal volume from 250 to 800 mL with 50 mL increased controlled automatically, the fraction of inspired oxygen (FiO_2) varies from 21-100% and variable Inspiration to expiration ratio (I:E) from 1:1 to 1:5.

Animal model. Eight four-week-old domestic pigs (*Sus scrofa domesticus*) were used as animal models for *ex vivo* testing. The weight ranged between 50-60 kg, and the same proportion of females and males was maintained. The sample size was calculated using the maximum estimation error of the upper limits of the risk values III and IV, established by the Physical Status Scale of the American Society of Anesthesiologists (ASA) [9] and considering variations implicit in previous studies [10]. A 95% confidence level was selected for estimating the proportion of events assuming a binomial distribution. The animals were kept in quarantine in the Large Animal Hospital of the School of Veterinary Medicine facilities at the National University of Costa Rica (UNA), where the preclinical study was carried out. The care, handling, and preclinical procedure were performed with the approval of the UNA´s Institutional Committee for Bioethics and Animal Care (CBBA, for its acronym in Spanish), authorization N° UNA-EMV-CBBA-ACUE-006-2020.

Induction of Acute Lung Injury (ALI). To emulate the pulmonary affections reported in patients with COVID-19, an injury test was established to evaluate the ventilator's performance in critical care conditions. To reach the typical life-threatening status, oxygen saturation was monitored until the lung edema conducted the O_2 SAT value under 70% (hypoxemia) [11] which reflects a disruption in the endothelial and epithelial barriers associated with ALI syndrome [12] commonly presented in ICU patients [13]. For this, a mixture of features reported by previous procedures was used to define the injury induction [14], [15], [16]. The animals were sedated intramuscularly (in the neck) using xylazine (3 mg kg^{-1}), ketamine (10 mg kg^{-1}), and butorphanol (0.2 mg kg^{-1}); followed by induction with intravenous ketamine (5mg kg^{-1}). Next, the endotracheal tube was placed, and the pig was connected to assisted ventilation (Matrx Ventilator, 3000) with inhalation anesthesia adding isoflurane (3%), in addition to a continuous infusion (CRI) of ketamine (3 mg kg^{-1} h^{-1}), xylazine (1 mg kg^{-1} h^{-1}) and butorphanol (0.2 mg kg^{-1} h^{-1}). Vital signs were continuously monitored (Biocare Monitor im12) to check the healthy condition of the animal. The procedure for lesion induction is as follows:

1. The subject's vital signs were checked using arterial gases (pH, pO_2/pCO_2, Base Excess, HCO_3^-, O_2 Saturation, and Lactate) determined on the I-Stat device (IDEXX).
2. The subject's vital signs were double-checked using a multiparameter monitor (systolic pressure, diastolic pressure, heart rate, respiratory rate, and oxygen saturation).
3. The subject's viability for the induction of the lesion was verified by the criterion of the head veterinarian after evaluating the pig's response to anesthesia and the stability of the vital signs.
4. The subject's head was maneuvered to place it outside the stretcher and in an accessible position (slightly raised) to favor fluid entry into the lungs.
5. The subject was disconnected from the ventilator. A funnel attached to a flexible hose (1/4¨ in diameter and 60 cm long) was placed inside the trachea that communicates directly with the subject's lungs.
6. Ringer's lactate solution (1.0-1.5 L) was gradually poured into the animal's lungs, attaching a flexible hose to the tracheal tube, and placing the funnel one meter above the animal. Decantation was stopped by confirming that the respiratory system was full of fluid (keeping the fluid level stable).

7. The subject´s head was maneuvered to place it in an accessible position (slightly inclined) to favor the exit of the fluid from the lungs.
8. After approximately 5 minutes of keeping the fluid inside the animal's lungs, the funnel was removed, and Ringer's lactate was removed alongside the alveolar surfactant using a suction pump (Medela, Basic) connected to the same hose by which Ringer's lactate was initially introduced at an approximate pressure of 250 mm Hg. This process usually took 30 seconds.
9. Once the first volume of lactate was withdrawn, a pause of around 5 min was given, where the animal was ventilated and stabilized for the subsequent lavage. Once stabilized and authorized by the veterinarian, the second wash was carried out, repeating the technique described above.
10. Once the second volume of lactate was withdrawn, the feasibility of continuing with the injury (third alveolar lavage) or the diagnosis of acute lung injury was confirmed based on the criteria of the veterinarian, the parameters of the monitor, and the I-stat measurements (in most of the animals at the second wash they presented changes suggestive of acute lung injury).
11. If the veterinarian diagnosed the induced lung injury, arterial blood samples were collected to quantify arterial gases using the I-Stat device, and the procedure of ventilation continued.
12. In cases where an additional wash was required, the procedure described above was repeated.

Safety and effectiveness evaluation. Animals diagnosed with lung injury were connected to the TEC-ventilator. After 10 minutes, the ventilator was set to 100% oxygen, and the animal was ventilated. Using the multiparameter monitor, the following parameters were monitored every 5-10 minutes and throughout the intervention: systolic blood pressure (BP), diastolic blood pressure (DP), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RESP) and blood oxygen saturation (O_2 SAT). After 20-30 minutes of ventilation, a blood sample was taken, and arterial gases pCO_2 (mmHg), pO_2 (mmHg), base excess (mmol L^{-1}), HCO_3^-mmol L^{-1}), O_2 SAT (%), and Lactate (mmol L^{-1}) were measured. Arterial blood gas quantification was repeated after 40-50 minutes of ventilation. Each animal was monitored for approximately 60 minutes until its condition was confirmed to be stable or irregular. Once the performance of the TEC-ventilator was monitored, the animal was euthanized using sodium pentobarbital at a dose of 75 mg kg^{-1}.

Safety endpoint. The device's safety was evaluated by recording complications associated with the use of the ventilator and monitoring fatal and non-fatal events during the intervention. Fatal complications were interpreted as events that would lead to death, are life-threatening, require hospitalization or prolonged hospital stay, and generate persistent or significant disability or incapacity.

Effectiveness endpoint. The device's effectiveness was determined by the percentage of subjects who managed to overcome the crisis due to the respiratory support function of the device. Three categories were established to measure this parameter: 1) Efficient: when the animal managed to overcome the crisis without problems and with only the use of the TEC-ventilator; 2) Partial failure: when the animal required additional assistance apart from the TEC-ventilator to overcome the crisis, and 3) Total failure: when the TEC ventilator failed to assist the animal, and therefore the subject died.

Statistical analysis. Descriptive statistics were applied to characterize the percentage of patients who suffered fatal and non-fatal complications related to ventilator use and effective respiratory assistance. If fatal and non-fatal adverse events related to ventilator use occurred, the percentage of cumulative risk would be calculated through the non-parametric Kaplan-Meier survival test (95% confidence, two-tailed) as a function of the time of the event. Quality control of the physiological parameter data was performed by checking the statistical assumptions of homogeneity of variances (Levene's test) and normality of data/residues (Anderson-Darling test, Ryan-Joiner test, Kolmogoro-Smirnov test). The preceding is to select the appropriate statistical comparison tests of parametric means.

In the case of arterial gases and vital signs of MAP, HR, and RESP, a one-way ANOVA (ANOVA F or ANOVA Welch, depending on the fulfillment of statistical assumptions) was applied to determine significant differences between the average values of the physiological parameters monitored at each stage. In the cases in which the ANOVA value gave significant differences ($p < 0.05$), a Tukey or Games Howell comparison of means was performed (according to the fulfillment of statistical assumptions). All tests were performed considering a confidence level of 95% ($\alpha = 0.050$) using the statistical software Minitab 19.1.1 [17].

Results and discussion

Safety and effectiveness evaluation. The use of the device was considered safe (Figure 2) since it did not produce complications of any type (fatal or non-fatal) in the subjects evaluated. Because the incidence of complications was 0%, the cumulative risk index was not calculated using the Kaplan-Meier survival test, reported as 0%. Regarding the level of effectiveness (Figure 3), it was found that in 100% of the cases, the animal was assisted by improving their respiratory condition, and using another respirator or alternatives was not necessary, so the percentage of partial or total failure was 0%. It is essential to mention that seven of the eight subjects evaluated showed adequate physiological conditions for the induction of lung injury and subsequent ventilation using the TEC-ventilator (TEC-V). One of them (pig 7) developed malignant hyperthermia after lung injury and was not included in the post-injury physiological measurements, as ventilator performance could not be compared with the other data from the individuals without malignant reaction to injury. The power curve for one-proportion estimation and the details of the vital signs monitored for each subject are presented in the supplementary materials.

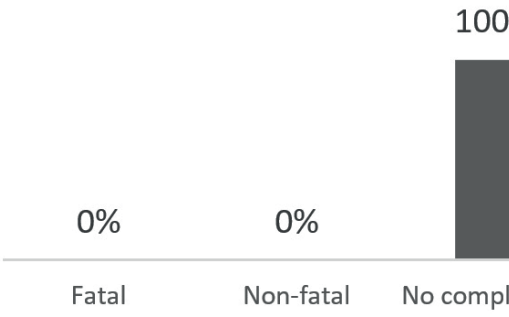

Figure 2. Percentage of animals with complications caused by the TEC-ventilator according to the type of complication.

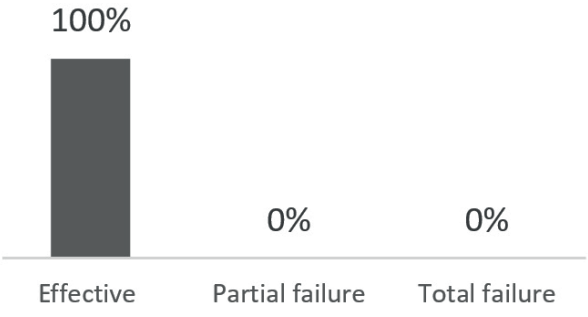

Figure 3. Percentage of animals according to the effectiveness of ventilation assisted by the TEC-ventilator.

Regarding the quality control of the data evaluated through the fulfillment of the statistical assumptions, it was obtained that, for most of the physiological parameters, the required homogeneity of variance was fulfilled, confirmed by the Levene´s test or the Multiple Comparisons

tests ($p > 0.050$), except for oxygen saturation (O_2 SAT), in which case the normality of the data allows Welch ANOVA + Games-Howell test. In the case of normality, it was also met in most cases ($p > 0.050$) when the data or residuals were evaluated using the Anderson Darling, Ryan-Joiner, or Kolmogorov Smirnov test, except for the data series of pO_2 (Post-injury 40-50 min TEC-V) and RESP (Pre-injury TEC-V, Pulmonary Injury and Post-injury 20-30 min TEC-V); however, it did not affect the selection of the inferential parametric test for these parameters since homoscedasticity was met and the central limit theorem was assumed for small samples that would potentially meet normality by increasing the sample size. The physiological parameters monitored (Figures 4, 5, 6) support the safety and effectiveness results.

Oxygen saturation (O_2 SAT). It measures the amount of oxygen in the bloodstream. Healthy level is between 96% and 100% in anesthetized patients, but animals with lung disease have a lower percentage unless supplemental oxygen is used [18]. Levels below 90% are considered hypoxemia, and lower than 80% is known as severe hypoxemia. [19]. The induced injury managed to place the animals in severe hypoxemia in all cases (average O_2 SAT = 67.13%) requiring the use of the ventilator to assist the patient's breathing. The recovery of the oxygen level in the blood brought to typical values by the TEC-ventilator after the lung injury (96.67-99.00%) was observed (Figure 4a), which remained at adequate levels for about one hour. The assisted oxygenation values achieved after the damage were statistically equal to pre-injury levels, as measured both on the commercial ventilator (Commercial V) and the TEC-ventilator. The observed changes in ventilation were rapid, as expected with assisted breathing equipment.

Oxygen pressure (pO_2). Another critical parameter monitored during the intervention was arterial oxygen pressure (Figure 4b). Its value reflects the state of the oxygen-capturing function of the lung [20]. In the healthy lung, the arterial partial pressure of oxygen (pO_2) is thought to remain almost constant [21]. Respiratory paO_2 oscillations of less than 16 mmHg have been detected in animals with intact lungs when abnormally large tidal volumes (TV) greater than 20 mL kg^{-1} or even 30 mL kg^{-1} were administered during mechanical ventilation [21]. Large swings in pO_2 have been observed on injured lung [22] as variable intra-respiratory shunting caused by cyclic atelectasis, causing pO_2 to increase during inspiration and decrease during expiration. According to the results, the oxygen pressure determined by both ventilators before lung injury indicated statistically similar values representative of a healthy lung ventilated at 100% oxygen (315.60-349.29 mmHg); when inducing lung injury, a significant decrease was observed, reaching values practically ten times lower (35.63 mmHg). With the ventilation assisted by the TEC-ventilator (100% oxygen) after the lung injury, the pressure was recovered over time, observing an incremental trend. After 40-50 minutes, there was a significant positive difference between the value at that time (153.67 mm Hg) and the representative at the time of injury. If this trend continues, values higher than those recorded 50 minutes post-injury could be recovered.

Carbon dioxide pressure (pCO_2). When ventilation increases in the body, the concentration of CO_2 in the extracellular fluid decreases since CO_2 is lost through the lungs [20]. The CO_2 typically dissolved in body fluids is 1.2 mmol L^{-1}, corresponding to a partial carbon dioxide (pCO_2) pressure of approximately 40 mmHg [23]. When the metabolic production of CO_2 increases, the pCO_2 will also increase simultaneously [20], [24], [25]. Figure 4c (pCO_2) presents the summary of the CO_2 partial pressure monitored during the intervention. It was observed an increasing trend in the CO_2 partial pressure. However, this increase did not become statistically significant at any monitoring points. In addition, it ranged in moderate values between 34.02-47.20 mmHg, which is associated with the effectiveness of the ventilation process, which manages to modulate CO_2 through the inspiration/expiration circuit. This positive action of the ventilation function mitigated the effect of lung injury on this parameter.

pH. The fluctuation of O_2 and CO_2 gases, measured as the resulting arterial pressure, produces changes in the body's acid-base balance, which is reflected in variations of blood pH [24]. In mammals, the average blood pH is about 7.4 [26] for the proper functioning of proteins, cell components and its homeostasis [26], [27]. The body carries out a series of modulations to balance the pH, including lung function to increase the elimination of CO_2 [30], some buffering chemical reactions (bicarbonate buffer system), as well as contributing to storage in red blood cells [28],[29], [30]. In the case of mechanical ventilators, the efficiency of the acid-base control respiratory mechanism is 50-75%; that is, it has a feedback gain of 1 to 3. This translates into a drop in pH of 7.4 to 7.0, and the lung can compensate up to 7.2 or 7.3. In general, the overall buffering capacity of a ventilator can be 1-2 times higher than some chemical extracellular fluid buffers combined [29].

The intervention results show that before the induction of the injury, both the commercial ventilator and the TEC-ventilator achieved hyperoxygenation (ventilation at 100% oxygen), translated into pH values statistically higher than those obtained in the lung injury. This value falls statistically at that point, decreasing as time increases (Figure 4d). This event is also justified by the results of the CO_2 partial pressure (Figure 4c), where the tendency is for the CO_2 level to increase and, consequently, produce a drop in the blood´s pH. However, these values are not critical or did not show an essential alteration in the acidification of the organism despite the significant statistical differences found.

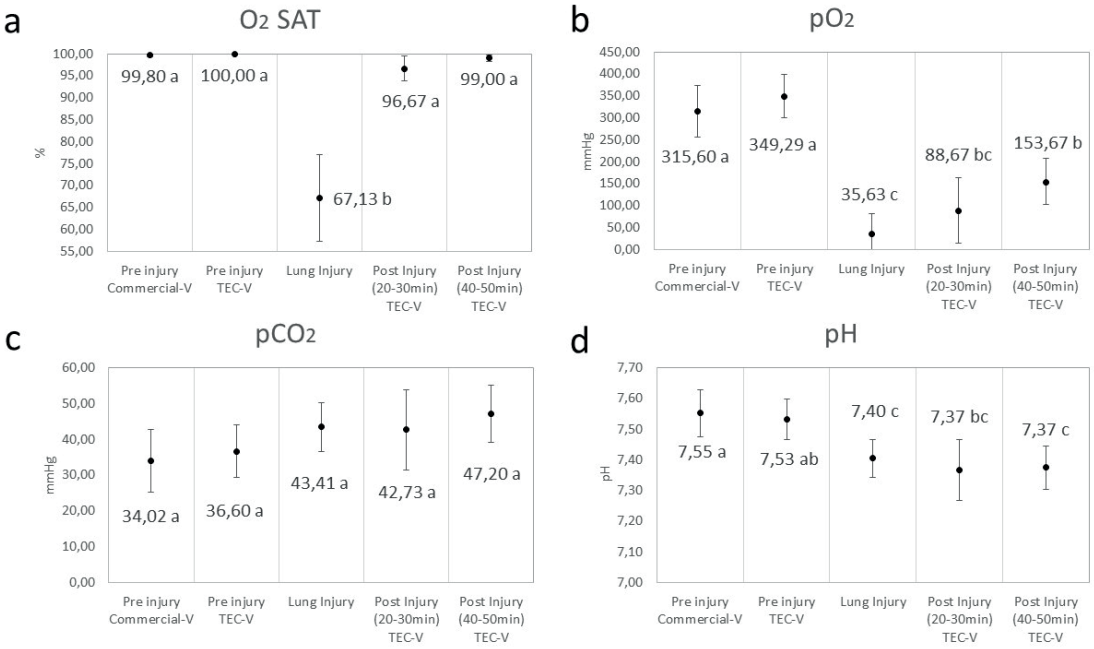

Figure 4. Physiological gas and pH parameters (mean ± SD) in pigs (n = 7) before and after lung injury and treated with the TEC-ventilator (TEC-V) or with the commercial ventilator. a) Blood oxygen saturation (O_2 SAT), b) oxygen pressure (pO_2), c) CO_2 partial pressure (pCO_2), d) pH. The 95% confidence interval is shown. Different letters indicate a significant difference ($p < 0.050$) (pairwise comparison). O_2 SAT by One-way ANOVA-Welch and Games-Howell test, other variables by One-way ANOVA-F and Tukey test.

Bicarbonate ion (HCO_3^-). The ability of HCO_3^- to undergo pH-dependent conversions is critical to its physiological role in maintaining the concentration of H^+ within a normal range and eliminating the significant accumulation of acids produced daily in the body [31]. It consists of an aqueous solution that contains a weak acid, such as H_2CO_3, and a bicarbonate salt, such as N_aHCO_3 [28]. Various reactions occur within the body so that the concentration of H_2CO_3 decreases,

which favors the reaction of H_2O and CO_2 to replenish the amounts of H_2CO_3 and favoring the elimination of CO_2 by the lung. It also decreases the blood levels of CO_2 and the excess of HCO_3^- in the blood; then, it is compensated by increasing its renal excretion [28]. Figure 5a shows that the variation in the intervention in this physiological parameter followed a very similar trend to that of CO_2 partial pressure and pH due to the previously explained relationship between all these parameters in search of physiological compensation.

Base excess. The same trend in pH and bicarbonate anion concentration was observed in base excess (Figure 5b) since it is also linked to blood CO_2 partial pressure. Base excess is the amount of acid required to restore one liter of blood to its normal pH at pCO_2 40 mm Hg and it is also expressed as mEq L^{-1}. A positive base excess would indicate a metabolic alkalosis, adding acid to return the blood to normal pH. A negative base excess value would indicate metabolic acidosis, meaning that acids must be removed to return the blood to normal pH [32].

The values observed in the results show that after the lung injury, there was a period where metabolic acidosis (-1.00 mmol L^{-1}) occurred due to the excess of CO_2 which accumulated in the body and subsequently recovered due to the buffering effect of the organism to positive values (2.17 mmol L^{-1}), which also evidences the respiratory assistance provided by the TEC-ventilator in the evacuation of CO_2.

However, the value measured for base excess does not depend exclusively on the variation of CO_2 in the body [32]. For this reason, the experimental values do not change immediately in correspondence with lung injury, as we observed in the case of pH and the bicarbonate ion. Base excess comprises blood hemoglobin concentration, plasma protein and phosphate concentration, and the ion concentration itself [33], [34].

Lactate. Regarding lactate, it is known that the increase in the levels of this metabolite is used as a marker of tissue hypoxia; if it is not resolved, it leads to the development of organ dysfunction-failure [34]. Lactate results from anaerobic metabolism [35]; therefore, it is necessary to improve the oxygen supply to the patient's tissues with increased lactate levels to improve the outcome of critically ill patients. Several studies aimed at improving tissue oxygenation in patients with increased lactate levels (hyperlactatemia) have decreased morbidity and mortality [36]. It can also predict mortality after severe blunt traumas [35], [37] and is associated with the degree of organ failure in patients with septic shock [38].

The results obtained (Figure 5c) in this study showed normal lactate levels close to 2 mmol L^{-1} when the patient was ventilated at 100% oxygen with the commercial ventilator and with the TEC-ventilator before the induction of the injury (2.32-2.28 mmol L^{-1}). The values of the metabolite evolved to 3.10 mmol L^{-1} once the damage was induced and reached the maximum of 5.38 mmol L^{-1} 20-30 minutes after the injury due to the deficiency of oxygen that is transported to the tissues; it is relevant to indicate that this change is not immediate due to the body's compensation. Therefore, the effect was delayed in time. However, at 50 minutes, it was observed that TEC ventilator-assisted oxygenation could begin to lower blood lactate levels (3.91mmol L^{-1}). Although the changes in the average values did not show a significant statistical difference (due to the variability in the measurement), the values do show relevant trends for the attending veterinarian, which allows modulating respiratory assistance to stabilize the patient (Figure 5c).

Mean Arterial Pressure (MAP). It is the diastolic and systolic pressure ratio [39]. Respiratory failure is an arterial oxygen pressure below 60 mmHg or carbon dioxide pressure above 45 mmHg. The clinical manifestations of an imminent respiratory failure are the increased breathing frequency and the acceleration in the respiratory effort [40].

Blood pressure was modulated to stabilize the pigs during and after the induction of the injury; on some occasions, the momentary pressure drop was below 50 mmHg (hypotension) because of the lung injury. It required the application of lobutamine to avoid adding physiological stress to the animal. The results show (Figure 5d) that pressure compensation allowed the animals to be stable. It is essential to keep in mind that the vital signs of the pigs are very similar to those of humans since they present a heart rate of 58 to 86 beats min^{-1}, oxygen saturation of 95 +/-5 percent, blood pressure of 100/60 mmHg +/- 10 mmHg, and the temperature parameter around 39°C +/- 5°C [41].

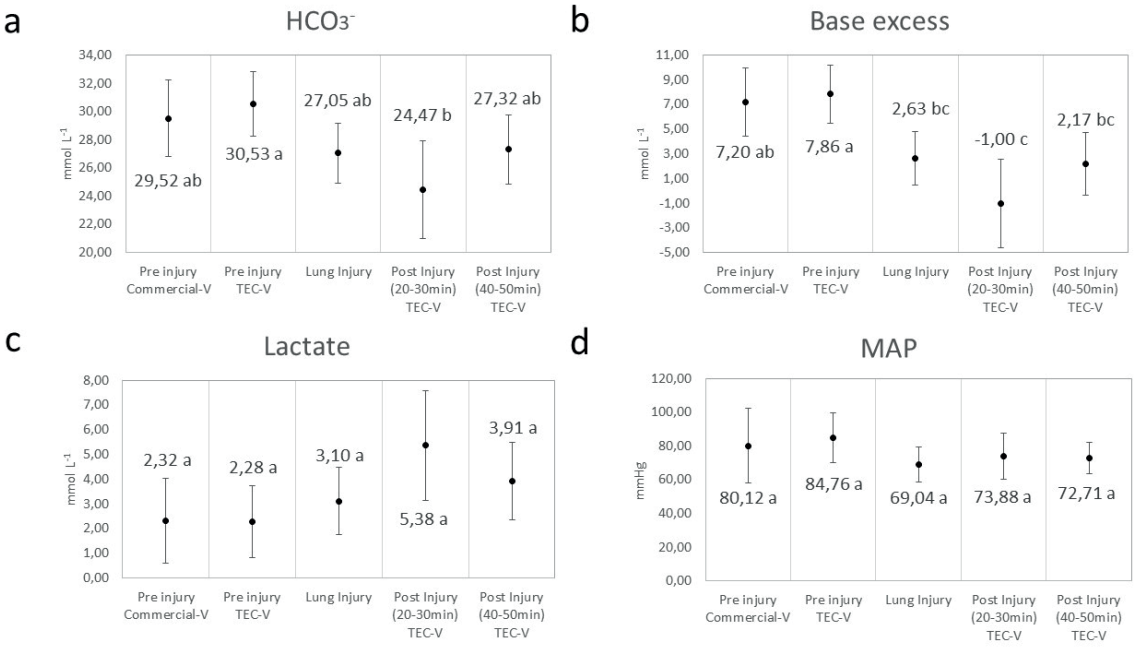

Figure 5. Other physiological parameters (mean ± SD) in pigs (n = 7) before and after lung injury and treated with the TEC-ventilator (TEC-V) or with the commercial ventilator. a) Bicarbonate (HCO_3^-), b) base excess, c) lactate, d) mean arterial pressure (MAP). The 95% confidence interval is shown. Different letters indicate a significant difference ($p < 0.050$) (pairwise comparison). One-way ANOVA-F and Tukey test.

Respiratory Rate (RESP). The respiratory rate plays an essential role in the CO_2 concentration of the extracellular fluid [42] [43]. Alveolar ventilation can modulate the concentration of CO_2, but it, in turn, is affected by the concentration of hydrogen ions. The reason is a decrease in the partial pressure and amount of O_2 in the blood when the pH decreases; therefore, the respiratory system is forced to improve ventilation through an increase in respiratory rate [43], [44]. Under normal conditions, the respiration rate of juvenile pigs ranges from 25-40 breaths min^{-1} [45].

Through the assisted ventilation function, the respiratory rate was modulated to help the animal receive enough oxygen to regulate his physiological level at adequate points and thus stabilize the changes in the acid-base. This was achieved by controlling the operation of the ventilator and thereby maintaining the frequency. The TEC ventilator proved efficient in modulating this parameter before and after the lung injury and was statistically equal to the commercial ventilator before the injury (Figure 6a).

Heart Rate (HR). Changes in HR are used to diagnose multiple disorders by reflexing the direct/indirect effect of physiological stress and the compensation by the autonomic nervous system [46], [47], [49]. The increase in heart rate compromises cardiac output due to the rise in the amount of oxygen consumed by the myocardium, while the reduction in the diastolic time can

lead to a decrease in the pumped blood volume [47]. The heart rate of animals can vary in a range of 60 to 150 beats min^{-1}, depending on factors such as the size of the animal, exercise, or emotional arousal [48]. In weaned pigs, the HR ranges from 90 to 100 beats per minute [45].

In the case of this study, respiratory rate monitoring functioned as a marker of stress and as a parameter to measure anesthesia in the animal. No significant variation in beats per minute was observed during the monitoring. The average values ranged between 98-75 and were helpful in the anesthesia regulation process, mainly during the induction of lung injury (Figure 6b).

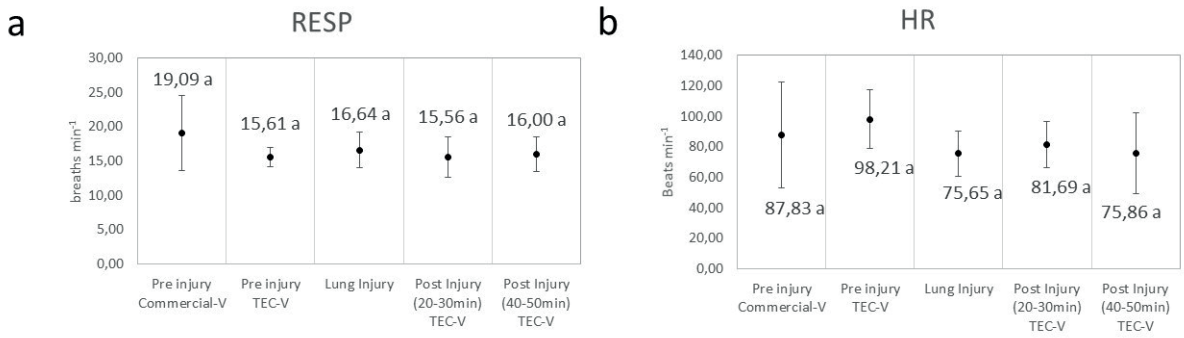

Figure 6. Respiratory and heart rate (mean ± SD) in pigs (n = 7) before and after lung injury and treated with the TEC-ventilator (TEC-V) or with the commercial ventilator. a) respiratory rate (RESP), b) heart rate (HR). The 95% confidence interval is shown. Different letters indicate a significant difference ($p < 0.050$) (pairwise comparison). One-way ANOVA-F and Tukey test.

Overall, the TEC-ventilator demonstrated that its operation was equivalent to the commercial control ventilator when statistically comparing the compensation of the vital signs of the evaluated animals. Additionally, the operation and handling of the device did not present a limitation for the attending veterinary physician, who had experience using this type of device. According to its regulatory parameters, indication of use, and current performance, this device could be classified as Type III. Its advantage over commercial ventilators within this category lies in its manufacturing cost (8,500 USD), which is less than half that of some commercially available models, and the potential local availability of units. Since it is an expensive resource, health centers generally do not maintain idle units.

The reason for using an animal model for evaluating medical devices, drugs, and therapies for human health, is based on the similarity between animals and humans. Although they do not fully replicate human conditions, they allow the application of procedures where the results obtained can be largely inferential to human beings [49], [50] and thereby reduce the risk of offering products and services to the market that would present a potential threat to people [51]. An example is a porcine model, which has a high anatomical, histological, and physiological similarity to the human being, which is particularly useful in the field of respiratory medicine because of the structure and distribution of the respiratory tract [52], [53]. This is critical for our objective when testing the safety and effectiveness of the ventilator, where intubation of the specimen is required, being one of the scenarios where animal models to date are difficult to replace.

Conclusions

The device under evaluation proved to be safe as it did not cause harm to the animals; the percentages of fatal and non-fatal complications caused by the ventilator was 0% in both cases. The TEC-ventilator was shown to be effective in managing respiratory failure in 100% of animals

with induced lung injury and ventilated with the TEC device. Compared to the commercial ventilator used as control, it demonstrated the ability to regulate monitored parameters to equivalent levels, as well as ease of use and the advantage of a lower price.

Supplementary material

Data from individual monitoring per animal is summarized in a multiparameter graph. Overall behavior and tendencies are detailed per animal since variations are expected regarding metabolic conditions. It will be provided under proper request.

Author Contributions

Conceptualization, A.Q-M, A.R-B, R.E-M and R.C-C.; methodology, R.E-M and R.C-C; formal analysis, R.E-M and R.C-C.; investigation, A.Q-M, A.R-B, R.E-M and R.C-C.; data curation, R.C-C and R.E-M.; writing—original draft preparation, R.C-C.; writing—review and editing, A.Q-M, A.R-B, R.E-M and R.C-C.; project administration, A.Q-M.; funding acquisition, A.Q-M. All authors have read and agreed to the published version of the manuscript.

Funding

This project was funded by Vicerrectoría de Investigación y Extensión, Instituto Tecnológico de Costa Rica. Grant VIE-5401-1490-2701 Special edition COVID-19 projects.

Institutional Review Board Statement

The animal study protocol was approved by the Institutional Committee for the Bioethics and Animal Care (CBBA for its acronym in Spanish) of the National University of Costa Rica (UNA), Veterinary Sciences (protocol code UNA-EMV-CBBA-ACUE-006-2020, 03 September 2020).

Acknowledgments

The authors thank the M.D. Carlos Estrada-Garzona for his support in human pneumology and critical care consultancy; MBA. Adriana Nanne-García for the administrative and strategic support for the link with the UCIMED alliance (University of Medical Sciences); the technical team of research assistants from the TEC, especially Eng. Fabio Rojas-Fernández, Eng. Anny Alfaro-López, Eng. Hamlet Loría-Mesén, Eng. María José Araya-Cárdenas, Eng. Luis Ramírez Anchía, and Eng. Wilson Bermúdez Campos and the veterinary team from the UNA Large Animal Hospital.

Conflicts of Interest

The authors declare no conflict of interest.

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