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Research Article

Development of a Porcine Model for the Testing of the RapidVent Emergency Ventilator for the Treatment of COVID-19

Sarah A Womack[1], Eliot Bethke[2], William P King[2], Derek J Milner[1], Marcello Rubessa[1], Paula Viero Marchioretto[1], Clifford F Shipley[3], Matthew B Wheeler[1,2*]

[1]Department of Animal Science, University of Illinois at Urbana-Champaign, Urbana, IL, United States of America
[2]Grainger College of Engineering, University of Illinois at Urbana-Champaign, Urbana, Illinois, United States of America
[3]College of Veterinary Medicine, University of Illinois Urbana-Champaign, Urbana, IL, United States of America
***Correspondence author:** Matthew B. Wheeler, Ph.D., Professor of Developmental Biology, Department of Animal Science, College of Veterinary Medicine, University of Illinois, 1207 West Gregory Drive, Urbana, IL 61801, United States of America; Email: mbwheele@illinois.edu

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Abstract

Background: The COVID-19 pandemic brought forward the need for rapidly producible and affordable ventilators due to widespread incidence of respiratory distress, which led to a desperate need for mechanical ventilators. To meet this need, a team was assembled to design a gas-powered emergency ventilator, named RapidVent. The interdisciplinary team designing RapidVent based the design of commercially available ventilators and used additive manufacturing to rapidly produce a prototype that was tested for over two million cycles. Once the prototype was designed and its functions were confirmed, it was ready to be tested in animals.

Methods and Findings: The pig (Sus scrofa) is well-studied for biomedical instrument testing, but ventilator testing using a live, healthy animal has not been explored. Three tests were performed to determine if RapidVent would work with a live subject and to see if adding weight to the ribs of a laterally recumbent animal could simulate labored breathing. The first was a pilot study to determine if the prototype would function while connected to a patient that is breathing on their own. The second test was used to determine if the device could withstand continuous extended use. The third test was to determine if the control parameters of the RapidVent prototype could be adjusted to control the physiological parameters of the pig.

Conclusion: The RapidVent Emergency Ventilator withstands continuous use over an extended period and allows for the control of physiological parameters of the pig. Weight added to the ribs of the animal may be a viable model for labored breathing with more evidence.

Keywords: COVID-19; Ventilator; RapidVent; Prototype; Animal Model; Swine

Introduction

Novel Coronavirus 2019, coined COVID-19 or SARS-CoV-2 caused widespread disease and a shortage of healthcare resources shortly after its identification in 2019. This coronavirus structurally resembles the Severe Acute Respiratory Syndrome (SARS) coronavirus that caused an outbreak of respiratory distress in 2003 [1]. Infection with SARS-CoV-2 causes diffuse alveolar damage and interstitial pneumonia [2]. Severe infections can lead to viral pneumonia and Acute Respiratory Distress Syndrome (ARDS) resulting in the need for intensive care such as hospitalization and ventilation support [3,4]. ARDS is described as "acute diffuse, inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight and loss of aerated lung tissue [5]". Mechanical ventilation is the most used treatment for ARDS in adults, decreasing the amount of work and oxygen cost of breathing, allowing oxygen stores to be used in vulnerable tissues [4,6]. Respiratory distress is the leading cause of COVID-19 deaths and the mortality of respiratory failure due to COVID-19 infection is higher than non-COVID related ARDS [7,8].

Swine, Sus scrofa, have been used extensively as a large-animal model for biomedical research in preclinical studies due to their similar anatomical and physiological characteristics to humans and ease of availability [9-12].

The shortage of mechanical ventilators at the beginning of the COVID-19 pandemic created a need for experimental ventilators to be rapidly produced and tested. One of these experimental ventilators, RapidVent (https://rapidvent.dev.engr.illinois.edu), was designed to provide COVID-19 patients with life-saving treatment during this time of limited resources [13]. RapidVent, a gas-powered emergency ventilator, was designed based off commercially available ventilators by an interdisciplinary team. This research was conducted to develop an animal model for the testing of the RapidVent experimental ventilator for the treatment of COVID-19.

Materials and Methods

The animal studies were approved by the University of Illinois Institutional Animal Care and Use Committee (IACUC) which supervises and ensures the ethical and responsible treatment of animals. Animals were used under a protocol (# 20071) approved by the IACUC.

Yorkshire cross bred pigs (n=7) age 6 months weighing 90-130 kilograms (200-290 pounds) were acclimated to the Physiology Research Laboratory (PRL) surgical holding area prior to the procedure being performed. The animals were fasted for a minimum of eight hours prior to sedation and intubation [13].

A sedation cocktail (TARK) of 1.4 mg/ml Telazol (tiletamine and zolazepam; Pfizer, New York, NY), 0.882 mg/ml Atropine (Neogen Corporation, Lexington, KY), 2.94 mg/ml Rompun (xylazine; Lloyd Laboratories, Shenandoah, IA) and 5.88 mg/ml Ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, IA) was administered intramuscularly at 0.1ml per kg of body weight of the animal [14]. Intravenous TARK was administered as needed through an ear vein cannula to achieve an appropriate level of sedation. The animal was then placed in sternal recumbency and an endotracheal tube was inserted into the trachea. Once intubated the animal was placed in lateral recumbency.

Anesthesia was maintained by a combination of inhalation anesthesia isoflurane via the endotracheal tube that was previously placed and IV sedation using Propofol (Propothesia, 10-20 mg/kg/hr CRI IV, Covetrus, Indianapolis, IN), Dexmedetomidine (Dexmedesed, 1 mcg/kg/hr CRI IV, Dechra Vet Products, Overland Park, KS) and Ketamine (Ketaset, 1-10 mg/kg/hr CRI IV, Fort Dodge Animal Health, Fort Dodge, IA). Dexmedetomidine was reversed via intramuscular administration of atipamezole (Antisedan, 0.16-2.0 mg/kg, Zoetis US, Parsippany, NJ).

During the trial, the respiration and heart rates of the pigs were constantly monitored. Body temperature, heart rate and respiration rate were recorded every 15 minutes for the duration of the trial using a pulse oximeter placed at the ear of the pig. Blood pH, partial pressure of carbon dioxide and partial pressure of oxygen were periodically monitored by taking a venous blood sample (1 ml/sample) and using a portable handheld blood gas analyzer (i-STAT, Abbott, Chicago, IL) [13]. End tidal CO2 was monitored with a portable electronic capnograph (N-85, Nellcor, Coviden/Medtronic, Minneapolis, MN).

After the ventilation trials, the animals were moved to the PRL holding area and allowed to recover from the anesthesia. Dexmedetomidine was reversed via intramuscular administration of atipamezole (Antisedan, Zoetis US, Parsippany, NJ). Excede (Pfizer, New York, NY) was administered as an antibiotic therapy immediately and one-week post-trial. Rectal body temperature and heart rate were taken every 15 minutes until the animal was able to maintain sternal recumbency. The animals were housed in the PRL holding area for 24 hours and were then moved to the Biomedical Housing area of the facility where they were individually housed but allowed fence line contact with other pigs [14]. Rectal temperature, appetite and behavior were monitored for two weeks following the ventilator trials [13].

Initial Three-Hour RapidVent Trial

The initial RapidVent prototype (Fig. 1) was tested for three hours. Pure oxygen was supplied through the ventilator from a 250-cu ft tank gas source. The ventilators were attached to the endotracheal tube via 1.6 m of 22 mm inner diameter corrugated tubing (Fig.1). Adjustments were made to the respiration rate to control the amount of CO_2 in the blood. During the final 30 minutes of the trial an 18 kg (40-pound) sandbag was placed on the pigs' ribcage to simulate abnormal breathing. During this trial, a Vortran

model 5011 emergency gas powered ventilator and two of the prototype RapidVent ventilators were tested. CO_2, flow and pressure sensors were placed after the ventilator and before the pig respectively to monitor the flow and pressure of the gas leaving the ventilator. Data was analyzed for correlations using the Pearson correlation coefficient method CORREL function and basic statistical functions in Microsoft Excel.

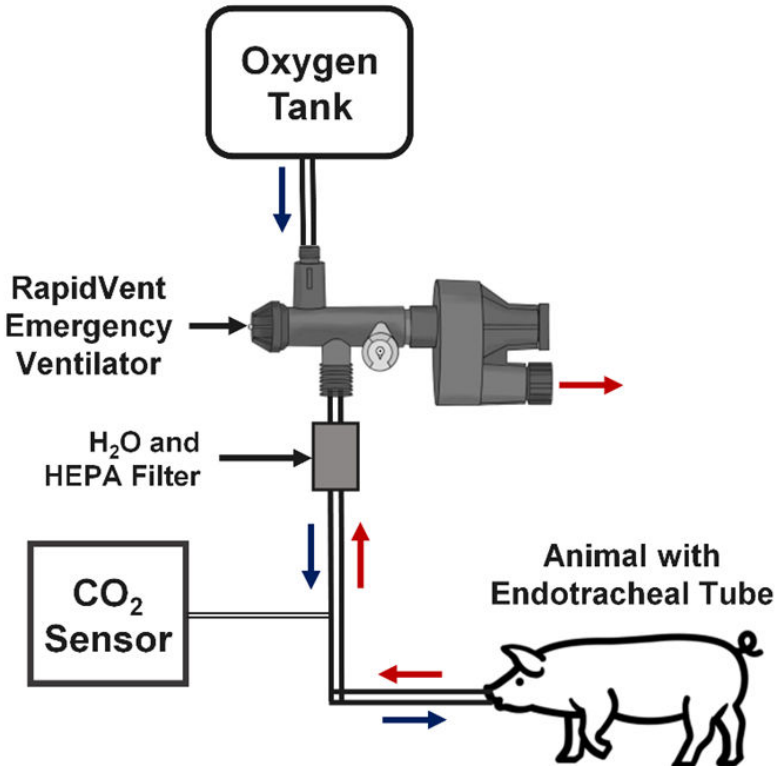

Figure 1: Schematic of the experimental setup.

Twenty-Four Hour RapidVent Trial

Two RapidVent prototypes were tested for a full 24 hours each. Pure oxygen was supplied through the ventilator from a 250-cu ft tank gas source. The ventilators were attached to electronic monitoring equipment located between the ventilator and the patient as described above (Fig. 1). The ventilators were attached to the endotracheal tube via 1.6 m of 22 mm inner diameter corrugated tubing (Fig. 2). The pigs were changed every 3-12 hours depending on the vital signs of the individual pig. This resulted in five pigs total being used to complete this trial. Data were analyzed for correlations using the Pearson correlation coefficient method CORREL function and basic statistical functions in Microsoft Excel.

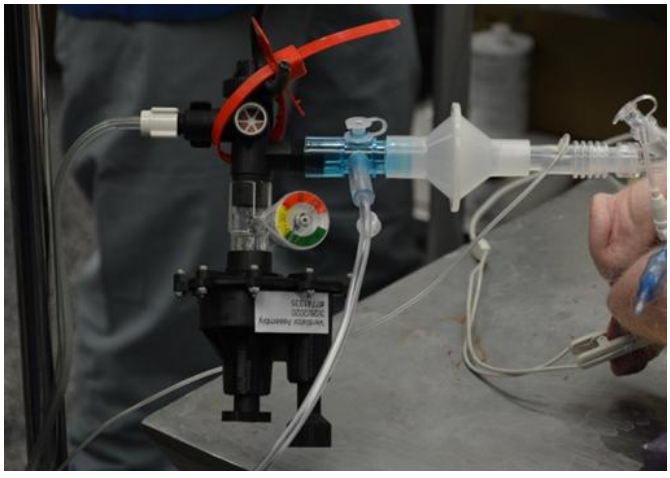

Figure 2: Photograph of the RapidVent Emergency Ventilator Prototype connected to a pig via endotracheal tube.

Short-Term Animal Test with Sensor Monitoring Station Inline After the Ventilator

One RapidVent prototype was tested for four hours. A CO_2 sensor was placed after the ventilator. Pure oxygen was supplied through the ventilator from a 250-cu ft tank gas source. Short pieces of 20 mm tubing were used to connect the gas supply, ventilator and endotracheal tube. Adjustments were made to the respiration rate to control the amount of CO_2 in the blood. An 18 kg (40-pound) sandbag was placed on the pigs' ribcage for approximately 30 minutes to simulate abnormal breathing. Data was analyzed for correlations using the Pearson correlation coefficient method CORREL function and basic statistical functions in Microsoft Excel.

Results

Initial Three-Hour RapidVent Trial

The heart rate, SpO_2 and body temperature of the pigs were maintained within normal ranges [15]. The mean heart rate of the animals was 108 bpm. This is within the normal range of 70-120 bpm for a pig of this size [15]. The mean blood oxygen saturation, SpO_2, was 89.9%. There was no correlation between the SpO_2 of the pig and any other variables. The mean body temperature with supplemental heat provided was 38.2°C (100.8°F). The initial pig's body temperature was negatively correlated with time, r=-0.92. (Fig. 3). No other variables were significantly correlated. There was no effect on any of the parameters measured when the sandbag was added to the pig's rib cage.

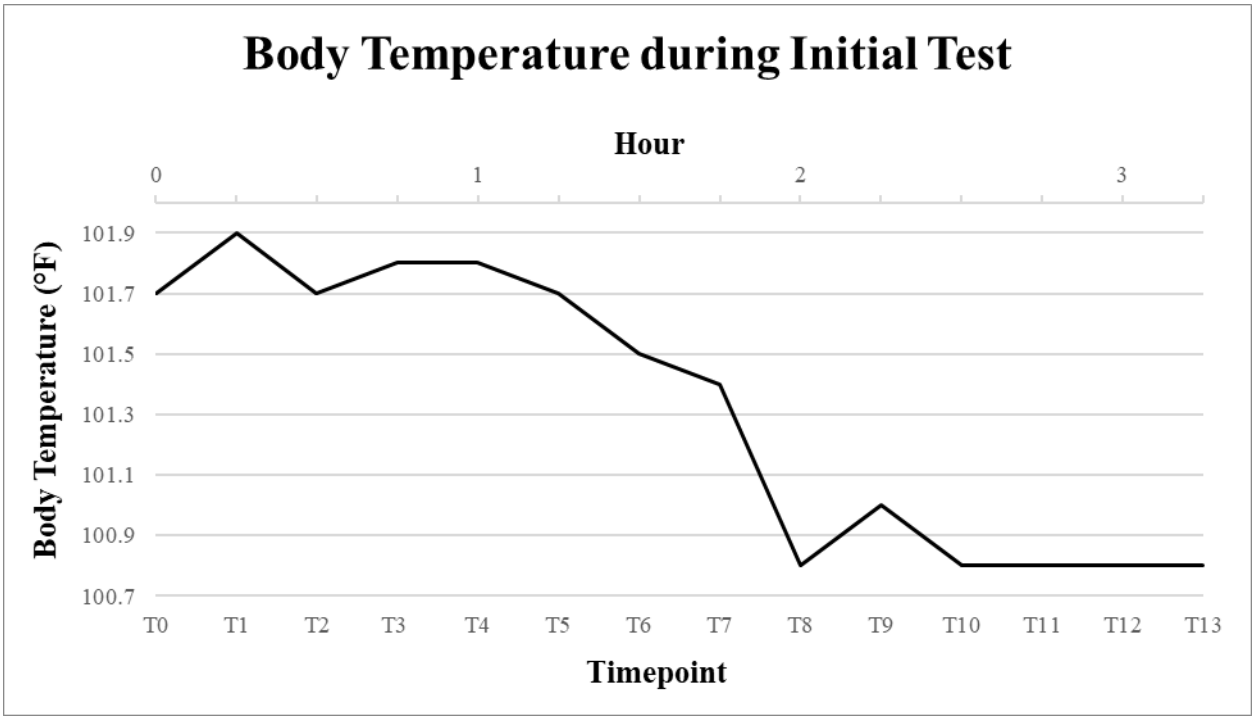

Figure 3: Body temperature of the pig is negatively correlated with time (r=-0.92). There is no effect to body temperature when the first RapidVent prototype is switch to the Vortran 5011, when the Vortran 5011 is switched to the second RapidVent prototype or when 18 kg (40 lbs) is added to the ribs of the animal.

Twenty-Four Hour RapidVent Trial

This test utilized five pigs - two on one RapidVent prototype and three on a second RapidVent prototype. There was no difference between the prototypes. Neither prototype experienced fatigue on the moving parts as indicated by the consistency of the animals' measured physiological parameters throughout the duration of the twenty-four hours. Each pig spent between three and twenty-four hours being ventilated by a RapidVent prototype.

The mean body temperature across all five pigs was 98.7°F, which is below the normal 101.6-104°F range for pigs [15]. This is explained by the duration of time under anesthesia. Each pig experienced a decrease in body temperature and supplemental heat was added (Fig. 4). Decrease in body temperature is expected while under anesthesia and is particularly noted after multiple hours under anesthesia [16]. There was no difference between each of the RapidVent prototypes that were used. Each device was

calibrated in until a "normal" respiratory rate and CO_2 level was achieved; at this point no significant degradation or change in performance post-calibration was observed.

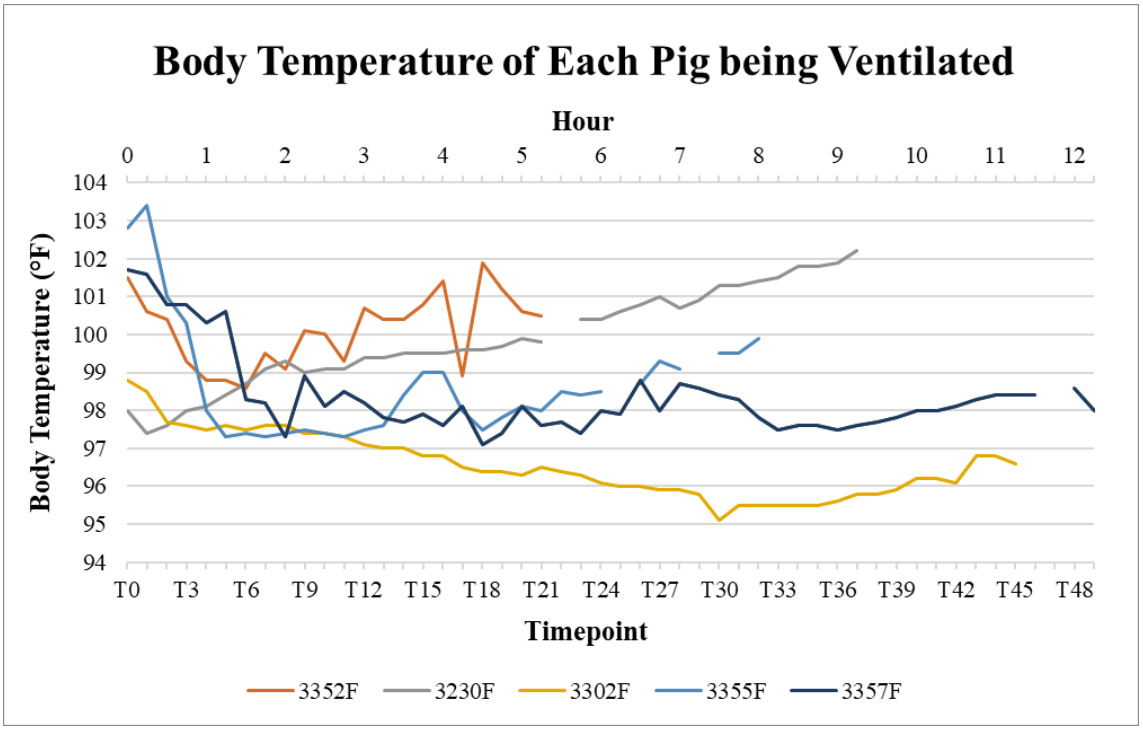

Figure 4: Body Temperature in °F for each pig while being ventilated with a RapidVent prototype.

The mean heart rate across all five pigs was 99.2 bpm. This is within the normal range of 70-120 bpm for a pig. Individual pigs' heart rates all had a mean within the normal range for a pig. There was no difference between each of the RapidVent prototypes that was used. The mean SpO_2 across all five pigs was 97% (Fig. 5). This is within an acceptable range for pigs spending multiple hours under anesthesia [16]. Individual pigs' mean SpO_2 all remained above 94%. There was no difference between each of the RapidVent prototypes that were used in this trial.

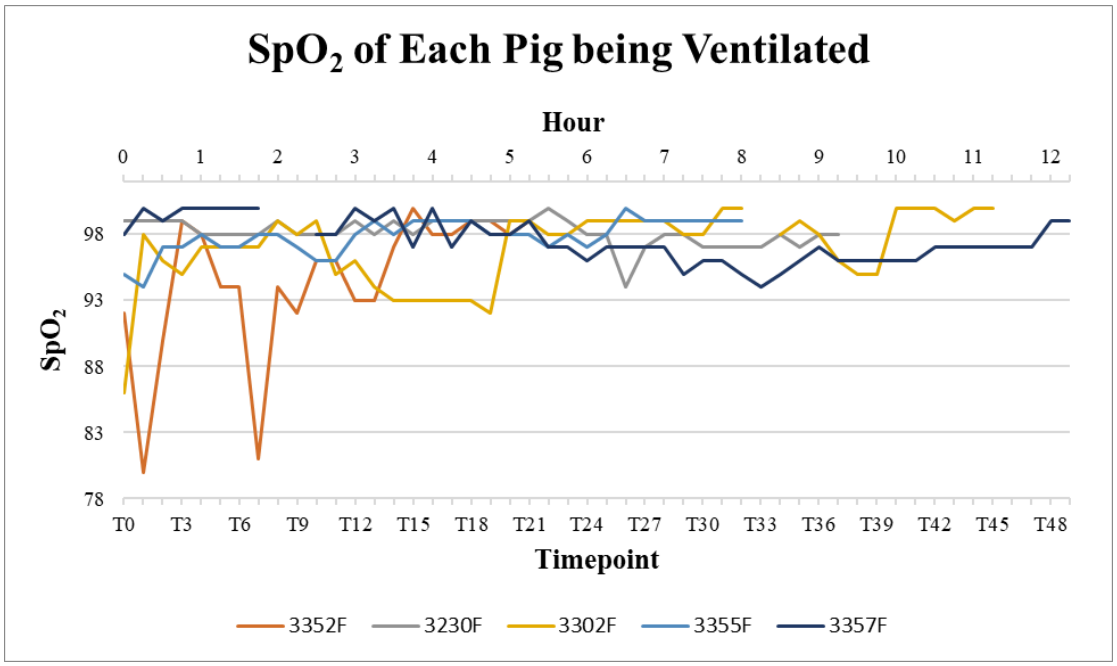

Figure 5: SpO_2 for each pig while being ventilated with a RapidVent prototype. All mean SpO_2 remained within a normal range.

Each of these measured parameters were not affected by which prototype was used or the duration of time the prototype was being tested. This result indicated that there was consistency across devices, which was a desirable outcome. Fatigue or failure of the moving diaphragm within each ventilator was not seen over the course of the twenty-four-hour trial.

Determination of when to remove each pig from the ventilation trial was made by the venous blood pH values [17]. These values were measured sporadically and were not able to be analyzed using any statistical methods. However, it was consistently observed that the venous blood pH values reached a value indicating respiratory acidosis on each pig after a period of time under anesthesia. Two of the pigs, numbers 3357F and 3352F, had no venous blood pH measurements. For each of the three remaining pigs, it was determined that they were in respiratory acidosis at a pH below 7.2. Supplementary IV sodium bicarbonate was administered to the pigs to bring their blood pH out of the acidosis range but was ultimately unsuccessful. This observation was determined to have been caused by the amount of dead space in the tubing connecting the oxygen source, RapidVent prototype and animal. The approximate tidal volume of a 200 kg pig is 1,400 ml and the calculated volume of the 182.88 cm long X 2.54 cm diameter tubing is 927 ml or 66% of the tidal volume. In this ventilation configuration, CO_2 could not be efficiently exchanged so the pH of the blood decreased and the animals became acidotic, pH ranged from 7.063 to 7.244. In the subsequent test, the length of tubing was decreased to account for this situation. It has been previously shown the tidal volume is related to oxygenation in high-frequency ventilation in healthy swine [18].

Short-Term Animal Test with Sensor Monitoring Station Inline After the Ventilator

The purpose of this test was to determine if the venous blood pH was able to be controlled by adjustment of the ventilation control to reverse the acidosis of the blood [17]. Carbon dioxide and water are the end products of metabolic processes, resulting in an increase of HCO_3^- in the body. Bicarbonate cannot be excreted through the lungs or efficiently through the kidneys, so protonation must occur to return it to CO_2 and H_2O. Acidosis occurs when there is a disruption in the body's ability to expel CO_2 from the body, which occurs through the lungs of air breathing species [19]. Increased partial carbon dioxide tension (pCO_2) causes an increase in HCO_3^- and a decrease in pH, leading to respiratory acidosis, because carbonic acid results when CO_2 is added to the water in blood [17]. This can be seen by utilizing the Henderson-Hasselbach equation [20]:

$$pH = pK \times \log\left[\frac{HCO_3^-}{0.03 \times pCO_2}\right]$$

Arterial or venous blood pH readings can be used to diagnose respiratory acidosis [21]. Respiratory acidosis is common in patients with a COVID-19 infection due to increased dead space in the lungs. Patients with respiratory acidosis may be given sodium bicarbonate intravenously with the intention of raising intercellular and extracellular pH [21]. The direct value of blood pH does not strictly indicate an outcome, but a blood pH below 7.2 in an ICU setting is associated with increased mortality [22]. In patients with ARDS, a pH below 7.15 is when sodium bicarbonate would be administered as a treatment [21].

The heart rate, SpO_2 and body temperature of the pig were maintained within normal ranges. None of the variables measured were correlated to each other. Two pulse oximeter devices were used to monitor the physiological parameters of this pig because it was noticed during the previous test that one device was reading consistently lower than the other device for each pig it was attached to. This was confirmed by the results. The heart rate of the pig measured via pulse oximeter placed at the ear of the pig ranged between 83 and 138 bpm with a mean of 103 bpm. The heart rate measured via pulse oximeter placed at the vulva of the pig ranged between 82 and 112 bpm with a mean of 94 bpm. This is within the normal range of 70-120 bpm for both pulse oximeters. The blood oxygen saturation, SpO_2, measured at the ear had a mean of 94% whereas measured at the vulva had a mean of 99%, both within an acceptable range. The mean body temperature was 102.4°F when provided with supplemental heat for the duration of the trial. The body temperature remained within a normal range and within 2°F. This shows that the RapidVent was able to maintain the animal's measured physiological parameters while the control parameters were being adjusted.

The pig began to experience a drop in pH approximately 75 minutes into being ventilated with decrease from 7.511 (T2) to 7.497 (T5) (Table 1). The pH continued to drop to 7.328 at 105 minutes into being ventilated (T7). Control parameters of the ventilator were adjusted and the pH was 7.453 at T4, 135 minutes into being ventilated. The pH was maintained relatively constant thereafter, with a slight increase at T5. In this test the length of tubing was decreased to 30 cm long X 2.54 cm in diameter, which

was a volume of 154 ml or 11 % of the pig's tidal volume. This is a configuration where CO_2 could be adequately exchanged with the atmosphere and with adjustments to the RapidVent the blood pH could be maintained between 7.328 and 7.566.

Timepoint	Minutes into trial	Venous Blood pH
T0	0	7.460
T1	30	7.511
T2	75	7.497
T3	105	7.328
T4	135	7.453
T5	165	7.566
T6	195	7.467
T7	210	7.437

Table 1: Venous blood pH at measured time points. The control parameters of the RapidVent prototype were adjusted to maintain the pH between 7.4 and 7.5.

Discussion

Novel Coronavirus 2019, coined COVID-19 or SARS-CoV-2 caused widespread disease and a shortage of healthcare resources [23]. The novel coronavirus, first identified in 2019, structurally resembles the Severe Acute Respiratory Syndrome (SARS) coronavirus that caused an outbreak of respiratory distress in 2003 [1,23]. This similarity gives the name SARS-CoV-2. Infection of SARS-CoV-2 virus causes a variety of symptoms ranging in severity including fever, chills, difficulty breathing, loss of taste or smell, congestion, diarrhea, vomiting, headache, fatigue and body aches ("Symptoms of COVID-19", 2021). Severe infections can result in viral pneumonia and acute respiratory distress syndrome resulting in the need for intensive care such as hospitalization and ventilation support. Despite stockpiles of ventilators, healthcare facilities around the world experienced shortages of essential supplies to treat patients. The RapidVent Emergency Ventilator was designed and tested to meet the healthcare needs that the COVID-19 pandemic presented.

Infection with SARS-CoV-2 causes diffuse alveolar damage and interstitial pneumonia [4]. This causes interstitial thickening which decreases lung capacity and alters the efficiency of gas exchange. Alveolar damage causes ventilation-perfusion mismatch that cannot be corrected with changes in VT or frequency of breathing resulting in hypoxemia [4].

COVID-19 Acute Respiratory Distress Syndrome (CARDS) is diagnosed when a patient has received a positive test for the virus and simultaneously fits the criteria for diagnosis of ARDS according to the 2012 Berlin Definition [8]. Respiratory distress is the leading cause of COVID-19 deaths, with 53% of deaths being due to respiratory failure and 33% of deaths being due to respiratory failure and cardiac failure [7]. The mortality rate of respiratory failure due to COVID-19 infection is higher than non-COVID related ARDS [8].

There are two types of CARDS, originally presented as Type I and Type II, now known as Type L and Type H respectively. Type L has distinct differences from a typical ARDS diagnosis. Patients with Type L CARDS exhibit high lung compliance, allowing the lung to accept larger tidal volumes than typical for an ARDS patient and causing a low response to PEEP. Type L CARDS patients also show lower lung weight on CT than Type H. These patients can benefit from oxygen therapy such as CPAP, BiPAP and high-flow nasal O_2 support [7]. Type H CARDS exhibits more typical ARDS characteristics. These patients have low lung compliance and tend to respond to high PEEP. Patients with Type H CARDS show extensive consolidations and have a higher lung weight than Type L on CT. Type H Patients may respond well to typical ARDS ventilation parameters such as high PEEP, low tidal volume and prone positioning [7]. The type of CARDS is not a direct correlation to the severity of disease or expected outcome to treatment, but are instead a guidance on the type of treatment the patient will respond to given the symptoms.

There are risks to providing mechanical ventilation to patients exhibiting CARDS symptoms. Lungs that accept high tidal volume are susceptible to over inflation and dead space which can cause VILI [24]. Reducing the PEEP trends an increase in lung compliance and decrease in the dead space of the lung in most patients [24].

In each test of the RapidVent Emergency Ventilator prototype, the animal's measured physiological parameters remained within a normal range except for the SpO_2 at the beginning of the initial test, which was explained by the variability in anesthesia. This information alone cannot be used to determine if the RapidVent Emergency Ventilator prototypes were appropriately ventilating the pigs because of the lack of effect seen across prototypes, pigs or length of time ventilating in each test. However, we were able to determine that the control parameters can be adjusted to control the venous blood pH of the pig.

The abnormal breathing model was not confirmed to cause abnormal breathing with these two short trials. There was no change in either of the pigs' physiological parameters when weight was added. More tests need to be performed to test the efficacy of the abnormal breathing model.

The combination of animal test and artificial lung results showed that the RapidVent Emergency Ventilator prototype meets the control parameters that were requested to gain Emergency Use Authorization in the United States. EUA approval was received on 23 September 2020 [25]. Upon completion, the design was released and licensed by Belkin, Inc. for manufacture and was subsequently renamed the FlexVent.

Conclusion and Perspectives

The animals measured physiological parameters remained within a normal range for the duration of the tests. The only significantly correlated variable was temperature post-anesthesia; all other measured variables were not significant. The venous blood pH of the animal was able to be manipulated by adjusting the control parameters of the RapidVent Emergency Ventilator prototype. The demand for mechanical ventilators has decreased significantly due to the release of vaccines targeting the novel coronavirus and its subsequent variants. No further tests of RapidVent are planned subsequent to the release of the design plans to Belkin. At this point, RapidVent (FlexVent) is not being manufactured for use in a hospital setting. Despite the decrease in need for mechanical ventilators for the treatment of COVID-19, there is potential for RapidVent to be used as an emergency or transport ventilator in other settings with more testing. The prototype can be used with multiple oxygen sources, is light weight, can be sterilized and can be stored for long periods of time. This collaborative initiative between animal scientists, biologists, engineers, physicians, medical clinicians, veterinarians and social scientists illustrates the power of the collective imagination, intellect and determination to benefit mankind at the University of Illinois.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval and Consent to Participate

The animal research presented here required approval from the University of Illinois Institutional Animal Case and Use Committee (IACUC) under Protocol # 20071.

Availability of Data and Materials

Data is available on request.

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