10D: Feasibility Study of a Novel Low-cost Brazilian Emergency Mechanical Ventilator

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Research

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Abstract

Background: The current need for pulmonary mechanical ventilation related to COVID-19 exceeds the ability of health systems worldwide to acquire and produce mechanical ventilators. The major cause of mortality in patients with this disease is hypoxemia secondary to an inflammatory storm in the lungs associated with thrombotic events. A partnership was established between the university and the private engineering and industrial automation sector to concept and design novel a low-cost emergency mechanical ventilator that could be rapidly available for use in emergency, transport or low-resource health care system, and attend the urgent demand of artificial respiratory system that is need worldwide. It was evaluated the viability of oxygenation and pulmonary ventilation with an emergency mechanical ventilation device called 10D-EMV in animal experiments. A two-stage sequential adaptive study was conducted in 10 sheep, divided into group I (PEEP valve close to the device) and group II (PEEP valve distal to the device). Each animal underwent mechanical ventilation for a total of 120 minutes.

Results: The mean oxygenation in group I and group II were 368 mmHg and 366 mmHg, respectively, while the mean partial pressure of carbon dioxide was 58 mmHg and 48 mmHg.

Conclusion: This study demonstrates the viability of the 10D device as a novel proposed emergency mechanical ventilator, in order to attend the pandemics demand. Further clinical studies in humans are needed to assess its safety and efficacy.

Background

Historically, humanity has been transformed by disruptive events such as terrorist attacks, natural disasters, and pandemics [1, 2]. The speed of transformation and communication in a globalized world is far greater than the capacity to resolve and manage these events. The worldwide spread of a novel virus emerged from Wuhan city (Hubei Province, China), that has a high rate of airborne transmission and that is associated with uncertain but significant mortality [3]. The severe acute respiratory syndrome (SARS) due to coronavirus-19 (COVID-19) infection, associated with thromboembolic complications such as deep venous thrombosis and pulmonary embolism (PE), acute mesenteric ischemia (AMI) [4], has been reported in severe COVID-19 patients [5].

Patients with underlying lung disease may develop respiratory failure under a variety of challenges and can be supported by mechanical ventilation, to maintain the organism oxygenation [6]. The treatment forces us to find collaborative solutions focussed on similar purposes, such as the need for survival.

The installed capacity of health services is insufficient to meet the demand for hospitalizations and exceeded the capacity of health systems worldwide to acquire, produce, or adapt tools as needed during a pandemic [7]. The Covid-19 pandemic has led to severe shortages of many essential goods and services, from hand sanitizers and N95 masks, to ICU beds and ventilators. Although rationing is not unprecedented, never before the world has been faced with the prospect of having to ration medical goods and services on this scale. [8]. Public health managers and emergency care providers have been

particularly concerned with the availability of mechanical ventilators, and concern comes from the experience with the 2001 anthrax attacks and the outbreaks of severe acute respiratory syndrome (SARS) in 2003, Middle East respiratory syndrome (MERS) and H5N1 in 2009 [9, 10].

Ventilators used in modern hospitals are highly functionally and technologically sophisticated, but prohibitively expensive for use in countries which are resource-limited health system [6]. The greatest cause of fatal outcome in patients with this disease is the development of SARS associated with thrombotic events in the microcirculation, promoting severe hypoxemia and multiple-organ dysfunction [11-13]. A number of pharmacologic regimens, including hydroxychloroquine-azithromycin, antiviral therapy (eg, remdesivir), and anti-IL-6 agents (e.g., tocilizumab), have been highlighted by investigators over the course of the pandemic, [14], and at the present there are over 300 clinical trials ongoing or preparing to enrol for COVID-19 disease. These trials focus primarily on pharmacologic therapies based on interrupting the viral life-cycle or preventing cytokine storm [14]. Despite the scientific community are gathering forces and resources to find a new pharmacological therapy and an effective vaccine to treat and prevent new infections, the number of patients with COVID-19 increase globally - there are 17.396.943 confirmed cases of COVID-19 including 675.060 deaths, reported to WHO [15]. Facing the exorbitant numbers of infected persons, a question was risen: How could medical care be provided equally if the number of infected is much higher than the number of ventilators available worldwide? Which lead the physicians to a re-discussion of the trolley dilemma [8, 16] or the *Doctor's Dilemma* of George Bernard Shaw [17]: In the eventuality of two patients with respiratory failure and only one ventilator, which patient to save [18-20]?

It is important to highlight that mechanical ventilators are life support devices for various conditions treated in intensive care units and are intended for patients who require assistance to maintain adequate ventilation due to diseases, trauma, congenital abnormalities, adverse drug events, or surgical emergencies [21].

Whether it will be necessary to ration ventilators will depend on the pace of the pandemic and how many patients need ventilation at the same time, but many analysts warn that the risk is high [8]. Some efficacy has been demonstrated in using a single ventilator to support multiple patients [11]. But facing these unprecedented ethical conditions, physicians, biotechnologists and engineers alike have launched widespread attempts to create a widely scalable ventilation alternatives, in order to increase the accessibility and supply of low-cost ventilators.

Even though these projects may represent important innovations, their manufacture and implementation depend on their supply, assembly, and distribution chains, in addition to experiments ensuring efficacy and safety for use in humans. In this scenario, the development of an low-cost effective emergency mechanical ventilator must not only address the underlying pathophysiology of a variety disease processes, including SARS caused by coronavirus, but must also be functionally designed to allow for large-scale construction and distribution, especially for low-resource developing countries.

There are already few teams around the world working on numerous emergency mechanical ventilator to attend the COVID-19 demand, such as RapidVent group [11, 22] or breathing machines that could potentially begin saving lives, as the group from Northwell Health that has found a way to convert a non-invasive BiPAP machine into an invasive ventilator for COVID patients [23].

To attend this urgent need, a novel low-cost Brazilian emergency mechanical ventilator called 10D-EMV was developed and evaluated in the current feasibility study presented.

Results

The values at time 0 (T0) were present in Table 1 (animal weight, respiratory parameters, mean arterial pressure, and heart rate) and in Table 2 (arterial blood gas analysis, haematocrit, and haemoglobin) showed no significant difference between the groups.

Table 1. Weight, respiratory parameters, mean arterial pressure, and heart rate at T0.

	Group I	Group II
Weight (kg)	44.4	45.8
Tidal volume (mL)	348.8	307.8
Respiratory rate (breaths/min)	12	12
Inspiratory/expiratory ratio	1:2	1:2
Peak pressure (cmH ₂ O)	20	19.75
Complacency static (mL/cmH ₂ O)	23.92	25.92
Plateau pressure (cmH ₂ O)	23.8	19.75
Mean arterial pressure (mmHg)	104.40	88.00
Heart rate (rpm)	74.80	101.60
PEEP (cmH ₂ O)	5	5

Table 2. Arterial blood gas, haematocrit and haemoglobin at T0.

	pH	PaCO ₂ mmHg	PaO ₂ mmHg	HCO ₃ ⁻	BE	O ₂ SAT (%)	HB	HT
Group I	7.50	38.00	318.62	28.46	5.26	99.72	9.32	14.30
Group II	7.49	41.44	350.62	30.50	6.46	99.50	9.14	13.16

Table 3 shows the arterial blood gas values after the animals were placed on the 10D device (T30 to T150). At all analysed times during the 120-minute period, there was no significant difference between

the groups, except that PaCO₂ was higher in group I at T60. During the experiment, the parameters within each group did not change significantly from T60 to T150.

Table 3. Arterial blood gas analysis of groups I and II at T60, T90, T120, and T150.

	T60		T90		T120		T150	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
pH	7.32	7.47	7.35	7.46	7.36	7.41	7.38	7.41
PaCO ₂ mmHg	62.54*	44.92*	63.24	46.36	57.08	52.50	52.45	51.94
PaO ₂ mmHg	337.06	348.28	383.68	376.20	385.80	371.40	366.35	370.78
HCO ₃	30.34	31.66	32.02	31.94	30.76	32.30	29.70	31.94
BE	2.42	6.98	4.58	7.06	3.76	6.22	3.35	5.88
O ₂ SAT	99.68	99.64	99.74	99.68	99.74	99.62	99.73	99.64

*p ≤0.05 = Statistically significant difference between groups

As seen in Table 4, there was no significant difference in mean arterial pressure within either group or between the groups at the different times evaluated. Peak airway pressure was significantly different between the groups at all evaluated times.

Table 4. Mean arterial pressure and peak airway pressure values.

	T60		T90		T120		T150	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
Mean arterial pressure (mmHg)	75.7	101.8	75.2	89.75	56	81	74.75	74.0
Peak pressure (cmH ₂ O)	24.00*	18.0	28.8*	18.8	30.67*	19	31.33*	19.6

*p ≤0.05 = Statistically significant difference between groups.

Discussion

The development of a low-cost EMV was first conceived by the Massachusetts Institute of Technology (MIT) in 2010 [6, 22] and was paused for reasons not described by the group of engineers. The principle of this EMV, called E-Vent MIT, was resumed during the COVID-19 pandemic in the United States, and improved with open-source programming. The mechanism, based on the automated AMBU, is similar to 10D-EMV device in its flow sensors, pressure sensors, alarms, and adjustments for tidal volume, respiratory rate, PEEP, and peak inspiratory pressure.

According to unpublished data [24], MIT researchers reported completion of experimental studies with animals and authorization by the Food and Drug Administration for use during the pandemic in humans. Simultaneously, in Brazil, an EMV prototype called Inspire, a low-cost open-source mechanical ventilator [25] is currently under assessment by the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*) after tests in humans were finalized. Comparing the devices is impractical due to the pandemic; however, collaborative networks are gathering to find solutions and, especially, to achieve production at scale to meet the emergency demand.

Some challenges observed in our experiment were related to the initial difficulty on removing CO₂ present in the circuit when coupling the tracheal tube, i.e., the volume in the respiratory circuit that does not participate in gas exchange in the lungs and for which the device does not have compensation sensors in this dead space. After modification of the PEEP valve, positioned near the endotracheal tube, ventilation was improved by controlling PCO₂ and volumetric capnography. Similar problems were found by the MIT researchers.

Important issues related to EMVs must be addressed, such as safety, efficacy, and large-scale production, especially regarding the durability of the AMBUs and the electronic systems of the devices.

Conclusions

The partnership between engineering, medicine and biotechnology that the coronavirus outbreak pushed pressions to create a worldwide translational work. All engineering communities were called to respond to this need to help our health care workers on the front line of this pandemic. The development, prototyping, and testing of EMVs are more than necessary due to the high transmissibility and ARDS caused by the new virus of COVID-19. The 10D device is come to achieve the goal of adequate oxygenation and ventilation in the experimental animal model and has potential application as a bridge-device during travel to a destination in emergency situations. Although the feasibility study of this new emergency mechanical ventilator was verified and accomplished, as presented in this paper, further pre-clinical studies are needed to validate the efficacy and safety of this new device.

Materials And Methods

Experiment design: This was an adaptive experimental study, with sequential design conducted with a single sample of 10 sheep sample (*Ovis aries*) [26-28], divided into two groups to determine whether the

10D mechanical ventilation device (Figure 1) could maintain oxygenation and ventilation. The duration of the test was 120 minutes.

The recommended safety outcome was survival of over 60% (stopping rule) of the experimental group using the device, for a time longer than 60 minutes. The 120 minutes of pulmonary ventilation experimental model duration was chosen due to the possibility of the new 10D-EMV device being used as a bridge device, i.e., in a situation of emergency transport to a destination.

The anaesthetic procedure started with pre-anaesthetic medication, namely, morphine at 0.3 mg/kg and 20 mcg/kg of detomidine, both intramuscularly. This was followed by induction with diazepam 0.25 mg/kg and general anaesthesia with propofol at a dose of 4 mg/kg, both intravenously. Atracurium 0.1 mg/kg was also given intravenously every 40 minutes.

Orotracheal intubation was performed with a standard 8.5-mm tube connected to a Hamilton C1 SW 2.2.2 mechanical ventilator. The ventilatory parameters defined were volume-controlled ventilation, FiO_2 100%, tidal volume (TV) 8 mL/kg, positive end-expiratory pressure (PEEP) 5 cmH₂O, and respiratory rate 12 rpm. The ventilator circuit was completed using low-compliance silicone tubes and a high efficiency particulate air (HEPA) protection filter. The auricular artery and the cephalic vein were cannulated for systemic blood pressure monitoring using a Dixtal DX 2010 multiparameter monitor and for blood sample collection.

The protocol was initiated (Figure 2) after stabilization of the animal. At 30 minutes, the animals that presented with a $\text{PaO}_2/\text{FiO}_2$ ratio ≥ 300 and/or oxygen saturation greater than 96% according to a pulse oximeter were connected to the 10D device, and this time was considered T30. The subsequent evaluations start from T60 up to T150.

The included animals that were fit for the experiment were placed on a 10D mechanical ventilator, and their parameters were adjusted according to the group, as show Figure 3:

Group I - five animals ventilated with TV = 8 mL/kg and PEEP = 5 cmH₂O with the PEEP valve proximal.

Group II - five animals ventilated with TV = 8 mL/kg and PEEP = 5 cmH₂O with the PEEP valve distal

The parameters evaluated were: (i) vital signs every 10 minutes, (ii) pulse oximetry, (iii) capnography, (iv) respiratory mechanics, (v) variables derived from the flow and pressure sensors of the 10D device, and (vi) blood gas and (vii) blood count variables.

At the end of the experiment, the animals were euthanized by induction of anaesthesia using propofol until total loss of protective reflexes, followed by potassium chloride for respiratory and cardiac arrest.

The sequential design and the experimentation began after approval by the independent committee on safety, and the data monitoring was assessed by means of interim analysis after accomplished and survival of sheep number 5.

Statistical analysis: The data were expressed by the mean obtained in each group. Student's t-test or the Mann-Whitney test were used to compare the variables between groups, as appropriate. Statistical significance accepted was $p \leq 0.05$. For all statistical analyses were used the program Prism version 5.0 (GraphPad, San Diego, CA).

Declarations

Ethics approval

The research project was approved by the Ethics Committee on Animal Use of the University of Marília under number CIAEP-01.2018.2014 (protocol 029/2020).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Conflicts of interest and Source of Funding

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Figures

Figure 1

Schematic diagram of the 10D mechanical emergency ventilator.

Figure 2

Flowchart of the study design.

Figure 3

(A) 10D device with a distal PEEP valve. (B) 10D device with a proximal PEEP valve.