Title
AmbuBox: A Facile Design of Automated Ambulatory Ventilator for Emergency Use

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AmbuBox: A Facile Design of Automated Ambulatory Ventilator for Emergency Use

By

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THESIS

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Committee in Charge

2021

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Abstract

Respiratory failure has been a common cause of death in patients infected by SARS-CoV-2 during the time of worldwide ventilator shortage. In early 2020, our team have introduced a fast-deployable and low-cost emergency resuscitator system, AmbuBox, in response to the rising demand of ventilators. The AmbuBox system uses a controllable pneumatic enclosure in conjunction with a standard manual resuscitator (or AmbuBag) to achieve the basic functionalities of a modern ventilator. It is a modularized system integrated with off-the-shelf components for ramp-up production capability at a competitive cost. However, the regulatory requirements for emergency use have not been considered. My project focuses on improving the AmbuBox system in accordance with regulatory consensus and documenting the design process in detail. As part of the initial effort to make AmbuBox publicly available, this project further studies the general process and requirements of FDA Emergency Use Authorization for ventilators. Through this project, I am able to implement key functionalities on the AmbuBox system and understand the expectations from FDA for emergency use approval.

Chapter 1: Introduction to The AmbuBox Emergency Use Resuscitator

1.1 Background

Ever since the beginning of the COVID 19 pandemic in early 2020, the number of cases of infection worldwide has surged. The disease-causing SARS-CoV-2, also known as severe acute respiratory syndrome coronavirus 2, has been associated with the development of acute respiratory distress syndrome (ARDS). More than 40% of COVID-19 infected patients developed ARDS according to an early study, the mortality rate of which being as high as 50% [1]. The deployment of ventilator units and intubation became essential to support oxygen delivery in highly compromised lungs [2]. By April 2020, there was an estimated peak demand for 115,000 additional invasive ventilators in the United States alone, far exceeding the ventilator supply available across the nation [3].

1.2 What is a Ventilator?

A ventilator, also known as mechanical ventilator, is a medical device that pushes air into a patient's lungs to support adequate gas exchange including oxygen delivery and carbon dioxide elimination. Such a device provides invasive mechanical ventilation in which intubation is needed. Moreover, there are devices meant to provide non-invasive mechanical ventilation (NIV) such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) sleep apnea devices, and manual resuscitators. [4] Additionally, in-home-use ventilators can be attached non-invasively. Among different types of mechanical ventilation devices, ventilators are commonly used for intensive care due to their capabilities of taking over breathing activities under severe respiratory conditions such as ARDS [4]. While ventilators have full control of breathing modes, other ventilation types may require some degree of spontaneous breathing or even manual operation. The CPAP or BiPAP devices working with face masks, for instance, deliver continuous positive airway pressure without specific breathing parameter

settings [5]. On the other hand, manual resuscitators equipped with self-inflating bags, known as the AmbuBags, are operated manually by medical professionals when hospital-grade ventilators are unavailable during emergencies [6].

Ventilators are expensive and difficult to build. Modern ventilators have complex control systems and pneumatic hardware systems, allowing them to deliver air at the precise amount and desired time. Due to their life-saving usage scenarios in medical emergencies and their invasive interaction with patients, ventilators face strict regulation and quality control in design and manufacturing [7]. As a result, a modern ventilator requires special expertise to build and can cost between $25,000 and $50,000 [8].

1.3 Meeting the Need

In the beginning of the COVID-19 pandemic, the worldwide outbreaks disrupted the global supply chain of medical equipment and related components, leading to an overall shortage of ventilator supply and increased manufacturing cost. Therefore, a need arose to meet the immediate demand of ventilators and develop a more affordable ventilation solution. By having a simpler and more cost-effective solution, the underdeveloped regions could utilize their basic infrastructure and manufacturing capacity to bridge the supply and demand gap [2]. Our team's early efforts focused on providing an innovative ventilation solution that sought to imitate the functionalities of conventional ventilators, in order to meet specific needs of COVID-19 patients with respiratory failure, offering fast-deployed emergency respiratory support at a significantly lower cost in response to the pandemic [8].

1.4 State-of-the-Art

Three categories of low-cost emergency ventilators under active development were identified: ventilators constructed by easily sourced and readily available components, sleep apnea device modifications, and the manual-resuscitator-based ventilators. [7]

The first category of low-cost ventilator was designed to simplify conventional ventilator designs to allow for rapid component sourcing and mass-scaled production during the pandemic. For instance, the VITAL ventilator by NASA's Jet Propulsion Laboratory [9], Mechanical Ventilator Milano (MVM) by Elemaster S.p.A. Tecnologie Elettroniche [7], [10] and the BreathDirect BDR-19 by Nectar. There also existed approaches used in the open-source maker space that bring down the cost further by substituting premium components such as proportional flow control valves with control valve actuators or pinch valves which could be conveniently sourced [11], [12]. Although these solutions avoided potential sourcing bottleneck, the assembly and calibration procedures for a network of control valves inevitably increased cycle time, making them less suitable for rapid deployment.

The sleep apnea device modifications were developed based off existing CPAP or BiPAP devices, as low-cost alternatives specialized in treating respiratory insufficiency. Some sleep apnea device manufacturers made breathing circuit and tubing modifications or variant models per the FDA's requirement of aerosolization mitigation. [13] In addition, maker projects like the VentilatorSOS led by researchers and clinicians from University of California, Berkeley and University of California, San Francisco converted existing sleep apnea devices into emergency ventilators. [14] Not to be confused with mechanical ventilators, these sleep apnea device modifications were meant to deliver continuous positive air pressure for minimal ventilatory support and only intended to serve those who could breathe spontaneously.

The manual-resuscitator-based ventilator was another popular approach pursued by a number of university design teams and medical device manufacturers, in an attempt to further simplify ventilator designs. They were built upon manual resuscitators, or AmbuBags with electrically powered components to achieve automated bagging of the self-inflating bags [6]. Overall, manual-resuscitator-based ventilators had the distinct advantage of availability, minimal number of components, simple mechanism, low cost, and the capability for rapid development. Any FDA-cleared manual resuscitator could essentially be modified for emergency purpose [13]. A list of the representative manual-resuscitator-based ventilator projects with relevant specifications and features is featured in Table 1.

Table 1. List of representative manual-resuscitator-based ventilator projects. [8], [15]

Product Name	Developers	Highlights
Austin P51*	Air Boost LLC	System built into a small luggage for great portability; uses mechanized paddles to squeeze AmbuBag
PREVENT*	PVA	Uses two actuating arms for squeezing; single-knob adjustment
Umbulizer*	Umbulizer LLC	Uses a motorized paddle for squeezing; mobile app available for real-time monitoring; single knob adjustment
Coventor Adult Manual Resuscitator Compressor*	University of Minnesota Medical School and Boston Scientific Corporation	Open-source; first-of-its-kind authorized by the FDA; uses a slider-crank mechanism for squeezing
OxVent	University of Oxford and King's College London	Pneumatic compression mechanism

*Devices received FDA EUA.

1.5 Introducing the AmbuBox

During the early development stage, we introduced a low-cost ventilator design, AmbuBox, using a controllable pneumatic enclosure and standard manual resuscitators that were readily available. The AmbuBox could be rapidly deployed during mass-casualty and pandemic situations with a minimal set of components needed. Our concept offered not only customizable breathing parameters to sustain breathing activity in the case of a respiratory failure, but also a user-friendly interface for operators, at a cost of less than $300. [8]

In my thesis, I will report the design history of the AmbuBox in accordance with the waterfall design pathway. I will also survey the features incorporated into the AmbuBox prototype based on regulatory requirements, and lastly, the required elements for the U.S. Food and Drug Administration (FDA) Emergency Use Authorization.

Chapter 2: Design Input and Standard Conformity

2.1 Key Reference

To encourage innovation during the initial ventilator shortage, the Association for the Advancement of Medical Instrumentation (AAMI) issued a series of ventilator guideline documents with the inputs from experienced engineers, clinicians and regulators including FDA officials. Out of which, the design guidance documents for emergency use resuscitator system (EURS), AAMI CR503:2020, provided targeted design constraints specifically for manual-resuscitator-based systems. More importantly, it was intended to guide the emergency use review by regulation authorities, namely the FDA. [16] The FDA also acknowledged the AAMI guidance documents and states that “if your proposed device is within the scope of the standards outlined in the AAMI guidances, please review this document and state in your

EUA submission whether your device conforms to the recommended standards outlined in the AMII guidance." [17] Therefore, I chose the AAMI CR503:2020 as the primary reference for the identification of engineering design specifications and applicable consensus standards of the manual-resuscitator-based AmbuBox system.

2.2 Identification of Design Constraints

As an EURS positioned for COVID-19 patient care in traditional healthcare facilities or converted healthcare spaces, my design needed to take various engineering metrics into consideration, for instance, the respiratory rate (in breaths per minutes) and tidal volume (in mL). Table 2 shows a detailed list of these engineering metrics and their target values based on the design constraints set forth by AAMI.

Table 2. List of engineering metrics and target values [16].

Engineering metric	Unit	Target value
Tidal Volume	mL	350-450, preferably 250-800
Max TV adjustment step	mL	50
Respiratory rate	bpm	10 - 30
Respiratory rate adjustability	bpm	<= 2
I:E ratio	-	1:2 or adjustable between 1:2 to 1:4
Built-in battery life	min	30

2.3 Identification of Needs

Besides providing targeted design constraints or engineering design specifications, the AAMI guidance extracted clauses from applicable medical device consensus standards (IEC 60601-1, ISO 80601-2-80,

etc.) which were recommended for developers to implement in their EURS products [16]. In general, conformity to consensus standards serves the purpose of promoting efficiencies in regulatory review and ensuring medical devices of similar types deliver consistent quality [18]. However, for the intention of driving rapid deployment of ventilator or EURS specifically, knowing that full conformity to applicable standards may not always be possible during the pandemic, the guidance document only identified a limited set of clauses and requirements from these standards. For instance, the implementation of various alarms, equipping backup power source, and protection scheme against hazardous conditions. [16] I further identified some of these elements as the AmbuBox's functional needs listed below:

1. Alarm conditions including electrical supply failure, EUR switched off inadvertently, maximum inspiratory airway pressure exceeds 40 cmH_2O, low inspiratory pressure (equivalent to disconnection alarm), continuing pressure, estimated tidal volume not achieved or exceeded (deviation of more than 20%).
2. Minimum indication to the operator about current settings and current delivery.
3. Internal power source providing at least 30 minutes of usage during power interruption, with provided means to indicate utilization and state of the internal power source.
4. Filters to be placed in the expiratory pathways.
5. Ability to measure flowrate. (Optional)
6. Ability to measure or control FiO_2. (Optional)

Although not specified in the AAMI guidance document, portability and affordability were also prioritized needs over the course of the design process. Other needs such as touchscreen interface and data logging were classified as less important needs, as shown in Figure 1.

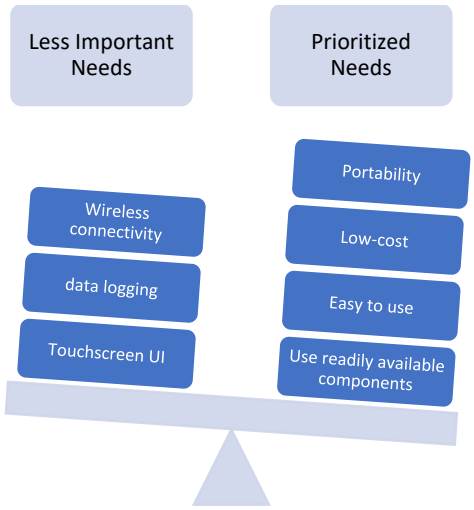

Figure 1. Additional needs assessment

Chapter 3: Design Process

In this chapter, the operating principles and design process of the AmbuBox EURS will be described in greater detail.

3.1 System Design Overview

The idea of the AmbuBox design is to allow for pneumatic control over the compression and expansion of a self-inflating AmbuBag. In other words, the self-inflating bag is squeezed in a pressure-regulated environment. The system itself adopts a modular and independent design scheme, assembled with off-the-shelf parts. It consists of a chamber module, a control module, and the breath circuit module. Figure 2 demonstrates the interconnection of the three independent modules and the pathway of air being delivered to the patient.

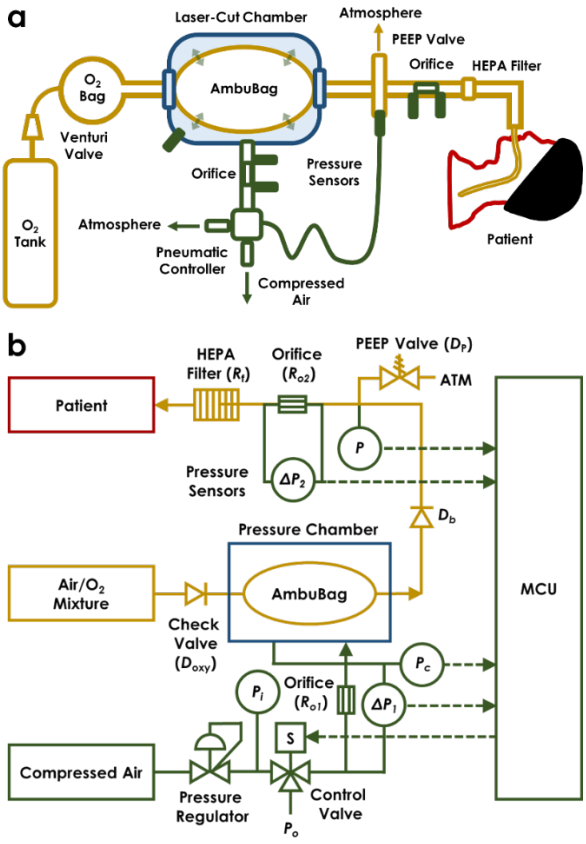

Figure 2. System diagram [8]. (a) Schematic illustration of the AmbuBox EURS; and (b) system-level block diagram of the control system, including the pneumatic valve control and signal transmission (dotted lines) from the sensors to the microcontroller unit (MCU).

As shown in Figure 2a, the chamber module (colored in blue) encapsulates the self-inflating bag on a manual resuscitator. It creates bidirectional sealing for the self-inflating bag such that the internal chamber space is fully isolated from the atmospheric environment. Positive air pressure (P_i) from a compressed air source is introduced to the chamber interior which then squeezes the self-inflating AmbuBag. A one-way valve (D_b) at the self-inflating bag outlet then opens, letting oxygenated air into the breath circuit. Releasing the chamber pressure (P_c) then allows the self-inflating bag to return to its fully inflated state. As the self-inflating bag expands, oxygenated air refills through another one-way valve (D_{oxy}). The control module (in green) is in direct supervision of the airflow in and out of the

chamber via a three-way solenoid valve (*S*), and therefore able to control the deflation cycle of the self-inflating bag. The control module consists of a microcontroller unit (MCU) with a few peripherals to pick up operator settings and adjust the inflation and deflation time accordingly. Other peripherals including flow sensors (R_{o1}, R_{o2}) and pressure sensors (P_c, P) monitor the chamber module and breath circuit. The breath circuit (in yellow) uses approved ventilators tubing and connectors to deliver oxygenated air from the manual resuscitator. Air exhaled by patients is exhausted through a HEPA filter and a standard adjustable PEEP valve.

3.2 Design Detail

In this section, I will describe the design process of each AmbuBox system module in greater detail.

Chamber module

As a proof-of-concept demonstration, the chamber module was initially made using a food storage container. Two circular openings were made on the food storage container on opposite sides to allow placement of the self-inflating bag. The container lip and the two openings were then sealed with hot glue. This early demonstration effectively created an air-tight chamber in which air pressure could be consistently built up.

In later iterations, we attempted to create a more robust chamber structure using 3D printing technology. The chamber CAD model adopted an oval-shaped interior to minimize the gap between self-inflating bag and chamber walls, so that an overall smaller internal volume would yield more responsive pressure control inside the chamber. As shown in Figure 3b, the 3D printed chamber (using 2.85mm PLA filament on Ultimaker 2 Extended+, support provided by the Engineering Student Design Center) was made of two components: an upper cap and a lower cap, both were identical. They were designed with

curved edges at the ends to best fit the contour of the self-inflating bag tips. The two caps were held together by metal hinges and closed by clasp clamps. Rubber strips were applied at the cap-to-cap interface to improve airtightness. This design aimed to reserve the function for convenient separation of the caps to quickly access the self-inflating bag in situations of emergency or system failure. However, my initial testing of the 3D printed chamber suggested poor airtightness performance at the chamber wall. By building up positive pressure inside the assembled chamber under water, excessive air leakage from the side wall was observed. Although I further optimized printer settings for higher infill density and increased wall thickness to create stronger air trap, the air leakage issue persisted. This was partially due to the leaky mesh structure in 3D printed parts using fused deposition modeling (FDM) technology. In addition, the nonuniformity of surface finish also made sealing the caps difficult. Other printing technologies such as SLA and PolyJet were considered, but these methods would be extremely costly.

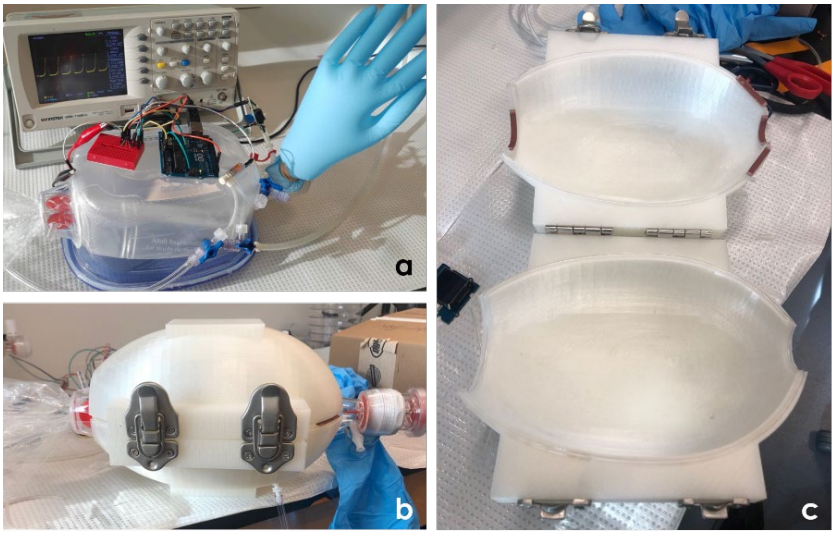

Figure 3. Prototypes of the chamber module. (a) Early demonstration made using food storage container; and (b-c) 3D printed assembly with hinging and locking mechanism.

Upon evaluation of the drawbacks of the 3D printing approach, we moved onto a similar dual-cap design using acrylic panels. Figure 4b-4d demonstrates the bidirectional sealing of self-inflating bag into an

acrylic chamber. Each of the two caps was prepared by laser ablation (Epilog Mini 18/24 laser system, Epilog Laser, Golden, CO) of five pieces of 0.5-inch-thick acrylic panels, with interlock structures designed for better alignment. I assembled and bonded the acrylic panels using acrylic cement (cat. no. 10315, IPS. Corporation, Compton, CA). I then installed four clasp clamps to hold and seal the two caps tightly with rubber bands attached to both heads of the self-inflating bag to enhance sealing. The use of acrylic panels significantly improved overall airtightness without critical air leakage.

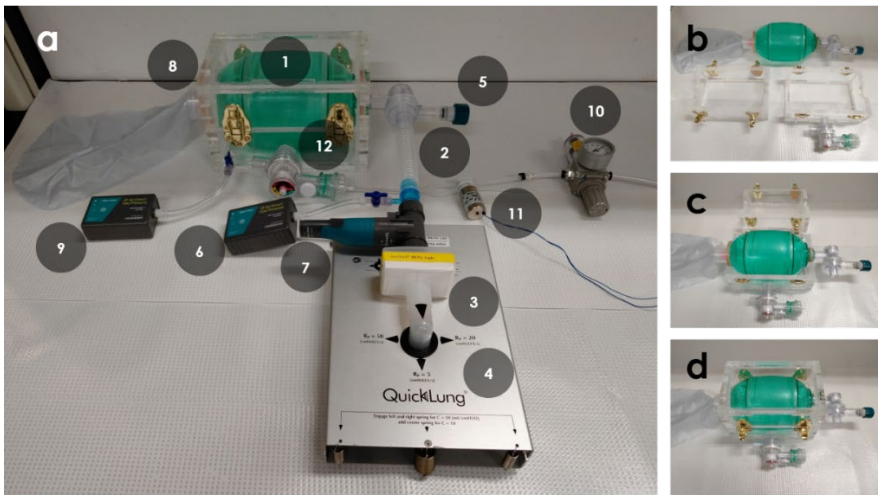

Figure 4. Overview of the testing system and assembly of AmbuBox [8]. (a) Photo of the chamber module and breath circuit for testing; and (b-d) the bidirectional sealing mechanism and the chamber assembly.

Breathing circuit

As shown in the testing system in Figure 4a, the self-inflating bag (1, AF5040MB, AirFlow manual resuscitator adult size, SunMed Medical, Marlton, NJ) was connected with an extension tubing (2) and a HEPA filter (3, ISO-Gard HEPA Light, Teleflex, Morrisville, NC) into a test lung (4, QuickLung Breather, IngMar Medical, Pittsburgh, PA). The exhausted air from the test lung exited through a manually adjustable PEEP valve (5, VP700, SunMed Medical) connected with the self-inflating bag. At the input

end of the self-inflating bag (8) where the O_2 bag was located, the fraction of inspired oxygen (FiO_2) could be regulated with a Venturi flow valve.

Control module & computer program

The core of the AmbuBox control module is an MCU (ATmega2560 on Arduino Mega R3, Arduino). As an overview, the MCU adjusts the opening and closure duration of a three-way solenoid valve (11, Masterflex 3-way solenoid pinch valve, Cole-Parmer, Vernon Hills, IL) to allow airflow (from pressure regulator, 10, SAW2000M-N02BG, PneumaticPlus, Torrance, CA) in and out of the chamber module at MCU-computed time constraints. We connected one end of the solenoid valve with atmosphere and the pressure regulator, while the other end was connected to the chamber with an adaptor (12) detached from a resuscitator. Due to a relatively high operating voltage of the solenoid actuator valve at 12V that the MCU cannot directly supply, a solid-state relay (KF0602D, Kyotto, Kytech Electronics, Shenzhen, China) and a 12V power adaptor were used to introduce a separate powering loop.

In the testing system, we used a pressure sensor (6, Go Direct Gas Pressure Sensor, Vernier, Beaverton, OR) and a spirometer (7, Go Direct Spirometer, Vernier) with the Vernier Graphical Analysis mobile application for quick data visualization. They were connected inline between the extension tubing and the filter with an adapter that was originally used for oxygen enrichment in CPAP machines. An additional Vernier pressure sensor (9) was connected to monitor the chamber pressure.

In the latest iteration, I utilize two miniature pressure sensors (MPX5050DP, NXP, Eindhoven, the Netherlands) to replace the Vernier pressure sensors to monitor simulated patient (QuickLung Breather, IngMar Medical) end pressure and the internal pressure of the chamber module. A disposable commercially available ventilator flow sensor (PN 281637 Medical Flow Sensor, Hamilton Medical, Reno, NV) as a replacement for the Vernier spirometer, is now integrated into the breath circuit. The pressure

drop across the flow sensor is then measured by a differential pressure sensor (SDP 816, Sensirion AG, Staefa, Switzerland) for the computation of flowrate and tidal volume. Besides the aforementioned sensing peripherals, the control module has a user interface. Once the system enters operation stage, the LCD display and two additional mini-LED bulbs as part of the interface together display monitored parameters and signal any alarm conditions. To better illustrate the user interface, my design sketch is shown in figure 5.

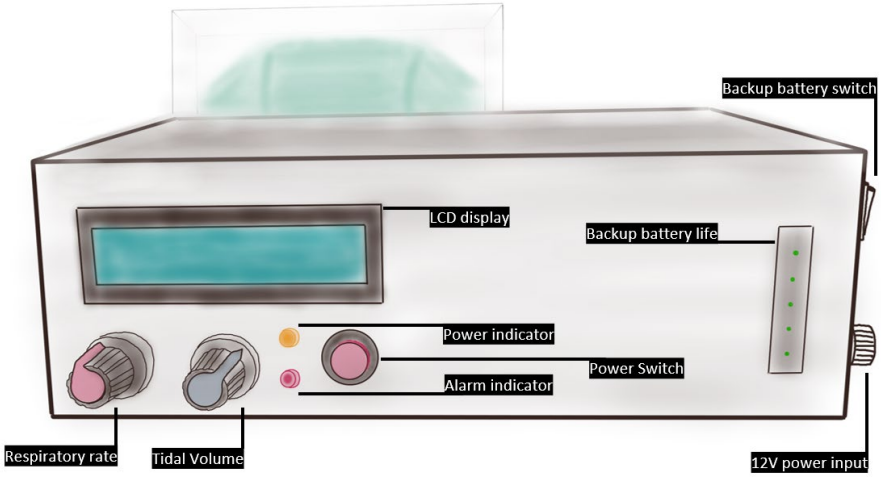

Figure 5. AmbuBox control module and user interface.

The AmbuBox control program is written in Arduino IDLE using C and C++. I program the MCU to read analog signals from the installed peripherals at a maximum frequency of 50Hz. User settings, including respiratory rate (RR) and tidal volume (TV), are denoted by the voltage drop across potentiometers (used as adjustment knobs). The analog voltage signals collected by the MCU at a specific knob turning position is transformed to corresponding respiratory rate and tidal volume. The pressure sensors communicate with the MCU through their designated voltage output pins. Collected pressure signals are also displayed in desired units (cmH_2O). Both user settings and pressures are collected simultaneously for responsive and timely system feedback. (See the communication roadmap in Figure 6) At the MCU

output terminals are the LCD panel, alarm LEDs and a solid-state relay. The solid-state relay receives ON/OFF control signal also at a maximum frequency of 50Hz so that the solenoid valve may respond in no more than 20ms delay. Both the LCD display and alarm LEDs get refreshed at a relatively lower frequency at 2Hz, which is sufficient for viewing system status. A cooling fan powered by the MCU's 5V output is attached to the solenoid valve to avoid overheating.

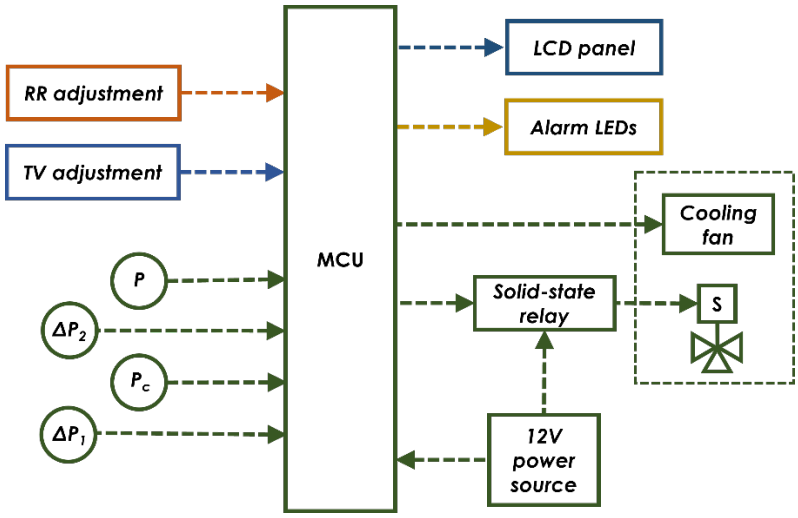

Figure 6. Communication roadmap of MCU and its peripherals.

The control system is powered by a 12V power adaptor with a built-in 12V, 3000mAh lithium-ion battery pack (TalentCell, Shenzhen, China) as the backup power source. I use a commercially available power Y cable to connect the system to these two distinct power sources as a simple power management scheme. Under normal operating conditions when the 12V adaptor is plugged in, the system runs on power supplied by the adaptor while the battery pack gets charged. With a potential power interruption, the system will then automatically be powered by the battery pack. The 12V, 3000mAh battery is expected to power the AmbuBox system (rated to be roughly 5W) for 7 hours. In order to provide indication of remaining battery life, I take advantage of the battery pack's status bar by integrating it on the user interface (see Figure 5). I also add the power indicator to show the current

source of power. When the backup battery is in use during power supply failure, resulting in a slight voltage reduction detected by a custom-built voltage sensor circuit, the power indicator lights up signaling that an immediate restoration of power is recommended.

Aside from power failure alarm, the alarm indicator LED is programmed to signal all other alarm conditions. Any ongoing alarm conditions will also be displayed on the LCD panel. As an example, for the alarm that signals tidal volume deviation by more than 20%, the system activates the alarm indicator LED and displays *"TV: (current set value) Error"*. Once the issue is resolved and the tidal volume falls back into the acceptable range, the alarm is cleared.

Parameter control & characterization

Adjustable parameters identified from the AAMI guidance document are PEEP, tidal volume, respiratory rate, and I:E ratio. Since a manual adjustable PEEP valve is included in the breath circuit, the adjustment of PEEP is done by turning the valve cap.

The respiratory rate (RR, in breaths per minute) is adjustable from 10 bpm to 30 bpm. At a respiratory rate of 10 bpm, each breathing cycle is allowed a duration of 6 seconds, and 2 seconds at 30 bpm. The correlation between the respiratory period (T, in seconds) and the respiratory rate can be described as T = 60/RR. With the breath period T, it can then be split into t_{insp} (inspiration time or inflation duration in the chamber, $t_{insp} = t_{infl}$) and t_{exp} (expiration time) to achieve a desired I:E ratio ($t_{insp} : t_{exp}$), given that T = $t_{insp} + t_{exp}$. However, since the self-inflating bag is passively compressed by air pressure developed over time, tidal volume (TV) is dependent on t_{insp} (or t_{infl}). As shown in Figure 7, my parametric study reveals that the tidal volume increases approximately linearly with t_{infl}. In other words, the expected tidal volume changes with respiratory rate and I:E ratio which are determining factors of t_{infl}.

I prioritize the adjustment of expected tidal volume in the AmbuBox, and as such the corresponding t_{infl} is computed in reverse based on the relationship found in the parametric study for specific lung parameters and system settings. Lastly, t_{infl} and respiratory rate are used to calculate I:E ratio. The I:E ratio can be considered a passively adjusted parameter, although it does change with respiratory rate and the expected tidal volume, illustrated in Figure 8 which I plot using the 1st order linear regression of *C20 R50* in the parametric study: $TV = 300.71t_{infl} - 37.869$. With varying lung compliance and resistance, the system needs to be optimized with the corresponding regression formula. The lowest tidal volume expected to be delivered by the AmbuBox is 250 mL, and therefore breathing modes falling under the dotted line (as shown in figure 8) cannot be supported by my design. A table of available modes is provided in the Appendix.

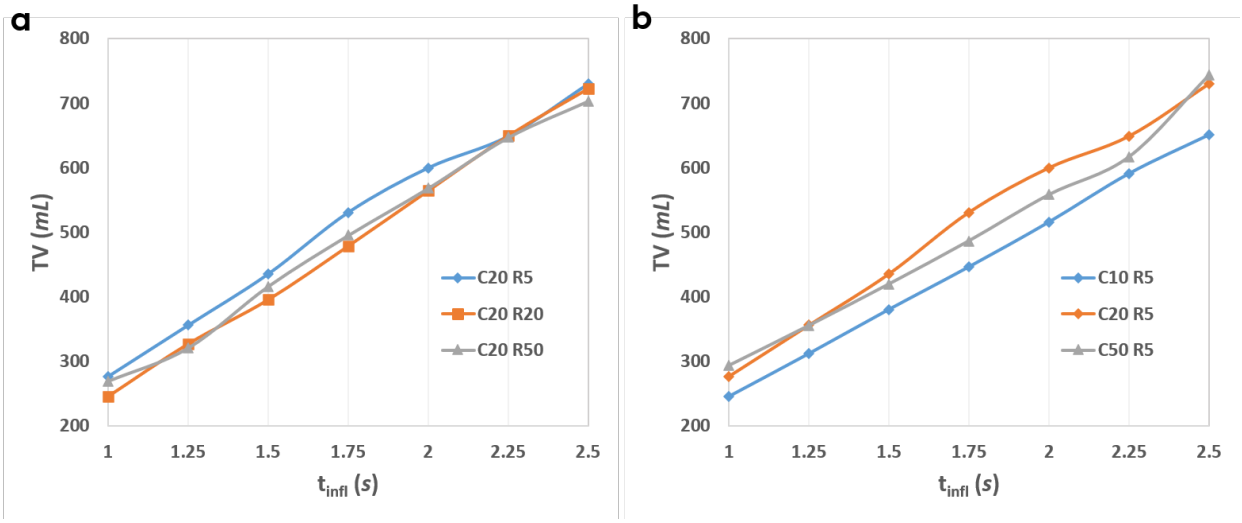

Figure 7. Parametric study of the AmbuBox. Tidal volume is dependent on inspiratory duration, (a)under the testing conditions of resistance (R) from 5 to 50 $cmH_2O/(L/s)$, compliance (C) = 20 mL/cmH_2O, peak end expiratory pressure (PEEP) = 5 cmH_2O, and input pressure (P_i) = 15 psi; and (b) under the testing conditions of C from 10 to 50 mL/cmH_2O, R = 5 $cmH_2O/(L/s)$, PEEP = 5 cmH_2O, and P_i = 15 psi.

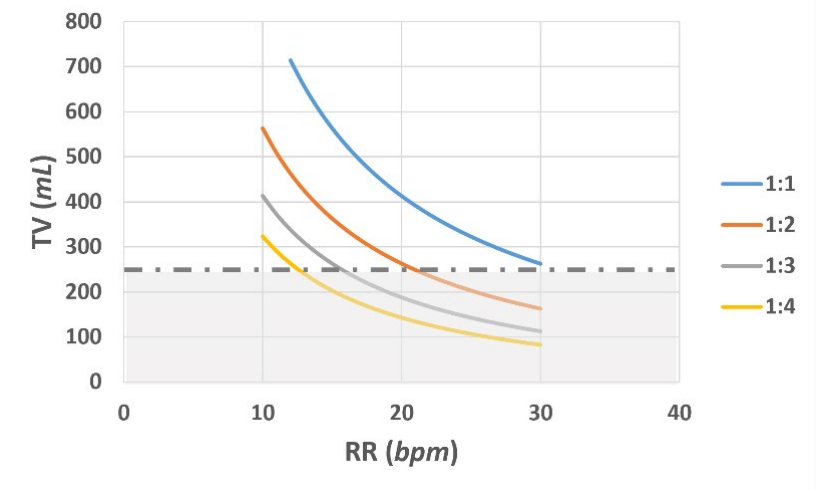

Figure 8. I:E ratio variation with respect to respiratory rate and expected tidal volume for C = 20 mL/cmH_2O, R = 50 cmH_2O/(L/s), PEEP = 5 cmH_2O, and P_i = 15 psi. See Appendix A1 for available modes. Respiratory rate of 10 bpm and 11 bpm at 1:1 ratio are not supported, since a potential risk of the self-inflating bag failing to fully inflate was identified from previous studies [8].

Chapter 4: Design Output

In this chapter, the latest AmbuBox prototype will be covered, including its basic functions and updated features.

4.1 System Assembly & General Behavior

My final AmbuBox system assembly is shown in Figure 9. It adopts an overall compact design for better space management in emergency care facilities. To better visualize the AmbuBox's pneumatic control over the active delivery of air into a simulated patient, the typical transient pressure, the flow rate, and the cumulative volume along the breath circuit and the pressure inside the AmbuBox chamber are plotted in Figure 10. The pressure and flow rate signals are collected with built-in sensors, while cumulative volume is computed by integrating discrete flow rate signals over time. The testing

conditions are as follows: compliance (C) is 20 mL/cmH_2O, resistance (R) is 50 cmH_2O/(L/s), PEEP pressure is 5 cmH_2O, and input compressed air pressure (P_i) is 15 psi. On the AmbuBox user interface (shown in Figure 9), respiratory rate is set to 12 bpm, and expected tidal volume is set to 570 mL. The resulting breath period T is measured to be 5s, which is adequate for the preset respiratory rate. The tidal volume turns out being 540 mL, off by about 5% from the expected amount. The resulting tidal volume is considered acceptable given that a 20% deviation is permitted [16].

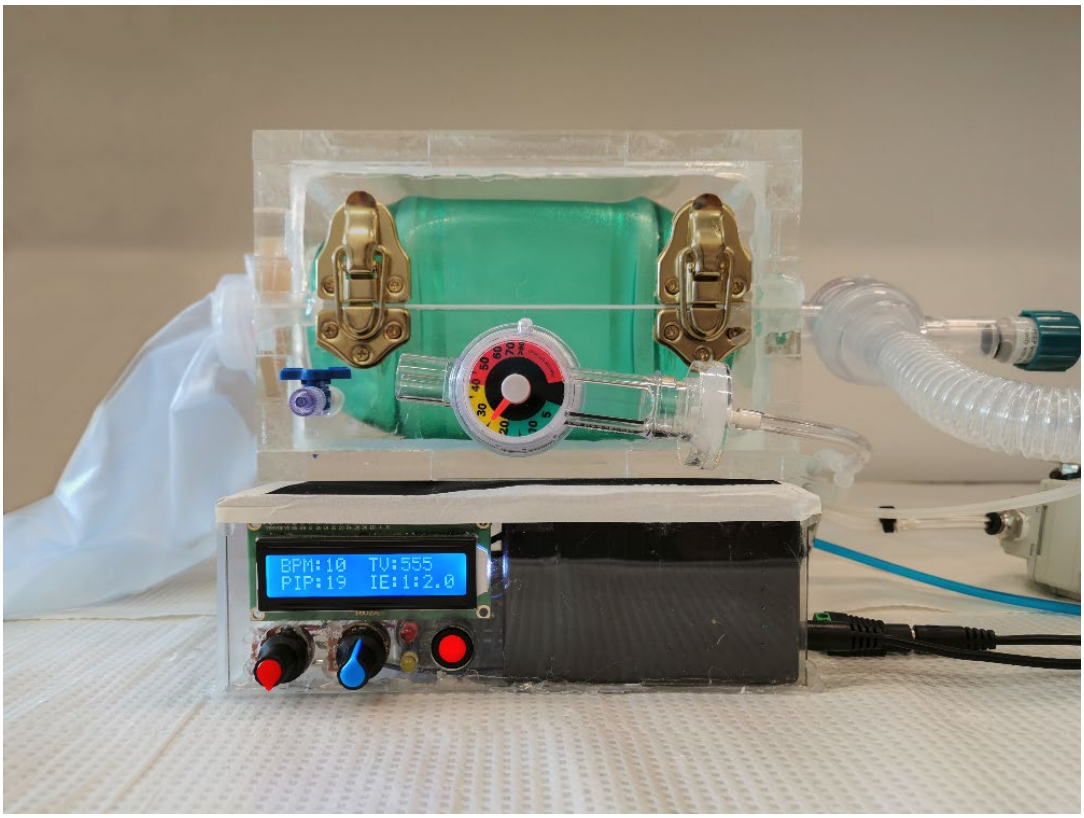

Figure 9. The AmbuBox system assembly, which consists of a chamber module (top), a control module (bottom) and the breath circuit (right). The LCD panel displays the peak inspiratory pressure (PIP), and settings for respiratory rate (BPM), tidal volume (TV) and I:E ratio (IE).

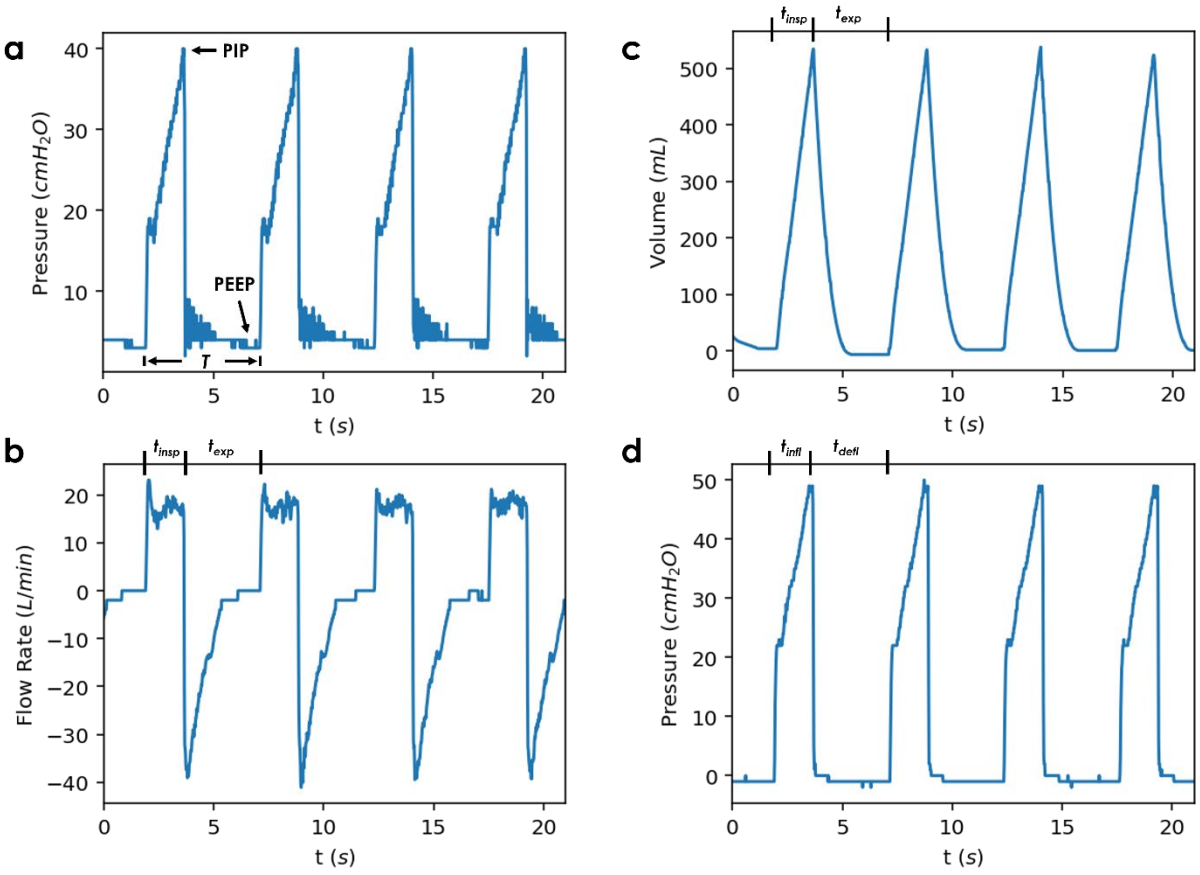

Figure 10. Real-time monitoring of the pressure and flow conditions in patient airway and AmbuBox chamber. Readings from the patient's breath circuit, including (a) airway pressure, (b) inspiratory flowrate, and (c) cumulative volume entering the patient lung. Readings from the AmbuBox chamber, (d) chamber pressure. The test conditions are as follows: compliance (C) = 20 mL/cmH_2O, resistance (R) = 50 cmH_2O/(L/s), positive end-expiratory pressure (PEEP) = 5 cmH_2O, chamber input pressure (P_i) = 15 psi, respiratory rate (RR) set to 12 bpm, and expected tidal volume set to 570 mL.

4.2 System Demonstration

I performed real-time adjustment of tidal volume and respiratory rate on the AmbuBox to further demonstrate the system's behavior. As shown in Figure 11a-11b, with all other parameters held constant, increasing the tidal volume takes effect immediately on the subsequent breath cycle and

drives the measured tidal volume up to the desired level. The corresponding PIP also experiences a significant increase. The actual respiratory rate remains stable during the tidal volume adjustment. Similarly, when only the respiratory rate is tuned up, shorter breath interval is reflected in figure 11c-11d, while the measured tidal volume stays approximately the same. Therefore, the AmbuBox system is capable of executing user commands in a responsive and reliable manner.

In Table 3, the specifications of the latest AmbuBox prototype are listed. All design constraints specified in Chapter 2 for emergency use have been successfully met. There are a few functional needs including alarm conditions for complete loss of power and continuing pressure that should be implemented in future iterations. These features can in fact be effectively delivered via software updates.

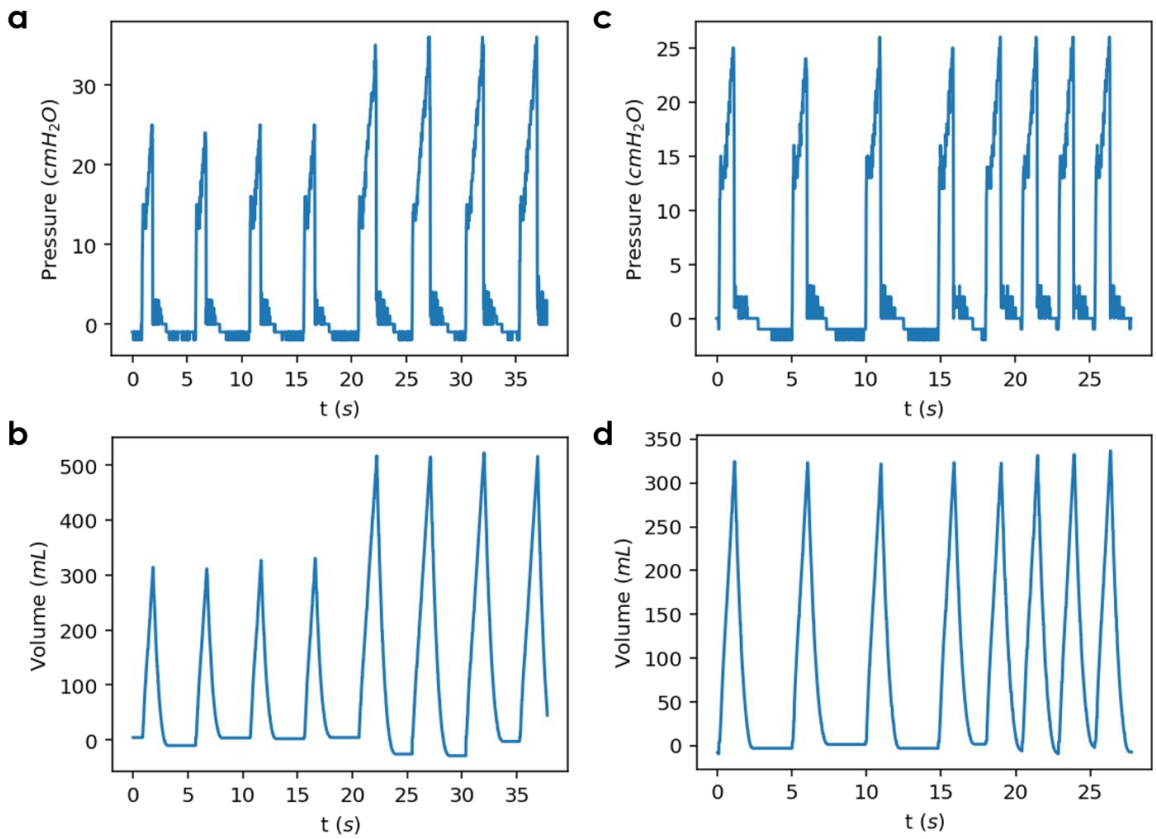

Figure 11. Demonstration of AmbuBox resuscitator system. (a-b) Real-time adjustment of tidal volume from 320 mL to 570 mL, under the testing conditions of compliance (C) = 20 mL/cmH_2O, resistance (R) =

50 $cmH_2O/(L/s)$, peak end expiratory pressure (PEEP) = 5 cmH2O, input pressure (P_i) = 15 psi, and respiratory rate (RR) = 12 bpm; (c-d) real-time adjustment of respiratory rate from 12 bpm to 20 bpm, under the testing conditions of C = 20 mL/cmH_2O, R = 50 $cmH_2O/(L/s)$, PEEP = 5 cmH_2O, P_i = 15 psi, and tidal volume (TV) = 340 mL.

Table 3. Specifications of the AmbuBox EURS.

Respiratory rate	10 - 30 bpm, adjustable in step of 1 bpm
Tidal volume	250 - 700 mL, adjustable in step of 5 mL
Inspiratory time	1 - 2.5 sec
Peak pressure	15 - 50 cmH_2O
PEEP	5 - 20 cmH_2O, adjustable
I:E ratio	1:1 - 1:4, passively adjusted
Parameter monitoring	PIP; tidal volume
HEPA filtration	Yes
Power	120V-240V power supply included; 7 hours of emergency battery life when external power supply becomes unavailable
Alarms	Power supply failure; maximum inspiratory airway pressure exceeds 40 cmH_2O; low inspiratory pressure; estimated tidal volume not achieved or exceeded

Chapter 5: Emergency Use Authorization

As part of the initial efforts to make AmbuBox publicly available, I also studied the general requirements for FDA Emergency Use Authorization (EUA) submission. Research methods used include official document review and one-to-one interview with medical device regulatory consultants.

In March 2020, the FDA issued an umbrella EUA to address shortage of approved ventilators. Ventilators that met specified criteria for safety, performance and labeling may be eligible for EUA. The criteria were specified in the Ventilator EUA Appendix A. In addition, ventilator devices were classified based on their intended use and working principle. Here, several types of emergency use ventilators were identified: continuous ventilator, emergency ventilator, emergency resuscitator, gas-machine, respirator, oxygen conserver, positive pressure breathing device, etc. [13], [15] The AmbuBox system developed in accordance to AAMI CR503:2020 falls into the category of emergency resuscitator. [16]

To gain ventilator EUA, the provided interactive review template may be used to document applicant and device information [15]. The interactive review template also checks for fulfillment of criteria specified in the Ventilator EUA Appendix A. Table 4 below outlines the structure of the interactive review template. Initial submission of completed interactive review template will be considered as pre-EUA submission. Upon submission of the template, collaboration with the FDA during the review process is needed to address any issue and the applicant may be asked to provide additional information. [15] To prepare for submission, I documented the status for all required materials outlined in Table 4 and provided some potential responses based on AmbuBox system specifically.

Table 4. Outline of the ventilator EUA interactive review template. [15]

Section	Subject	Description and Attempted Response
Basic information	Purpose of submission	Request for the addition of the AmbuBox Emergency Resuscitator device to the Ventilator EUA.
	Applicant, brand name and model number	MiNI Lab; AmbuBox 1.0
	Indication for use	Description: Circumstances or conditions that the device would be used. Any emergency situation in which ventilation is required and an FDA approved mechanical ventilator is not available.
	Regulatory information (Approval/Clearance status in US)	The device has not been marketed in the US.
	Marketing authorization in any other country	The device does not have marketing authorization in other country.
	Unmet need	The Ventilator Emergency Use Authorization (EUA) was issued in response to concerns relating to insufficient supply and availability of FDA-cleared ventilators for use in healthcare settings to treat patients during the Coronavirus Disease 2019 (COVID-19) pandemic.

Section	Subject	Description and Attempted Response
EUA section II information	Product labeling	Description: A copy of product labels and instructions for use is needed
	Applicable standards	Description: As discussed previously, conformance to the recommended standards outlined in the guidance needs be stated. The device has been designed, evaluated, and validated in accordance with the recommended standards outlined in the AMII Emergency Use Resuscitator Systems Design Guidance (AAMI/CR503:2020) and the End User Disclosures for Emergency Use Resuscitator Systems (AAMI/CR504:2020). Applicable standards identified from AAMI/CR503:2020 (also found in Appendix A) include the following: IEC 60601-1, Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. ISO 80601-2-80 First Edition 2018-07: Medical Electrical Equipment - Part 2-80: Particular Requirements for Basic Safety and Essential Performance of Ventilatory Support Equipment for Ventilatory Insufficiency
	Quality system	Description: Documentation of quality management system (QMS, in compliance with either 21CFR Part 820 or ISO 13485:2016) is needed from a certified medical device manufacturer who makes the device. Developing QMS from scratch on university campus is also considered as an option. This would involve initial resource allocation for labor, materials, machines and software, plus the following processes: document and records management, design controls, risk management, training, supplier management and complaint handling. The development of QMS on campus is expected to take 4-18 months depending on resources available. (Consultation service provided by Core Compliance, MEDIcept and Regulatory Compliance Associates)

Section	Subject	Description and Attempted Response
EUA section II information	Power supply	The device is designed with U.S. power adaptor.
	Authorized labeling	Description: Applicant needs to confirm that the Fact Sheets (provided) and labeling/instructions for use will be shipped with the device. The product will be accompanied by the Fact Sheets identified above and the instructions for use.
EUA section IV conditions of authorization	Conditions of authorization	Description: Applicant needs to provide a written confirmation for the conditions for sponsors set forth in Section IV of the Ventilator EUA. UC Davis MiNI Lab AmbuBox Team (I) will be meeting the conditions for sponsors set forth in Section IV of the Ventilator EUA. 1) I will make ventilators, ventilator tubing connectors, and ventilator accessories available with the authorized labeling. 2) I must comply with all applicable labeling requirements under the FD&C Act and FDA regulations, except for unique device identification requirements. 3) All descriptive printed matter relating to the use of the authorized ventilator, ventilator tubing connector, or ventilator accessories listed in Appendix B will be consistent with the authorized labeling. No descriptive printed matter relating to the use of the authorized ventilator listed in Appendix B may represent or suggest that this product is safe or effective for the prevention or treatment of COVID-19.

Section	Subject	Description and Attempted Response
EUA section IV conditions of authorization	Conditions of authorization	4) I will have a process in place for reporting adverse events of which they become aware to FDA per mandatory reporting requirements under 21 CFR Part 803. Adverse events of which the manufacturer becomes aware will be reported to FDA. 5) I will ensure that any records associated with this EUA are maintained until otherwise notified by FDA. Such record will be made available to FDA for inspection upon request. 6) Through a process if inventory control, I will maintain records of the healthcare settings to which they distribute the ventilators, ventilator tubing connectors, or ventilator accessories and the number of each such product they distribute. 7) I will be authorized to make additional information relating to the emergency use of the product that is consistent with, and does not exceed, the terms of the letter of authorization. 8) I will notify FDA of any authorized distributor(s) of the product, including the name, address, and phone number of any authorized distributor(s), and provide authorized distributor(s) with a copy of the EUA.
Criteria for safety, performance and labeling (from Appendix A of the EUA)	Declarations of Conformity	Description: Need to have DOC for applicable standards, or use the test report formatted by AAMI to show conformity to applicable standards.

Section	Subject	Description and Attempted Response
Criteria for safety, performance and labeling (from Appendix A of the EUA)	Device specifications and instructions for ventilators and accessories	Description: Specification sheet and user instruction needs to be attached.
	Reprocessing and shelf-life information	Description: Information on how to reprocess reusable components and shelf-life needs to be provided.
	Facility requirements	Description: Gas connection type, gas type, gas source and environmental controls. The AmbuBox system requires at least medical air or ambient air supply at or above 15 psi to operate. Oxygen supply and negative pressurized environment are recommended.
	Labeling requirements for conditions of use	Description: Applicant needs to confirm device specifications (including ventilatory parameters), information regarding alarms, device reprocessing instructions, and other instructions are included in the labeling.
Benefit/Risk assessment		Description: Risk benefit analysis needs be outlined.
Interactive review log		See Appendix Supplementary Table 3.

Conclusion

The AmbuBox project was a reflection of the collaborative nature of our team in order to help support the wellbeing of our species in the context of a global pandemic. The development of the AmbuBox required the application of multiple engineering skills including rapid prototyping, programming, electrical circuitry, and signal processing. I specifically worked on improving the AmbuBox design in accordance with consensus standards to ensure all fundamental user needs were met and that the value of the AmbuBox as an emergency use resuscitator could be recognized by regulatory officials. My work delivered a fully functional AmbuBox system prototype which met all design constraints. There remains additional work to be done to achieve improved safety and reliability. According to the study of ventilator emergency use regulation, risk management plays a huge factor in the decision of regulatory officials. Therefore, understanding and mitigating the potential failure modes and underlying risks are important for obtaining regulatory approval, and the safety of patients.

Appendix

Supplementary Table 1. Tidal volumes at different respiratory rate and I:E ratio settings. (C = 20 mL/cmH_2O, R = 50 cmH_2O/(L/s), PEEP = 5 cmH_2O, and P_i = 15 psi)

BPM \ I:E Ratio	1:1	1:2	1:3	1:4
10	-	564	413	323
11	-	509	372	290
12	714	463	338	263
13	656	425	309	-
14	607	392	284	-
15	564	363	263	-
16	526	338	-	-
17	493	316	-	-
18	463	296	-	-
19	437	279	-	-
20	413	263	-	-
21	392	-	-	-
22	372	-	-	-
23	354	-	-	-
24	338	-	-	-
25	323	-	-	-
26	309	-	-	-
27	296	-	-	-
28	284	-	-	-
29	273	-	-	-
30	263	-	-	-

Supplementary Table 2. Timing study of inspiratory time (t_{insp}). Boxes marked in green represent valid settings. Boxes marked in red represent unsupported settings.

	I:E ratio	1:1	1:2	1:3	1:4
BPM	**breath period/interval (t)**				
10	6	3	2	1.5	1.2
11	5.454545455	2.727272727	1.818181818	1.363636364	1.090909091

12	5	2.5	1.666666667	1.25	1
13	4.615384615	2.307692308	1.538461538	1.153846154	0.923076923
14	4.285714286	2.142857143	1.428571429	1.071428571	0.857142857
15	4	2	1.333333333	1	0.8
16	3.75	1.875	1.25	0.9375	0.75
17	3.529411765	1.764705882	1.176470588	0.882352941	0.705882353
18	3.333333333	1.666666667	1.111111111	0.833333333	0.666666667
19	3.157894737	1.578947368	1.052631579	0.789473684	0.631578947
20	3	1.5	1	0.75	0.6
21	2.857142857	1.428571429	0.952380952	0.714285714	0.571428571
22	2.727272727	1.363636364	0.909090909	0.681818182	0.545454545
23	2.608695652	1.304347826	0.869565217	0.652173913	0.52173913
24	2.5	1.25	0.833333333	0.625	0.5
25	2.4	1.2	0.8	0.6	0.48
26	2.307692308	1.153846154	0.769230769	0.576923077	0.461538462
27	2.222222222	1.111111111	0.740740741	0.555555556	0.444444444
28	2.142857143	1.071428571	0.714285714	0.535714286	0.428571429
29	2.068965517	1.034482759	0.689655172	0.517241379	0.413793103
30	2	1	0.666666667	0.5	0.4

Supplementary Table 3. Interactive review log.

Date	**Type of Interaction** (phone/ email/ formal submission-DCC)	**Brief Description** (e.g., questions asked/ feedback from FDA received / any word documents included)
11/9/2020	Email	FDA confirmed that they were still taking ventilator EUA applications.
11/12/2020	Email	Asked about identifying US agents and manufacturer. FDA directed us to Ventilator FAQ webpage.
12/18/2020	Email	Asked about the requirements for DOC. FDA directed us to Device Advice webpage for more information.
12/23/2020	Email	Asked about the relevancy of AAMI guidance documents for ventilator EUA regulation. FDA quoted the AAMI guidance documents on 01/12/2020.
01/05/2021	Email	Asked for the latest update on IRT. FDA confirmed the latest version is the one being posted.
01/11/2021	Email	Asked about recommendations for animal studies and clinical tests. The response is that animal studies and clinical tests are not currently a requirement set forth by specific standards or the AAMI guidance documents.

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