Multiplex Ventilation: Solutions for Four Main Safety Problems

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BACKGROUND: The COVID-19 pandemic has led to an increased demand for mechanical ventilators and concerns of a ventilator shortage. Several groups have advocated for 1 ventilator to ventilate 2 or more patients in the event of such a shortage. However, differences in patient lung mechanics could make sharing a ventilator detrimental to both patients. Our previous study indicated failure to ventilate in 67% of simulations. The safety problems that must be solved include individual control of tidal volume (V_T), individual measurement of V_T, individualization of PEEP settings, and individual PEEP measurement. The purpose of this study was to evaluate potential solutions developed at our institution. METHODS: Two separate lung simulators were ventilated with a modified multiplex circuit using pressure control ventilation. Parameters of the lung models used for simulations (resistance and compliance) were evidence-based from published studies. Individual circuit-modification devices were first evaluated for accuracy. Devices were an adjustable flow diverter valve, a prototype dual volume display, a PEEP valve, and a disposable PEEP display. Then the full modified multiplex circuit was assessed by ventilating 6 pairs of simulated patients with different lung models and attempting to equalize ventilation. Ventilation was considered equalized when V_T and end-expiratory lung volume were within 10% for each simulation. RESULTS: The adjustable flow diverter valve allowed volume adjustment to 1 patient without affecting the other. The average error of the dual volume display was –17%. The PEEP valves individualized PEEP, but the PEEP gauge error ranged from 17% to 41%. Using the multiplex circuit, ventilation was equalized regardless of differences in resistance or compliance, reversing the "failure modes" of our previous study. CONCLUSIONS: The results of this simulation-based study indicate that devices for individual control and display of V_T and PEEP are effective in extending the usability and potential patient safety of multiplex ventilation. *Key words: mechanical ventilation; emergency ventilation; COVID-19; lung simulator; split ventilation; surge ventilation; national stockpile; differential ventilation; ventilator sharing; ventilator shortage; simultaneous ventilation; dual ventilation.* [Respir Care 2021;66(7):1074–1086. © 2021 Daedalus Enterprises]

Introduction

Since the late 2000s there has been concern for a possible mechanical ventilator shortage due to a pandemic or mass casualty situation. A major problem in a pandemic resulting in respiratory illnesses includes availability of ventilators capable of safely ventilating patients with ARDS.[1,2] The rapid progression of COVID-19, causing acute respiratory illness in many people simultaneously, has re-opened the issue of a ventilator supply shortage.[3-5] In the spring of 2020 a surge of patients with acute hypoxemic respiratory failure requiring mechanical ventilation required the release of ventilators from the Strategic National Stockpile, with ventilators being delivered to a number of states experiencing shortages. These ventilator shortages spawned several reports describing circuit modifications that allow mechanical ventilation of 2 or more patients with a single ventilator.[4,6] Sommer et al[7] described a system for ventilating 2 patients with a single device in 1994, which involved a "bag-in-the-box" system, as is commonly accomplished using anesthesia devices. In 2002, Lerner[8] received a patent for a system he termed "multiplex ventilation," describing a device with a single gas source, a controller, and a series of flow regulators to provide support for up to 8 patients. Fortunately, neither system ever needed to be tested on patients.

An early suggestion for ventilating multiple patients with a single ventilator was naïve, assuming equal distribution of ventilation by visual observations while disregarding the necessity of quantitative measurements.[2] A follow-up study in 4 sheep demonstrated the potential dangers of multiplex

ventilation when lung mechanics were unequal among the animals,[9] Branson and Rubinson[10,11] warned that, in both instances, the potential existed for unintended consequences resulting from dissimilar respiratory mechanics. Smith and Brown[12] ventilated 2 volunteer subjects with a single intensive care ventilator using noninvasive ventilation in 2009. They also used a modified split circuit with no within-circuit modifications to alter the distribution of ventilation. In 2012, Branson and colleagues performed a multi-compartment lung model study of multiplex ventilation, demonstrating the limitations and potential dangers of such a technique.[13]

Since January 2020, a number of investigators have published descriptions of multiplex ventilation that address the necessity of safe ventilation. Some researchers have added one-way valves to the split circuit in an attempt to prevent cross-contamination and rebreathing of CO_2.[14-16] The limitation of adding a one-way valve is that some ventilators are designed to sense a change in pressure or flow at the expiratory valve to allow for a patient-triggered breath. If a one-way valve is in place, the capability for patient trigger might be affected.[15,16] For patient synchrony and to inhibit one patient from controlling the breathing frequency of the other, sedation and paralysis of each patient would be required. Because the safety of using neuromuscular blockade beyond 48 h is unknown, this requirement alone limits the amount of time multiplex ventilation can safely be implemented.[17] Many studies have reported that multiplex ventilation is safest when using pressure control ventilation rather than volume control ventilation.[15,16,18,19] Volume control ventilation poses risks as a rapid change in impedance (ie, change in resistance or compliance) for one patient (eg, tube occlusion or removal from ventilator) would greatly affect the volume delivery to the other.

Recent studies address the shortcomings of the rudimentary circuit approach and suggest modifications with the goal of providing individualized ventilation secondary to patient matching. Prior to implementing multiplex ventilation, patients' lung mechanics and ventilation requirements must be matched accordingly to prevent mismatched ventilation.[14,20] While the initial matching of patients may still be necessary, in-circuit modifications have been presented as a way to adapt ventilation as each patient's lung mechanics change. Proposed requirements for ventilation to be discrete include dual control of tidal volume (V_T), PEEP, F_{IO_2}, and some system of patient monitoring.[15,16,18,20-22] Chatburn et al[15] described the key components of a successful multiplex system as one that allows independent control of V_T and PEEP as well as individual monitoring of these controls. The ability to individually control volume delivery is essential for multiple reasons. If one patient has a sudden change in lung mechanics (eg, decreased compliance or increased resistance), there needs to be a way to quickly adjust the circuit so that the other patient's ventilation is not affected while changes are made to resolve ventilation to the first patient. When a patient has a decrease in compliance, there is lower lung volume at the end of exhalation (end-expiratory lung volume, EELV), leading to the risk of atelectrauma and a drop in P_{aO_2}. To resolve this issue, PEEP can be adjusted to increase EELV. PEEP adjustment must be independent because if the other patient does not require an increased PEEP, there is a risk of lung overdistention and hemodynamic instability.[15]

The first reported cases of using invasive multiplex ventilation for humans occurred in June 2020.[3,4] Beitler and colleagues described support of 3 pairs of patients matched

QUICK LOOK

Current knowledge

The idea of multiplex ventilation has been revisited since the COVID-19 pandemic. Many studies have tried to resolve the safety problems suggested when ventilating > 1 patient on a ventilator. Many circuit design ideas have been tested on test lungs or lung simulators, but few have been used in animal or human studies. The resolution of safety problems must be confirmed before its use with human subjects can be justified.

What this paper contributes to our knowledge

Results from this simulation-based study confirm that the modified multiplex circuit allows for individualization of patient ventilation when there are differences in patient respiratory mechanics. This circuit design solves the main safety issues of multiplex ventilation: partitioning flow to individually control V_T, a means of measuring volume delivery to each patient, the ability to individualize PEEP to each patient in the event that one patient requires a higher PEEP than that set by the ventilator, and a means of measuring the individual PEEP set to each patient.

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Supplementary material related to this paper is available at http://www.rcjournal.com.

Mr Branson has disclosed relationships with Mallinckrodt, Pfizer, Vyaire, Ventec Life Systems, and Zoll Medical. Mr Chatburn has disclosed relationships with IngMar Medical, Vyaire, and Promedic Consulting. The other authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.08749

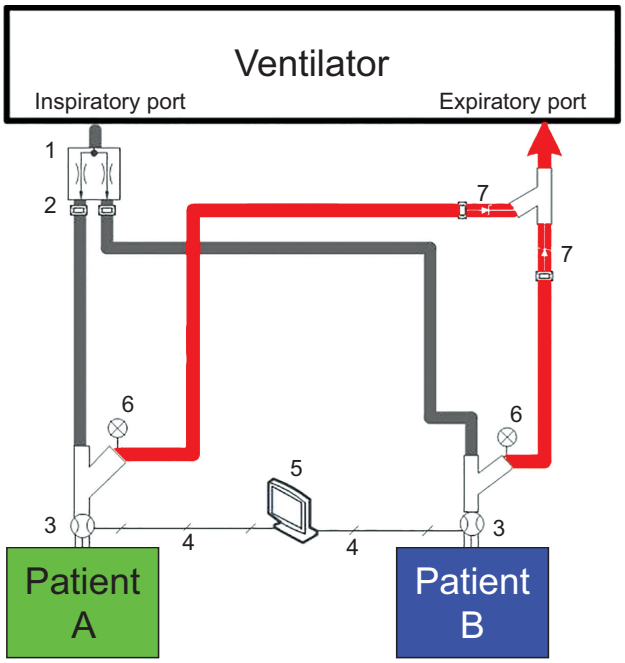

Fig. 1. Modified multiplex ventilation circuit, (1) adjustable flow diverter valve (AFDV), (2) one-way valves, (3) flow sensor, (4) flow signal from flow sensor, (5) dual volume display, (6) disposable PEEP display, (7) PEEP valve with internal one-way valve.

for similar respiratory requirements and respiratory mechanics.[4] They used a split circuit where V_T and pressure were monitored but not individually controlled. An anesthesia ventilator was used for 1 patient pair, and an ICU ventilator was used for 2 other patient pairs. All 6 patients were managed for a short time (ie, 1 patient up to 48 h). Levin et al[3] described a system for multiplex ventilation with a circuit configuration that controls V_T with a flow restrictor valve and monitors volume with spirometry. There was no control or monitoring of individual PEEP. After testing the circuit on a high-fidelity lung simulator, the authors reported a trial of multiplex ventilation on 2 pairs of patients, albeit for only 1 h each.[3] Even though there were no deaths in this small study sample, there are still important dangers in the inability to individualize and monitor ventilation for each patient.

We believe that the studies done thus far have been unsuccessful in managing all the complexities of multiplex ventilation with dynamic changes in lung mechanics. In an attempt to find a more complete and safe way to implement multiplex ventilation, the purpose of this study was to resolve the main problems previously presented by Chatburn et al[15]: (1) the ability to direct inspiratory flow to individualize V_T, (2) the ability to individualize PEEP to manage EELV of each patient, and (3) a way to properly measure delivered V_T and PEEP to each patient. We evaluated several circuit modifications, including a custom flow diverter valve, a custom-designed dual V_T display, in-line PEEP valves, and disposable pressure gauges to monitor PEEP. The study hypothesis was that these proposed hardware solutions would allow providers to avoid failure of multiplex ventilation due to large differences in respiratory system mechanics after patient matching. The primary hypothesis was that these modifications could avoid the simulated failure conditions described previously.[15] A secondary hypothesis was that the control and display devices provided sufficient accuracy for this application in a clinical situation.

Methods

The experimental design of this study was intended to replicate the original multiplex ventilation study by using the exact same lung models, breathing simulators, and ventilator.[15] The original experimental conditions were used to test and compare the ability of the new circuit design to correct failed trials.[15]

Multiplex ventilation was accomplished using a split patient circuit as described by Chatburn et al[15] with some modifications for control and display of V_T and PEEP. The multiplex circuit is simply 2 separate inspiratory and expiratory limbs (with their Y-connectors) connected in parallel as shown in Figure 1. The multiplex circuit was connected to 1 Servo-i ventilator (Maquet Getinge Group, Rastatt, Germany) and connected directly to each lung simulator as shown in Figure 1. A circuit test was not performed on the ventilator as the extended circuit would fail a patient circuit test. All experiments in this study were run at room temperature, without a heated humidifier in line and with the ventilator set at an F_{IO_2} of 0.21.

Five different sets of in-circuit additions (ie, adjustable flow diverter valves [AFDV], PEEP valves, auxiliary volume display [AVD-19], flow sensors, and disposable PEEP gauges) were labeled and used for repeated measures testing. Once each device was tested individually, the entire multiplex circuit (Fig. 1) was tested. The same dual-patient circuit tubing was used for the entire study.

A pair of ASL 5000 breathing simulators (software version 3.6 IngMar Medical, Pittsburgh, Pennsylvania) were used to create the patient simulation and obtain measurements of the outcome variables.[15] The ASL 5000 is a computer-driven piston controlled by the equation of motion where the operator can set parameters to realistically simulate patient inspiratory effort, compliance, and resistance.[23] The use of a high-fidelity lung simulator has been recommended in the use of testing alterations to the multiplex ventilation circuit.[24]

The simulation parameters of the ASL 5000 consist of a single-compartment lung model (compliance and resistance) and an effort model (patient inspiratory muscle effort represented as change in pressure over the inspiratory time). Both the effort model (passive) and lung models

Table 1. Simulator Lung Models

Experiment	A		B		C		D		E		F
Use Case	Balanced Resistance and Compliance		Unequal Compliance		Unequal Compliance (Extreme)		Unequal Resistance		Unequal Resistance (Extreme)		Unequal τ (Extreme)
Patient	1	2	1	2	1	2	1	2	1	2	1	2
Diagnosis	ARDS-Mild	ARDS-Mild	ARDS-Mild	ARDS-Severe	Normal	ARDS-Severe	ARDS-Mild	ARDS-Mild	ARDS-Mild	Asthma-ARDS	ARDS-Severe	COPD
Resistance, cm H_2O/L/s	10	10	10	10	10	10	10	15	10	30	10	25
Compliance, mL/cm H_2O	45	45	45	20	50	20	45	45	45	45	20	60
τ, s	0.45	0.45	0.45	0.2	0.6	0.2	0.45	0.68	0.45	1.35	0.2	1.5

τ = time constant: resistance × compliance

were set to replicate the design of the original study.[15] The effort model was set to represent paralyzed patients with zero muscle force ($P_{max} = 0$). The lung parameters for resistance and compliance were evidence-based and set to represent realistic values reported from human studies.[15,25,26] The simulation models used were implemented to replicate a scenario of ventilating 2 patients with different lung disease states (Table 1).

The AFDV is a device that was 3D-printed after prolonged discussion and prototype testing on the part of the authors in collaboration with the Department of Engineering at the Cleveland Clinic and engineers at Parker Hannifin, the manufacturer of the valves (Figure 2). The AFDV is a flow-proportioning device designed to allow for the division of inspiratory flow from the ventilator to 2 separate patients to individually control V_T. The AFDV is a Y-piece that connects to the ventilator on the inspiratory flow output and can be manually rotated to adjust V_T distribution. The AFDV is specially designed such that splitting the flow does not decrease the total cross-sectional area of the 2 inspiratory limbs of the circuit. That is, as the valve is rotated, flow resistance to 1 patient increases (decreasing flow) while the flow resistance to the other stays the same (maintaining flow). By keeping the cross-sectional area the same, the pressure waveform is unchanged during pressure control ventilation as the valve is adjusted, resulting in an unchanged V_T (see the supplementary materials at http://www.rcjournal.com).

The AFDV can be rotated in 1 of 2 directions (labeled A and B as shown in Fig. 2) to decrease flow to 1 patient. That is, moving the indicator toward A decreases the V_T to patient B and vice versa. The degree of valve rotation is indicated by tick marks labeled A1–10 and B1–10. When the valve is centered (ie, tick mark 0), the flow to each output is equally split and both patients will get the same V_T if they have identical lung mechanics.

For the COVID-19 pandemic, IngMar Medical produced an inexpensive auxiliary volume display, called the AVD-19 (Figure 3). It is a small (3.5" × 2" × 5.5") enclosure containing signal-processing electronics and display hardware. The signals come from 2 disposable variable-orifice flow sensors (Figure 3). The display shows 2 V_T values that are updated with every breath. Above the displayed volumes, the AVD-19 displays the fraction of total volume output by the ventilator that each patient receives (expressed as a percent). The volumes displayed by the AVD-19 are "as measured," meaning that they are uncorrected for humidity, temperature, or barometric pressure. During clinical application (ie, when a heated circuit or heat and moisture exchanger is used), the sensors would be exposed to gas from either the patient or a humidifier at barometric pressure and temperature-saturated conditions (ie, BTPS). The volume differences at these 2 temperatures (28–37°C, corrected to Kelvin 301–310°K) are clinically

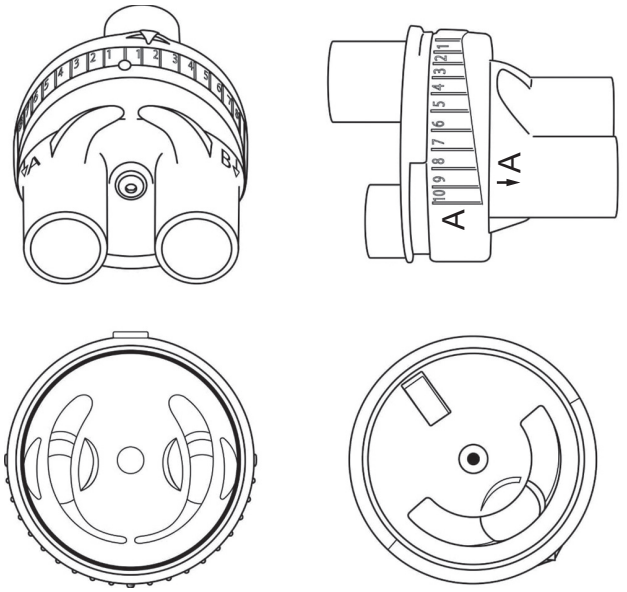

Fig. 2. Adjustable flow diverter valve. Bottom images show exploded view.

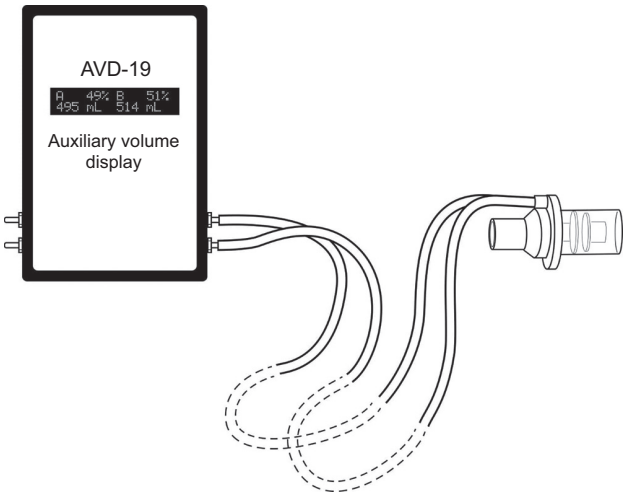

Fig. 3. Ingmar Medical auxiliary volume display with flow sensor.

unimportant. The lower limit for volume measurement of the AVD-19 is ~ 200 mL.

Two in-line magnetic PEEP valves (Instrumental Industries, Bethel Park, Pennsylvania) were used to individually adjust PEEP at the distal end of each patient expiratory circuit. The PEEP valve consists of 2 sections (see the supplementary materials at http://www.rcjournal.com). The first section consists of a magnet attached to the end of a rotating, adjustable thumbscrew. The second section contains a metal plate surrounded by a flexible rubber diaphragm that allows unidirectional flow. As the magnet is advanced closer to the diaphragm using the thumbscrew, an attractive force is produced between the 2 sections. This force creates a back pressure within the expiratory circuit resulting in PEEP (ie, it is a threshold flow resistor). As well as producing PEEP, the valve acts as a one-way valve to prevent CO_2 rebreathing, an important component of a multiplex circuit.[15]

Two disposable PEEP gauges (Portex Disposable Manometer 70–008201EA, Smiths Medical, Minneapolis, Minnesota) were used to display the individual PEEP set by the in-line PEEP valve (see the supplementary materials at http://www.rcjournal.com). The PEEP gauges consists of a clear plastic tube with a spring-loaded piston. It is open to the atmosphere with display markers for pressure in cm H_2O. The display markers are in intervals of 2.5 cm H_2O until marker 10. After marker 10, the displayed intervals become less precise and increase in intervals of 10 cm H_2O. The disposable PEEP gauge is simple in design and is typically used for positive expiratory pressure therapy. This PEEP gauge was chosen because of its low cost and easy accessibility during a pandemic.

Five sets of devices were evaluated. For each device performance trial, once the recordings stabilized (at least 20 breaths), volume and PEEP were recorded directly from the Real-Time Analysis feature offered by the lung simulator software. Values reported from the lung simulator (corrected for body temperature and pressure saturated with water vapor, BTPS) were considered the "true" values when assessing the error of the new devices.

The purpose of evaluating the AFDV and AVD-19 was to determine the performance of the flow diverter valve in its ability to individually control V_T and to test the measurement error of the AVD-19. The ventilator settings were adjusted so that the exhaled V_T on the ventilator read 1,000 mL, assuming each lung simulator would be receiving 500 mL (see the supplementary materials at http://www.rcjournal.com) when the lung models of the simulators were identical. The mode was pressure control continuous mandatory ventilation with set-point targeting.[27]

For the evaluation of the AFDV, the disposable PEEP gauges were removed from the circuit to avoid any leaks. Before each device test, the AVD-19 was calibrated per manufacturer's instructions. For calibration of the AVD-19, a test lung was ventilated with 500 mL V_T using a single patient circuit. Per the manufacturer instructions, the 2 flow sensors were connected in series between the circuit Y-connector and the test lung. The AVD-19 was considered calibrated when the percentages of volume distribution were displayed to be within ± 2% of each other (eg, A: 49% and B: 51%).

The lung models of the 2 lung simulators were set to represent identical patients (Table 1, Experiment A). For each trial, the AFDV was first set to the middle (zero) mark. The volumes were evaluated in Real-Time Analysis on the lung simulators. Once the values stabilized, the V_T value displayed

on each lung simulator was recorded. The same steps were taken with the AFDV at positions A1–10 and B1–10. This was repeated with 5 different AFDVs. When each AFDV was at its maximum adjustment (ie, position A10 or B10), the opposite patient circuit was disconnected from the simulator to determine the ability to remove 1 patient from multiplex ventilation without disturbing the other.

To evaluate AFDV performance, 5 volumes were recorded from the lung simulator at each mark on the flow diverter valve. These volumes were averaged and graphed to show the change in volume at each valve adjustment. When adjusting the AFDV toward patient A (A1–10), the valve was considered successful in individualizing volume if the volume delivery to patient A did not change and the volume delivery to patient B declined as the valve was advanced closer to tick mark A10. This holds true in the reverse scenario when adjusting the valve to B1–10.

To evaluate AVD-19 performance, we first corrected the device measurements to BTPS. We did this because, in actual use, the flow sensor would be exposed to exhaled gas that is heated and humidified by the patient. Each true value of volume recorded from the lung simulators was averaged and compared to the averaged measured volumes from the AVD-19 (error = [measured – true]/true, expressed as a percent).

The purpose of testing the PEEP valve and the PEEP gauge was to evaluate the performance of the setup's ability to individually control PEEP and to determine the error of the measurement of the PEEP gauge. The ventilator was set to match the original paper except for the set PEEP (0 cm H_2O instead of 15 cm H_2O; see the supplementary materials at http://www.rcjournal.com). For the testing of the PEEP valve and display, the AVD-19 and flow sensors were not included in the circuit because they were not necessary in determining PEEP.

For each trial, both PEEP valves were initially set to provide no additional PEEP, which was determined by the PEEP gauge reading and simulator PEEP display. Starting with patient A, the thumbscrew of the PEEP valve was advanced until the disposable PEEP gauge read 2.5 cm H_2O. Once stabilized (upon visual inspection), the PEEP displayed by lung simulator was recorded. The PEEP valve was then adjusted so that the display increased by increments of 2.5 cm H_2O until reaching a PEEP reading of 15 cm H_2O. The same procedure was used with the PEEP valve for patient B. Five sets of PEEP valves and displays were tested and recorded in the same sequence. Thus, Set PEEP was the reading on the PEEP gauge produced by adjusting the PEEP valve, and True PEEP is the end-expiratory airway pressure measured by the lung simulator.

The ability of the PEEP valve to individualize PEEP was confirmed if a positive correlation was observed between an adjustment of the PEEP valve and the PEEP reported from the lung simulators. The average of each measurement replication (ie, 5 circuits) of PEEP at each PEEP setting and the percentage errors were calculated. The error of the disposable PEEP gauge was calculated using true PEEP reported from the lung simulators and the measured PEEP from the PEEP gauge (error = [measured – true]/true, expressed as a percent).

For the evaluation of the modified patient circuit system performance, the ventilator mode was again pressure control continuous mandatory ventilation with set-point targeting, and the settings were selected to simulate clinical settings when ventilating a patient in respiratory failure secondary to ARDS. These settings were the same as the original multiplex ventilation trial except for the PEEP setting.[15]

Baseline values (Experiment A in Table 1) were obtained using 1 multiplex ventilation circuit. The AFDV and PEEP valves were both set to zero, and the same lung simulator models (ie, ARDS-mild) were ventilated to replicate the findings of the original study. Once baseline values were established, experiments B–F were conducted. The following steps were taken during each experiment by 1 operator to reverse the previous noted failure modes.[15] First, the PEEP valve(s) were adjusted to equalize EELV in both lung simulators. Equalization was acceptable once the 2 EELVs were within 10% of each other. Second, the flow diverter valve was adjusted to equalize V_T delivery to each patient within 10%. Lastly, the inspiratory pressure (above PEEP) on the ventilator was adjusted to achieve the V_T target of $\sim$ 450 mL on the AVD-19. Once the difference in EELV and V_T was $\leq$ 10% between simulated patients, the adjusted settings and outcome variables were recorded.

The capability of the multiplex circuit to correct the ventilation of unbalanced lung mechanics was determined by the following variables: V_T (both in mL and mL/kg, assuming an ideal body weight of 70 kg for each patient), minute ventilation ($\dot{V}_E$), EELV, and calculated values for estimated P_{aCO_2} and pH.[15] To mimic the use of the circuit in a clinical setting, V_T values were reported from the AVD-19 and converted into BTPS. PEEP was reported from the disposable PEEP gauge (to the nearest 2.5 cm H_2O), and the AFDV adjustment was recorded (to the nearest half tick mark). Because a simulated lung was used, the compliance of the lung did not change when adjusting PEEP; therefore, EELV (in L) was recorded directly from Real-Time Analysis on the lung simulator. $\dot{V}_E$ was calculated as a product of the recorded V_T and set frequency on the ventilator ($V_T \times 20$ breaths/min). The same calculations used in the original study were used to obtain values of estimated P_{aCO_2} and pH.[15] P_{aCO_2} was calculated as $\left(0.863 \times \dot{V}_{CO_2}\right) / \left[\dot{V}_E \times \left(1 - \frac{V_D}{V_T}\right)\right]$, where 0.863 is the correction factor required to report the equation in units of cm H_2O, $\dot{V}_{CO_2}$ is CO_2 output (assumed to be 200 mL/min), and the dead space fraction (V_D/V_T) was set at 0.50, which was estimated to be the average dead space of patients with COVID-19 at the Cleveland Clinic (instrument dead space was assumed to account for some

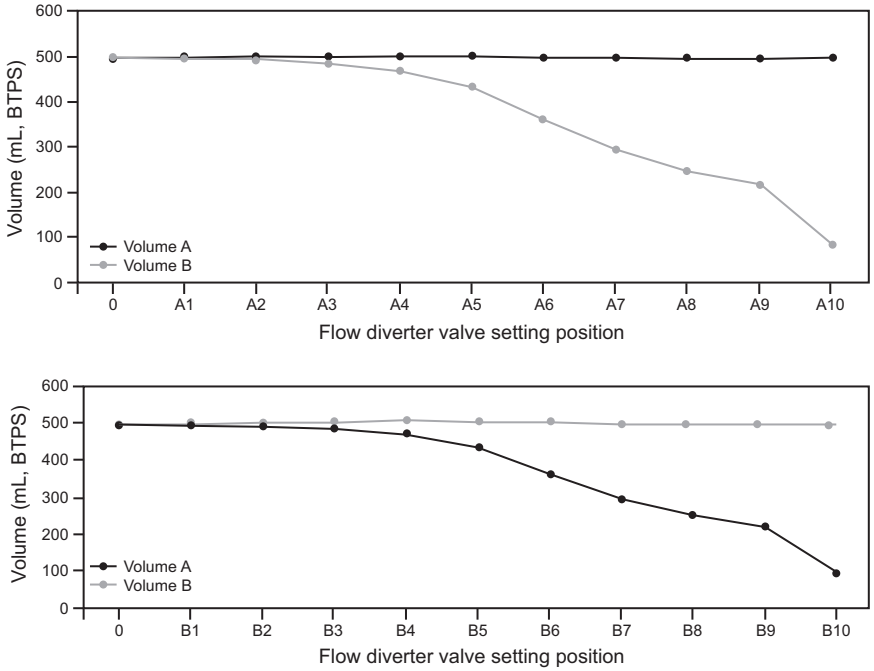

Fig. 4. Adjustable flow diverter valve performance. BTPS = barometric pressure and temperature saturated conditions.

unknown portion of this dead space).[15,28] The dead space to V_T ratio (V_D/V_T) in the original study was 0.50, resulting in a calculated dead space volume (V_D) of 0.225 L for this study.[15] The estimated pH was calculated as $6.1 + \log\left(\frac{24}{0.03 \times P_{aCO_2}}\right)$, assuming that bicarbonate concentration is normal (24 mEq/L) in acute respiratory distress secondary to ARDS. [15,28]

The difference of any value between the 2 simulated patients was calculated by taking the absolute difference of the 2 recorded values and dividing it by the average of the same 2 values. To interpret the data and conclude that a previously failed mode was corrected, the values had to meet these requirements: the measured equalized V_T of each patient must be $\sim$ 450 mL and fall within the range of 4–8 mL/kg, V_T and EELV must be $\leq$ 10% between each patient, and calculated pH must be in the acceptable range of 7.20–7.45.

Results

In all cases, mean values are reported without standard deviations because the random errors of measurements during this kind of simulation study are so small that they are clinically unimportant. The performance of the AFDV is shown in Figure 4. When the AFDV was set to zero, both patients received the same volume. Figure 4 illustrates that as the valve was turned, the patient (in the direction that the valve was turned) had a minimal change in volume, while the other patient received an almost linear decline in volume until the valve reached tick mark 10 (representing maximum occlusion). When each valve was in position 10, the opposing circuit was able to be removed from the patient without affecting ventilation to the other or causing a ventilator alarm. If the patient is disconnected without occluding the circuit (ie, if disconnected before reaching position 10), the ventilator will give a disconnect alarm. The difference in the volume reported by the lung simulator and the AVD-19 (both corrected to BTPS) is displayed in supplementary materials (available at http://www.rcjournal.com). The average error of the AVD-19 was –17% across all measurements, excluding those for AFDV setting 10. Setting 10 was omitted because the AVD-19 was not designed for volumes below $\sim$ 200 mL (see the supplementary materials at http://www.rcjournal.com). The V_T values reported by the AVD-19 underestimate true volume delivery (ie, the error is negative). The AVD-19 in circuit 1 and circuit 4 had a much lower percent of error (average error –8.1%) than the AVD-19 in circuits 2, 3, and 5 (average error –20.9%).

The performance of the PEEP valve and PEEP gauge are displayed in the supplementary materials (available at http://www.rcjournal.com). We observed that the ventilator did not recognize an increase in PEEP set by the PEEP valve because the PEEP displayed on the ventilator was always what was set on the ventilator; this may not be true with other kinds of ventilators. Because the inspiratory pressure on the ventilator was set and an increase in individual PEEP was not recognized, the change in pressure (ΔP = inspiratory pressure – PEEP set by PEEP valve) decreased as individual PEEP increased. Therefore, the simulator with the

higher PEEP received less V_T. Hence, unlike normal pressure control ventilation with this ventilator, during multiplex ventilation V_T was not independent of PEEP adjustment, adding complexity to the procedure. The PEEP gauge resulted in overestimating the true PEEP to each patient by a large amount, ranging from 17% to 41%. The error in measured PEEP increased as the PEEP increased.

The experimental data for the use of the modified multiplex circuit in patients with varied lung mechanics are shown in Table 2. As in the original study (with an unmodified circuit), experiments A and D produced no important differences in the outcome variables and did not require any manipulation of the valves. As noted above, the reported PEEP in Table 2 was from the PEEP gauge, which overestimated actual PEEP. Because experiments A and D required no adjustments to the PEEP valves, the actual PEEP to each patient would be 5 cm H_2O (ie, the PEEP set on the ventilator).

The lung mechanics conditions resulting in unacceptable EELV and gas exchange in the absence of the AFDV and PEEP valves observed in the original study[15] were corrected with the adjustment of 3 parameters: PEEP valve, AFDV, and inspiratory pressure. Adjustments to the AFDV, PEEP valves, and inspiratory pressure allowed for individualized ventilation and the ability to equalize ventilation so that the difference in outcome variable was less than 10% per each patient pair.

Discussion

The AFDV is designed to be used during multiplex ventilation with the ventilator set to pressure control continuous mandatory ventilation. Reported methods used to deliver individual V_T (ie, pinching the circuit or using a ball/globe valve to restrict flow) increase the resistance of the overall circuit.[18,22] In pressure control continuous mandatory ventilation mode, the ventilator aims to maintain the constant pressure set and during inspiration the ventilator will sense and adapt to any increase in resistance across the system. To adjust for increased resistance, the ventilator decreases the inspiratory flow to maintain the set inspiratory pressure (ie, pressure = flow × resistance). A decrease in flow over the set inspiratory time will result in decreased volume delivery to both patients. The resistance added to the inspiratory limbs using the reported methods also create the potential of pressure alarms being reached, leading to early cycling of inspiration.[29] To combat the negative outcomes of added resistors, Raredon et al added a bypass around the resistors so that the ventilator does not sense the impedance in the circuit.[29]

The design of the AFDV (Figure 2; see the supplementary materials at http://www.rcjournal.com) demonstrates how the rotation of the valve does not change the cross-sectional area of the system, thus resulting in no change in the impedance. This is why the volume to the first patient stayed the same as the volume to the second patient decreased. There were no major differences in the outcomes between the 5 flow diverter valves, which indicates excellent quality control of the product. Clinically, the AFDV is useful in multiple ways: (1) it allows for the individualization of volume delivery to 2 patients; (2) it acts as a Y-connector in the inspiratory limb, thus eliminating the need for an additional piece of equipment; (3) it is 3D-printed and thus inexpensive and easy to produce; (4) it eliminates the need to disconnect the circuit to add individual resistors or to create a bypass around the resistors; and (5) if necessary, it allows for circuit disconnection (eg, for endotracheal tube occlusion, resuscitation, transition to a single ventilator) without causing harm to the connected patient.

To put the accuracy of the AVD-19 into perspective, we consulted ISO standard 80601–2-12: Medical electrical equipment - Part 2 - 12: Requirements for basic safety and essential performance of critical care ventilators. The standard says that "if the ventilator is equipped with delivered volume monitoring equipment, the accuracy of the delivered volume monitoring equipment shall be disclosed in the instructions for use. For actual delivered volumes > 50 mL, the accuracy of the delivered volume monitoring equipment shall be within $\pm$ 4.0 mL + 15% for the actual delivered volume." Therefore the accuracy range of the AVD-19 (from –15% to –24%) was reasonable. The AVD-19 allowed for individual monitoring of the V_T, but the inconsistency in the error among the 5 different devices indicates limited quality control of the current product. Knowing the average error of the volume readings would allow the clinician to make appropriate adjustments in the event that the AVD-19 had to be used clinically. Even though there are more accurate devices, such as a volumetric CO_2 monitor, the lower cost of the AVD-19 is an advantage. If the AVD-19 were to be used clinically, it would be wise to lower the V_T goal based on the expected –17% error (ie, the device underestimates the delivered V_T). This can best be calculated by the equation corrected as follows: Target V_T = ideal body weight × target mL/kg × 0.83. For example, the display goal range for V_T dosage = 4 mL/kg × 0.83 to 8 mL/kg × 0.83. Thus, if the patient ideal body weight was 70 kg, the target range for V_T dosage using the AVD-19 would be 70 kg × 4 mL/kg × 0.83 to 70 kg × 8 mL/kg × 0.83 = 232–465 mL. A recent study suggests that because patients with COVID maintain a relatively normal lung compliance, and often show little pulmonary recruitability, a tidal volume range above 4-6 mL/kg may be acceptable.[30]

The outcomes of the PEEP valve testing demonstrate the capability for individual PEEP control. Because the gas simply passes through the valve without any exit to the atmosphere, using the device does not pose a contamination risk. Of importance during multiplex ventilation of real

Table 2. Experimental Data for the Modified Multiplex Circuit

Experiment	A			B			C			D			E			F		
Use case	Balanced Resistance-Compliance			Unequal Compliance			Unequal Compliance (Extreme)			Unequal Resistance			Unequal Resistance (Extreme)			Unequal τ (extreme)		
Patient	A	B	Δ	A	B	Δ	A	B	Δ	A	B	Δ	A	B	Δ	A	B	Δ
Diagnosis	ARDS-Mild	ARDS-Mild		ARDS-Mild	ARDS-Severe		Normal	ARDS-Severe		ARDS-Mild	ARDS-Mild		ARDS-Mild	Asthma-ARDS		ARDS-Severe	COPD	
Valve setting*	0			B7			B8			B5			B6.5			A6.5		
P_I, cm H_2O*	15			29			38			18			28			34		
PEEP display	7.5‡	7.5‡		10	20		10	20		7.5‡	7.5‡		10	7.5		30	7.5	
ΔP, cm H_2O	15	15		24	14		33	23		18	18		23	25.5		9	31.5	
Dual display V_T, L	0.456	0.455	0.2%	0.458	0.456	0.4%	0.428	0.456	–6.3%	0.443	0.450	–2%	0.442	0.441	0%	0.464	0.437	6%
$\dot{V}_E$, L/min	9.1	9.1	0.2%	9.2	9.1	0.4%	8.6	9.1	–6.3%	8.9	9	–2%	8.8	8.8	0%	9.3	8.7	6%
$PaCO_2$, mm Hg	38	38	–0.2%	38	38	–0.4%	40	38	6.3%	39	38	2%	39	39	0%	37.2	39.5	−6%
V_T, mL/kg†	6.5	6.5	0.2%	6.5	6.5	0.4%	6.1	6.5	–6.3%	6.3	6.4	–2%	6.3	6.3	0%	6.6	6.2	6%
EELV, L†	0.282	0.282	0.0%	0.291	0.291	0.0%	0.329	0.319	3.1%	0.27	0.282	–4%	0.338	0.314	7%	0.488	0.505	−3%
pH†	7.43	7.42	0%	7.43	7.43	0.0%	7.4	7.43	–0.4%	7.41	7.42	0%	7.41	7.41	0%	7.43	7.41	0%

* Values are the adjusted settings to equalize ventilation between patient A and patient B.
† Values are considered the most important clinical outcomes.
‡ PEEP valve was not adjusted (producing zero PEEP above the ventilator setting).
τ = time constant: resistance × compliance
P_I = inspiratory pressure above set PEEP on the ventilator
ΔP = driving pressure for inspiratory flow = (P_I + vent PEEP) – measured PEEP
$\dot{V}_E$ = minute ventilation
V_T = tidal volume
EELV = end-expiratory lung volume

patients, we observed that the ventilator we used did not recognize an increase in PEEP set by the PEEP valve. The PEEP displayed on the ventilator was always what was set on the ventilator. However, ventilators other than the Servo-i used in this study may respond differently. We noticed a decrease in volume delivery as the individual PEEP valves were adjusted to increase set PEEP. This is because the inspiratory driving pressure of the system (ie, peak inspiratory pressure – total PEEP, with total PEEP being ventilator set PEEP + auto PEEP + individual PEEP set) was decreased as the total PEEP was increased. Roy et al[31] performed a study on in-line PEEP valves and reported using a bypass circuit resulting in the ventilator being "blinded" from the PEEP within the circuit. In other words, because the ventilator bypassed the adaptions within the circuit, the ventilator was only able to sense the PEEP set by the ventilator.[31] This should result in the same findings noted in our study. We did not record the effect of individual PEEP control on V_T delivery as it was not the intention of the study, but this should be investigated in future research. The use of PEEP valves is not unique to our study, but there has been no mention in other studies of their effect on volume delivery.

The disposable PEEP gauge used for this study was intended to be accessible and affordable in emergency situations. The PEEP gauge is vented to the atmosphere but only on the other side of the gauge indicator piston, and we speculate that little or no leak of patient circuit gas can occur. We found that the PEEP values displayed on these gauges are highly inaccurate and overestimate the actual PEEP. Therefore, during multiplex ventilation of humans, PEEP would be adjusted based upon improvements in oxygenation (S_{pO_2} and P_{aO_2}). In the emergency use of multiplex ventilation, a more precise measurement device of PEEP would be ideal, but perhaps is not necessary.

We started the study by evaluating each component that served as a modification of the basic multiplex circuit. We believe that this understanding led to developing a systematic approach to adjusting the individual components to equalize ventilation in each trial: (1) adjust PEEP to equalize EELV (or to improve lung compliance/oxygenation), (2) adjust AFDV to equalize volume delivery, and (3) adjust inspiratory pressure to meet the 4–8 mL/kg V_T range. However, we found the adjustments required to equalize ventilation were time consuming and required a fairly high level of skill. During clinical use, the adjustments need to be timely and accurate to provide safe ventilation to each patient. Consistent practice (with a simulator) is vital in mastering proper skill in adjustment of settings while maintaining patient safety.

In Table 2, P_I is the set inspiratory pressure above the ventilator-set PEEP (always 5 cm H_2O). However, ΔP, the pressure driving inspiratory flow, is (P_I + 5) – measured PEEP. Measured PEEP is that generated by the manually adjusted PEEP valve. This is the first level of complication. The second level is that the resultant ΔP does not seem to correlate with the lung mechanics and V_T because of the added effect of the flow diverter valve. For example, in the case of ARDS-mild + ARDS-severe, the flow diverter valve increased air flow resistance for the mild patient and decreased air flow resistance for the severe patient. As a result, the mild patient required a higher ΔP and the severe patient a lower ΔP for essentially the same V_T values as in the baseline case (ARDS-mild + ARDS-mild). For this reason, we suggest that, during clinical application, ΔP is ignored and attention is focused on the displayed V_T values.

Even though these circuit modifications made equalization of ventilation possible, patient matching prior to placement on a multiplex circuit may still be important.[14,20] Matching patient lung mechanics allows the clinician to start at a baseline of equal ventilation. Then, when 1 patient has a significant change in resistance or compliance (as the disease progresses), adjustments can be made to maintain adequate gas exchange. As recent discussions have emerged, Cook[32] noted that little is known about the safety of multiplex ventilation and there must be evidence of an increase in survival rate to outweigh the risk of shared ventilation. Even though our circuit was not tested on human subjects, multiple safety features were included in the individualization and monitoring of ventilation with the intention of minimizing the risks. This multiplex circuit is intended to be used in conjunction with individual patient monitoring of oximetry and capnography that is already implemented in the ICU. At this time, our design does not overcome the need for deep sedation or neuromuscular blockade when implementing multiplex ventilation. This is mainly due to the problem of breath triggering by 1 patient inadvertently increasing the breathing frequency of the other patient. Depending on the design of the ventilator, triggering in general may be adversely affected by the in-line PEEP valves. Furthermore, the issue of individualized F_{IO_2} may still need to be addressed.

Review of Prior Research

Studies of Rudimentary Multiplex Circuit Design In 2001, Neyman and Irvin[2] tested a rudimentary split ventilation circuit and reported equal distribution of ventilation according to subjective measures. Many studies have used a similar circuit design to demonstrate the extent to which differences in patients' lung mechanics (resistance and compliance) affect the volume delivery split between them.[13-15,33] Some studies have presented solutions for reducing the risks of implementing multiplex ventilation. Both Webb et al[14] and Kheyfets et al[20] performed studies using computer software to model proper matching of patients prior to using multiplex ventilation. Webb and

colleagues[14] paired patients based on their lung mechanics and reported that the lung compliance difference must be < 12 mL/cm H_2O and the oxygen saturation index must be < 2 mm Hg between patients before sharing a ventilator. Kheyfets et al[20] created contour plots as a possible tool for creating groups of similar patients for ventilator sharing. Patient matching is necessary in the initiation of multiplex ventilation, although any drastic change in patient lung mechanics would alter the ventilation between patients. Both Chatburn et al[15] and Hermann et al[18] have addressed problems that must be solved to overcome possible changes in lung mechanics. Both studies noted that pressure control ventilation offers increased safety compared to volume control ventilation. To improve the safety of multiplex ventilation, there must be a way to individually control and monitor V_T and PEEP to each patient in the circuit.

Studies Using Test Lungs In the attempt to individually control volume, PEEP, and F_{IO_2}, Stiers and colleagues tested the addition of a flow restrictor valve, an in-line PEEP valve, and an oxygen bleed-in.[22] Each device was individually adjusted to show its impact on volume delivery, PEEP, and F_{IO_2} within the test lung.[22] The system was not tested as a whole to demonstrate necessary adjustments when lung mechanics change. Raredon et al[29] presented modifications to the multiplex circuit, which included adding extra tubing to bypass the in-circuit modifications that would affect the ventilator. This study was performed on test lungs but is planned to be tested in an animal model.

Studies Using Lung Simulators One study[21] built a circuit based on the "bag-in-the-box" concept from Sommer et al[7] to provide individualization of volume delivery to 2 simulators. The design of this study lacked individual monitoring of volume and PEEP. From an equipment standpoint, the extra parts required to make this set-up would require additional resources, and this added complexity raises concern for potential disconnections and failures. The study performed by Daoud et al[19] used adjustable gate-valves in both the inspiratory limb (to restrict flow and adjust V_T) and the expiratory limb (to adjust for PEEP) within each patient circuit. The usage of the Hamilton G5 ventilator allowed for individual monitoring of 1 patient at a time by switching between 2 flow sensors with a stopcock.[19] This design allows monitoring of patient ventilation data individually. However, this would require constant adjustments of the stopcock to get real-time data for each patient. The clinician would only know of an acute change in 1 patient if the monitor was set on that patient at that time. Clarke and colleagues[34] used a clamp on the patient endotracheal tube to adjust the resistance of the tubing to individualize V_T. This approach raises a safety concern as the resistance of an endotracheal tube is already high and only minor changes could be made before the patient tube is fully occluded. The clamp on the endotracheal tube may also eliminate the ability to suction the patient. A number of patients in the COVID-19 population at the Cleveland Clinic have had large amounts of highly viscous secretions and have required frequent suctioning. Another study attempted to split ventilation between patients using a valve that switches between patients every other breath.[35] This design was not tested and was critiqued for its limitation in the allowed inspiratory time due to the breathing frequency having to be doubled.[36]

Studies Using High-Fidelity Simulators The concept of ventilating > 1 patient on a ventilator raises many concerns for patient safety. Multiple studies so far have designed devices to address these safety issues. While the devices may be promising, they lack sophisticated testing in their ability to resolve the major safety problems. The use of high-fidelity mannequins has been recommended when testing multiplex circuit devices.[24] High-fidelity lung simulations allow for multiple parameters to be set to replicate evidence-based values, which results in more accurate data.[26] The use of high-fidelity mannequins allows for detection of possible failures within a multiplex circuit, as well as simulated practice for clinicians prior to implementing the system clinically. So far, there has only been 1 study regarding the safety problems with multiplex ventilation.[15] As far as we know, the present study is the first that tests the safety solutions to multiplex ventilation on a high-fidelity simulator.

Studies Using Animal Subjects The majority of the testing of multiplex ventilation has consisted of bench studies using test lungs. A small sample of testing has been implemented with animal and human subjects. The rudimentary design of multiplex ventilation was first tested on sheep in 2008. Even in the short amount of time the sheep were ventilated, there were many changes in each sheep's P_{aCO_2} and P_{aO_2}.[9] These results suggest the dynamic changes in each subject's respiratory mechanics and reiterate the necessity of constant patient monitoring. In response to the COVID-19 pandemic, Srinivasan et al[16] created an "iSave" circuit configuration that was designed to be used with volume control ventilation. This circuit was tested for a short period of time on test lungs and later on pigs.[16] Though the authors did not discuss why volume control was chosen over pressure control for this study, it would be necessary to know how long any pig may have received volumes above their 8 mL/kg dosage range when there were drastic changes in the other pig's lung mechanics and circuit adjustments were required.

Studies Using Human Subjects At this time there has been no need for the use of multiplex ventilation due to a ventilator shortage, and there have only been a few studies that

have tested it on human subjects. Only 1 of the 3 studies to date has used a modified circuit to address patient safety.[3] All multiplex studies performed on human subjects to date have small samples and ventilated the patients for a short period of time.[3,4,12] Because of these limitations, it is difficult to draw any conclusions regarding the safety and feasibility of using multiplex ventilation for longer periods of time. It should be noted that the goal of multiplex ventilation is to serve as a bridge to acquisition of additional ventilators, not a prolonged solution. Patient studies have shown that the monitoring and work load of the caregivers increases with the use of multiplex ventilation. This is counterproductive in a mass casualty scenario.

Limitations

The main limitation to this study is that it was a simulation-based study and had a small sample of possible lung mechanics. We did not evaluate the impact of spontaneous breathing and the attendant safety concerns. The AVD-19 was a prototype device and was not intended for use on human subjects. It could be improved upon if multiplex ventilation became an actual emergency practice. Because the limitation of the AVD-19 accurately reading volumes < 200 mL, this device would be limited to use in adult patients.

The effect of individual PEEP is likely to be different in humans compared to a simulator. For example, the lung simulator does not have the ability to recruit or improve compliance as PEEP is increased. Finally, in this study, we did not adjust for individual F_{IO_2} values, though we believe it could be implemented by a simple bleed-in of 100% oxygen at the flow necessary to improve patient oxygenation.[22]

Conclusions

This study solves the 3 main problems presented in the original study: (1) the ability to individualize V_T, (2) the ability to individualize PEEP, and (3) a means of measuring delivered V_T and PEEP to each patient.[15] This study confirms that, despite large differences in respiratory mechanics, it is possible to individualize ventilation to each patient during multiplex ventilation. We found that the AFDV allowed individual control of V_T and even allowed for circuit disconnection from the ventilator without disrupting ventilation to the other patient or causing unnecessary alarm activation. The results of the display devices (AVD-19 and PEEP gauge) demonstrated acceptable measurement error for emergency application. If used clinically, knowing the error range of these devices will help the clinician make educated decisions when interpreting the measurements provided. While this design demonstrates the ability to individualize ventilation, it must be noted that the AVD-19 and AFDV are not currently available for clinical use. The AFDV is in the process of receiving a patent. Going forward, the application of multiplex ventilation is still recommended to be a last-resort option in ventilating patients and should only be used if there are absolutely no ventilators available for single-patient ventilation.[37]

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