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System Design Verification for Closed Loop Control of Oxygenation With Concentrator Integration

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ABSTRACT Background: Addition of an oxygen concentrator into a control loop furthers previous work in autonomous control of oxygenation. Software integrates concentrator and ventilator function from a single control point, ensuring maximum efficiency by placing a pulse of oxygen at the beginning of the breath. We sought to verify this system. Methods: In a test lung, fraction of inspired oxygen (FIO_2) levels and additional data were monitored. Tests were run across a range of clinically relevant ventilator settings in volume control mode, for both continuous flow and pulse dose flow oxygenation. Results: Results showed the oxygen concentrator could maintain maximum pulse output (192 mL) up to 16 breaths per minute. Functionality was verified across ranges of tidal volumes and respiratory rates, with and without positive end-expiratory pressure, in continuous flow and pulse dose modes. For a representative test at respiratory rate 16 breaths per minute, tidal volume 550 mL, without positive end-expiratory pressure, pulse dose oxygenation delivered peak FIO_2 of 76.83 ± 1.41%, and continuous flow 47.81 ± 0.08%; pulse dose flow provided a higher FIO_2 at all tested setting combinations compared to continuous flow ($p < 0.001$). Conclusions: These tests verify a system that provides closed loop control of oxygenation while integrating time-coordinated pulse-doses from an oxygen concentrator. This allows the most efficient use of resources in austere environments.

INTRODUCTION

Achieving adequate oxygenation is one of the primary goals of mechanical ventilation. Techniques and devices for achieving this goal—via adjustment of fraction of inspired oxygen (FIO_2) concentration, positive end-expiratory pressure (PEEP), and mean airway pressure—vary greatly.[1] In adults, adequate oxygenation is typically considered an SaO_2 (arterial oxygen saturation) >90% and PaO_2 (arterial oxygen pressure) >60 mm Hg.[2] However, oxygen delivery goals can be more easily monitored by the noninvasive and ubiquitous pulse oximeter, with adequate oxygenation goals having been defined as SpO_2 (peripheral oxygen saturation) of 94% ± 2%.[3]

In the normal hospital setting, oxygen usage to achieve these goals is typically of little concern, as the supply is virtually limitless. In far-forward military medical operations, however, oxygen becomes a limited resource to be conserved. The burdens of oxygen procurement are significant, with estimates quantifying it as up to 30% of the entire logistical footprint necessary to provide medical care during combat operations.[2] In addition, recent experiences of asymmetric warfare in Operation Iraq Freedom and Operation Enduring Freedom have emphasized the need for lightweight and mobile options that are still able to provide meaningful support to the critically ill or wounded patient before, during, and after surgical intervention.[3] Similar concerns over oxygen availability are applicable on the domestic front in possible incidences of disaster management that would require mass casualty care.[4]

A possible solution that has been explored more thoroughly in recent years is that of closed loop or autonomous oxygenation (and ventilation in general), which allows for computer control of ventilator settings in order to achieve predetermined oxygenation goals. Studies have presented a growing body of evidence that closed loop systems are more effective at both maintaining a goal oxygenation level and doing so while using less oxygen, as compared to manual clinician care, and patient outcomes have been equal or improved.[2,3,5–7] Such systems allow for a more precise and gradual maintenance of SpO_2 goals, while also providing for rapid correction mechanisms in the instance of a hypoxemic event.[3,8] In the midst of a conflict with a characteristic injury of traumatic brain injury, this constant maintenance is particularly significant since even a single hypoxemic event in patients with head injury is associated with poor outcome.[9] Furthermore, such fine tuning also addresses the occurrence of hyperoxemia (usually only monitored in the neonatal population), decreasing its prevalence by avoiding clinician bias toward over-oxygenation, and reducing FIO_2 to nontoxic levels (<0.60).[2,7]

Portable oxygen concentrators (POC) have also come to the forefront as a means of supplying oxygen in austere settings. In the immature military theater, electricity is often the first aspect of a more established infrastructure that becomes available. With POCs running off batteries and being able to be plugged in for indefinite use, oxygen delivery is ensured while eliminating the logistic burden of cylinders or liquid oxygen.[10] Air transport of critical patients has similar logistic and additional safety restraints in the use of oxygenation

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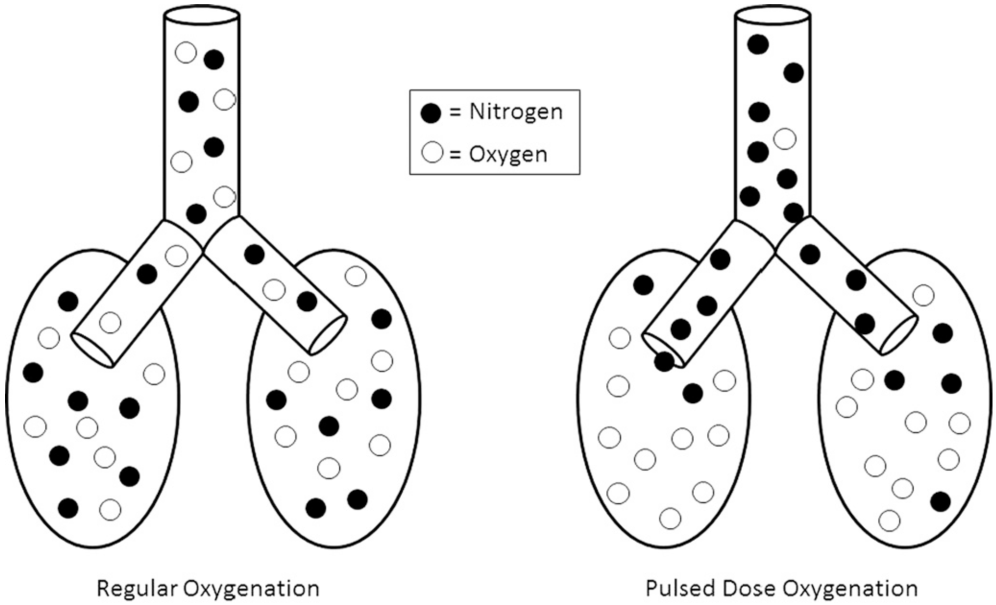

FIGURE 1. A rough illustration of the oxygen distribution strategies in regular/continuous flow oxygenation versus pulse dose oxygenation. An example fraction of inspired oxygen/FIO_2 of 0.50 is shown in the diagram on the left. With pulse dose (right), the same amount of oxygen is used, but more of it is delivered to the part of the lungs where it is used.

support equipment. Along with the ability to concentrate and provide oxygen in a continuous flow, POCs have also been developed that allow for the collection of concentrated oxygen in an internal reservoir and a following periodic release in the form of a pulse dose of oxygen. As early as 1990, this method of delivery was shown to be clinically effective and to utilize substantially less oxygen.[11] In addition, by administering the pulse dose at the beginning of a breath cycle, one can ensure that the oxygen-rich gas enters first and travels to the sites of actual alveolar exchange, being "pushed" in by room air for the remainder of the breath, which will remain unutilized in the anatomic dead space (illustrated in Fig. 1).[12] Operation in pulse dose as opposed to continuous flow mode also results in significantly less power consumption.[10]

This study seeks to begin to integrate the aforementioned needs and advances into a single system that will be able to more effectively and efficiently provide for patient oxygen needs. Using the autonomous FIO_2/SpO_2 control system developed and demonstrated by Johannigman et al[3] as a basis, this new system integrates the use of an oxygen concentrator into the control loop as well (Fig. 2). The objective of this study was a proof-of-concept for the design validation of such a system, verifying successful functioning of a circuit integrating both ventilator and concentrator into a coordinated system controlled entirely by computer, providing adequate oxygenation while consuming minimal resources. It was hypothesized that in the functional system, pulsed dosed delivery of oxygen would prove more effective and efficient compared to continuous flow.

METHODS

The experimental setup was run entirely through a coordinating computer program on a personal computer (PC); from here, component devices were controlled and data were stored. The ventilator and oxygen concentrator system was connected to a test lung (TTL, Michigan Instruments, Grand Rapids, Michigan).

Equipment

All equipment used for experimentation was unmodified. The SeQual Eclipse 3 POC was used (Chart SeQual

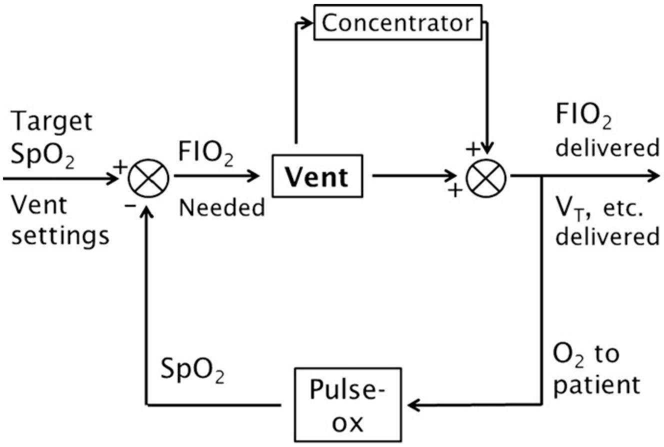

FIGURE 2. Closed Loop Control Diagram with Concentrator Integration. FIO_2, fraction of inspired oxygen; SpO_2, saturation level of O_2 in hemoglobin; V_T= tidal volume.

Technologies, Ball Ground, Georgia). The Eclipse 3 was selected due to its oxygen generating capabilities, and due to the fact that ruggedized versions are available for applications in austere/military settings. The mechanical ventilator used was the Impact 731 (Impact Instruments, West Caldwell, New Jersey). The Impact 731 was also selected due to its propensity for use in austere setting, such as its employment by U.S. Air Force Critical Care Air Transport Teams (CCATT).[13] These devices were connected to a PC and controlled externally through a program on the computer developed by Sparx Engineering (Manvel, Texas). The program ensured that these devices (in addition to other measurement devices) were all able to work together in a coordinated fashion controlled by a central entity, but it did not alter the way that each individual component functioned.

Measurement

Oxygen readings were collected by an O_2Cap Oxygen Analyzer (Oxigraf, Mountain View, California). The sampling tubing for the instrument was positioned just before the test lung inlet in the ventilator circuit. A pneumotachometer (Hans Rudolph, Shawnee, Kansas) was also utilized before the test lung in order to record pressure and flow data. Both devices recorded data continuously, and the data collection program saved files to the PC for later analysis. Although oxygen data (in terms of FIO_2) was of primary interest, pressure and flow readings, as well as recordings of internal device settings and metrics, were also collected.

Experimental Factors

The experiment was designed in order to verify function across a full range of clinically-relevant ventilator settings. In particular, end-points were drawn from previous study of observed values during recent CCATT flights.[13] Tidal volume (V_T) was examined at three levels: 350 mL (“min”), 550 mL (“mid”), and 750 mL (“max”). These V_T were paired with an appropriately inverse respiratory rate (RR): 22 breaths per minute (bpm), 16 bpm, and 10 bpm, respectively. These pairs were tested in a range of outputs for both continuous flow (3, 2, 1 Lpm) and pulse dose (192, 128, 64 mL). For continuous flow, oxygen was allowed to collect in a reservoir connected to the ventilator inlet. Additionally, tests were performed both with the absence of PEEP (0 cmH_2O), and with the presence of PEEP (10 cmH_2O). The test lung was set to a constant compliance of 0.03 L/cmH_2O. All tests were run at an inhalation:exhalation (I:E) ratio of 1:2.8. The ventilator was operated in volume control mode. When reported in pulse dose groups, V_T represent total V_T; the pulse dose volume given from the concentrator is accommodated for so that the ventilator delivers proportionately less air in order to achieve to total set V_T (min, mid, or max). For pulse dose mode, the burst of concentrated oxygen was administered a set amount of time before the start of each breath as defined by the ventilator. Larger doses were given a longer period of time: 1,000 ms before start of ventilator breath for 192 mL pulse, 750 ms prior for 128 mL, and 500 ms prior for 64 mL. This timing allowed a sufficient period for the pulse dose to be administered before the ventilator breath and then primarily be “pushed in” in front of it, rather than primarily mixing with the air from the ventilator. Values tested are summarized in Table I.

TABLE I. Experimental Parameters

V_T Total	350 mL	550 mL	750 mL
RR	22 bpm	16 bpm	10 bpm
PEEP	0 cmH_2O	10 cmH_2O	
Continous Flow	3 Lpm	2 Lpm	1 Lpm
Pulse Dose	192 mL	128 mL	64 mL
Pulse Timing	−1,000 ms	−750 ms	−500 ms
Compliance	0.03 L/cmH_2O		
I:E Ratio	1:2.8		

Summary of values tested for various experimental factors. Tidal volume (V_T) and respiratory rates (RR) are specifically paired; pulse dose and timing are specifically paired; all other factors were tested in all combinations. Bpm, breaths per minute; I:E, inhalation:expiration; PEEP, positive end-expiratory pressure.

The system was allowed to stabilize at each new group of settings before measurements were used. Each data point represents the results from three consecutive breaths over three separate trials for each combination of settings. FIO_2 was the metric of chief interest.

A small separate set of trials was performed to measure the accumulated bolus volume delivered by the concentrator at different RRs. This allowed for quantification of which rates the concentrator was able to “keep up with” when set to deliver a bolus of 192 mL. Measurements were taken from 10 to 26 bpm, increasing by two. The system was given time to stabilize at each new setting. The data points each represent the average of three consecutive breaths during three separate runs.

Statistical Analysis

All data are expressed as mean ± SD. Comparisons between pulse dose and continuous flow concentrator modes at a given group of settings were done by two-tailed Student’s *t* test. Comparisons between multiple settings within a given group were accomplished via analysis of variance. A p value < 0.05 was considered significant.

RESULTS

The volume of data generated by the study precludes the comprehensive inclusion of all results. As the highest concentrator settings in both modes (3 Lpm for continuous, 192 mL for pulse) resulted in the greatest oxygen delivery, we will focus on the presentation of these results when applicable.

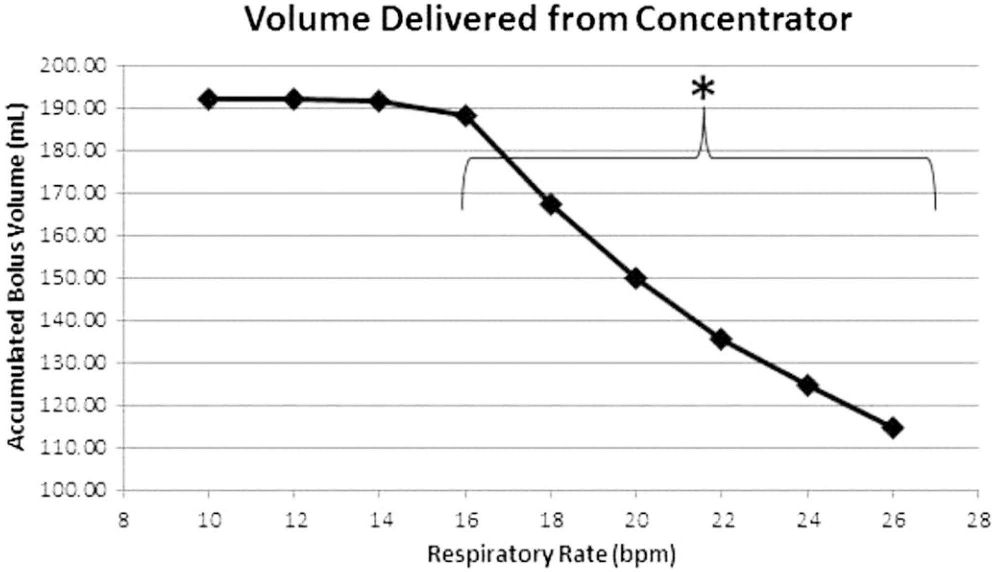

FIGURE 3. Results of concentrator rate testing. The data points represent the maximum volume able to be delivered at a given respiratory rate; $p < 0.05$ versus goal setting of 192 mL. (NB: Standard deviations are too small to appear on graph.)

Concentrator Rate Testing

When set to deliver 192 mL, the accumulated bolus volume output by the concentrator averaged within 5 mL of the set amount up through a rate a 16 bpm. Volume delivered at each rate was very consistent, with a standard deviation of less than 2 mL in all groups. After 16 bpm, the true volume delivered began to drop off linearly as RR increased. At a RR of 22 (rate used for the low-volume pulse-dose experimental group), true volume of concentrated oxygen delivered was 135.44 ± 1.01 mL; for a RR of 26 (maximum rate tested/clinically relevant), volume was 114.67 ± 1.37 mL. Compared to the set volume goal of 192 mL, all groups at 16 bpm and higher delivered an actual volume that was significantly less ($p < 0.05$ for all). At 16 bpm, the drop in actual volume delivered was about 4 mL; although this was significant statistically, it is not likely to be significant clinically. Results are illustrated in Figure 3.

System Function Verification

Although all data and settings can not be fully presented and analyzed here because of their large scope, the function or dysfunction of the system may still be reported across all settings. The system design was indeed able to operate as intended and deliver a time-coordinated $FIO_2 > 0.21$ at all settings and combinations tested. Function was verified for RR of 10, 16, and 22 bpm; V_T of 350, 550, and 750 mL; PEEP of 0 and 10 cmH_2O; continuous flow of 3, 2, and 1 Lpm; and pulse dose of 192, 128, and 64 mL.

Delivered FIO_2

The two different concentrator modes produced distinct patterns of oxygenation (Fig. 4). The continuous flow mode produced a much more steady-state type oxygen delivery overall. The pulse dose mode demonstrated more cyclic behavior, with periods of markedly high FIO_2 immediately preceding the start of the ventilator breath, and then falling off into more distinct lows near 0.21 as the room air is administered behind the pulse. The placement of the FIO_2 spike just before the start of the ventilator breath verifies that the pulse was being administered at the time it was programmed to be.

FIO_2 results are highlighted here for the most clinically average ventilator settings studied: RR of 16 bpm and total V_T of 550 mL. The peak FIO_2 delivered in pulse dose mode was 76.83 ± 1.41% without PEEP and 70.95 ± 8.49% with PEEP. In continuous flow mode, the highest FIO_2 delivered was 47.81 ± 0.08% without PEEP and 47.18 ± 0.07% with PEEP. For this setting—and all others examined—pulse flow provided decisively increased peak FIO_2 values when compared to continuous flow at paired ventilatory factors ($p < 0.001$ in all

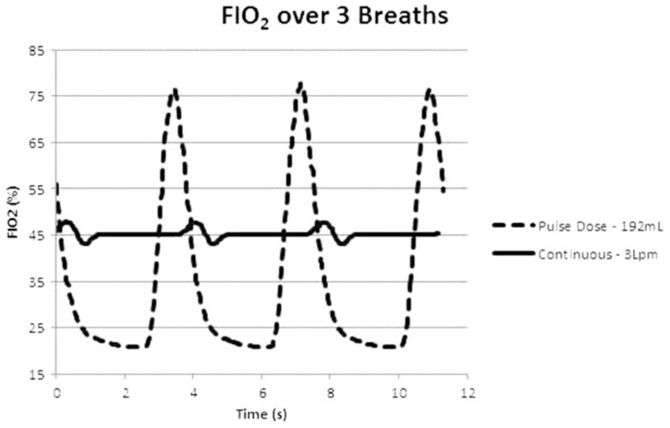

FIGURE 4. Characteristic oxygenation patterns produced over the course of three breaths by both Pulse Dose and Continuous modes at a representative respiratory rate of 16 bpm and a tidal volume of 550 mL. FIO_2, fraction of inspired oxygen.

TABLE II. Oxygenation (Measured via FIO_2) Produced at Various Setting Combinations

Average FIO_2 at Max Output			Average ± SD	Peak FIO_2 at Max Output			Average ± SD
0 PEEP	Min	Cont	49.39 ± 0.54	0 PEEP	Min	Cont	49.61 ± 0.49
		PD	42.45 ± 2.03			PD	76.19 ± 3.20
	Mid	Cont	44.95 ± 0.32		Mid	Cont	47.81 ± 0.08
		PD	34.30 ± 2.40			PD	76.83 ± 1.41
	Max	Cont	47.50 ± 0.21		Max	Cont	57.20 ± 0.08
		PD	32.07 ± 6.12			PD	76.57 ± 2.81
10 PEEP	Min	Cont	48.50 ± 0.06	10 PEEP	Min	Cont	49.01 ± 0.08
		PD	39.49 ± 2.47			PD	72.21 ± 3.76
	Mid	Cont	44.42 ± 0.13		Mid	Cont	47.18 ± 0.07
		PD	34.59 ± 3.97			PD	70.95 ± 8.49
	Max	Cont	50.77 ± 0.12		Max	Cont	58.17 ± 0.13
		PD	34.02 ± 1.25			PD	73.47 ± 3.32

A representative data set is shown in the table depicting the results of the maximum outputs of both oxygenation modes: 3 Lpm for continuous flow and 192 mL for pulse dose. In the table, Min = 350mL/22 bpm, Mid = 550 mL/16 bpm, and Max = 750 mL/10 bpm with a $p < 0.001$ for continuous flow (Cont) versus pulse dose (PD) in each comparison. PEEP, positive end-expiratory pressure.

cases). For FIO_2 over the course of the entire breath, pulse dose averaged 34.30 ± 2.04% without PEEP and 34.59 ± 3.97% with PEEP. Continuous flow averaged 44.95 ± 0.32% without PEEP and 44.42 ± 0.13% with PEEP. This difference was statistically significant for both PEEP groups ($p < 0.001$).

The highest peak FIO_2 delivered by the system was 76.83 ± 1.41%; this occurred with 192 mL pulse dose, no PEEP, RR 16 bpm, and V_T 550 mL. The lowest peak FIO_2 delivered by the system was 31.57 ± 0.14%; this occurred with 1 Lpm continuous flow, no PEEP, RR 16 bpm, and V_T 550 mL. The highest peak FIO_2 delivered by continuous flow was 58.17 ± 0.13%, occurring at a 3 Lpm flow, RR of 22, V_T of 10, PEEP of 10 cmH_2O. For all groups, as concentrator output decreased, FIO_2 decreased.

These and other values for FIO_2 across various settings for the maximum output of each concentrator mode (3 Lpm flow, 192 mL pulse) are shown in Table II.

DISCUSSION

The study was able to successfully evaluate the oxygen provision capabilities of a novel ventilatory system. The closed loop control system was able to operate effectively across a full range of ventilator settings reflective of those encountered in the military critical care environment.[13] The oxygen concentrator was effectively integrated into the system, providing either sustained continuous flow or time-coordinated, computer-triggered pulse doses at the beginning of a breath cycle. In contrast to past work,[12] which relied on positive pressure from the ventilator to initiate a pulse dose, this system's oxygen concentrator was operated independently, and thus allowed for the use of PEEP as well, which should virtually always be present. Because this study was designed primarily to be a proof-of-concept for the system, the mere fact that the system functioned properly and produced meaningful FIO_2 results is a distinct attainment in itself. This project was designed to be able to take recent positive achievements in closed loop ventilation and oxygenation as well as with POCs and pulse dose oxygenation, and to begin to merge it all together into a comprehensive and autonomous respiratory care system. The successful operation of this ventilator/concentrator set-up was a significant milestone in achieving that goal.

The oxygen-generating capabilities of the system were found to be quite robust in both modes. This is significant for a number of reasons. First, the medical logistical burden of providing oxygen in austere locations has already been stressed.[2,3] The advantages of being able to have an electric/battery-run device that can provide a patient with oxygen indefinitely are obvious; the necessary electric infrastructure to accomplish this is typically present, even in most far-forward settings. Second, it has previously been shown in research on Air Force CCATT patients that 68% of patients require an oxygen flow of less than 3 Lpm, and that an average FIO_2 of 49% corresponded to a fully healthy SpO_2 of 98%, with a majority of patients being managed in the 40 to 50% range.[13] Our system was either on par with or exceeding these values, suggesting that the POC represents a viable method of oxygen procurement, and is a good choice for inclusion in the closed loop system.

Pulse dose delivery of oxygen, in particular, was shown to generate markedly higher capabilities in terms of maximum FIO_2 provision, routinely providing oxygen in excess of 75%. In prior work with acute lung injury, pulse dose oxygenation has been shown to lead to significantly improved PaO_2:FIO_2 ratio when compared to continuous flow in volume control mode.[12] Additionally, power consumption of the SeQual Eclipse POC has been previously measured, consuming an average of 151 W at a continuous flow of 3 Lpm and 103 W at a pulse dose setting of 192 mL.[10] This means that in pulse dose mode, the concentrator consumes 68% as much power, while providing an FIO_2 up to 161% greater (computed at 3 Lpm flow, 192 mL pulse, middle RR and V_T, no PEEP); this equates to a 237% increase in efficiency of oxygen delivery by choosing pulse dose mode.

Our system allows for full effectiveness by being able to appropriately apply this superior efficiency. This is done by being able to use the developed computer program to coordinate the control of the ventilator and concentrator, ensuring that the ventilator compensates for the delivered volume from the concentrator (such that V_T is not in excess of that set by the clinician), and that the concentrator pulse is timed to be automatically administered just before the start of the ventilator breath. In this way, the gas at the start of the inhalation sequence is essentially supplied by the concentrator rather than the ventilator, and the most oxygen-rich gas is what is utilized for exchange at the alveolar level. Pulse dose oxygenation allows for the utilization of the oxygen-rich gas—which can be a precious commodity in far-forward conditions—only in active respiratory space, and avoids supplying "superfluous" oxygen to the anatomic dead space where exchange does not occur (Fig. 1).

Next steps for the project include the creation of a full "lookup" table of provided FIO_2 values at given settings. This information will be used to create more robust programing, which the software can draw upon in order to fulfill given oxygenation/ventilation goals (i.e., the program will have options of how to increase or decrease FIO_2 in order to adjust for changes in SpO_2 while simultaneously satisfying other ventilatory settings such as V_T or RR). This is largely encompassed by the data generated from this study, but it could be filled in and expanded to provide greater resolution and range if desired. Such a lookup table would thus eliminate any potential issues caused by the decreasing amount of oxygen provided at higher RRs (as seen in Fig. 3) by having already accounted for the FIO_2 that will actually be delivered.

This also provokes thought on how the concept of FIO_2 is viewed. FIO_2 is regarded mainly as a therapeutic value, determining the oxygen content provided to a sick patient. However, it may be more useful to in fact consider FIO_2 in a diagnostic sense—or to consider it not at all in the case of autonomous control. For instance, a patient being on 70% oxygen may be more indicative of his level of lung injury than of the quality of his care. What's more, the virtually ubiquitous report of oxygen conservation under closed loop control indicates that patients were likely hyper-oxygenated to begin with.[2,3] The clinician drive to prevent the well-known and serious deleterious effects of hypoxia eschews the murky fact that hyperoxemia may have noxious effects at well, and possibly at FIO_2 above only 0.40.[7,14] A possibility for improved patient care exists if the decisions are put in the unbiased hands of the computer program, which can adjust FIO_2 to whatever means necessary to achieve and maintain normoxia (SpO_2 = 94% ± 2%). This autonomous integrator—satisfied by this design—could thus both improve patient care and conserve resources, without the care provider having to get wrapped up in the process. This offers a significant freedom to tend to other clinical responsibilities, as FIO_2 was found to be the most frequently adjusted ventilation parameter in the management of critically ill patients under military care.[13]

The current study also has several limitations. First, it is of course only a model, having been performed on a test lung. In vivo studies will be needed, likely first with a porcine model of acute lung injury, then moving on to clinical studies. The critical addition here will be the monitoring of the actual effect of the system on SpO_2 and blood gases; and using the SpO_2 reading to be able to provide active feedback and thus let the closed loop control operate freely and fully, as studied previously in the absence of the concentrator.[3] Being a passive test lung, the model also did not incorporate the addition of any spontaneous breathing; a fully capable system would have to be able to adjust for this. Testing may also be desired in different ventilation modes: this study only considered volume control mode, not pressure control or other variations. Likewise, testing was done at only a single standard lung compliance; this choice was made mainly to eliminate the inclusion of an additional variable of negligible significance at this point in system verification. However, consideration may be paid to the effect of this value in future experiments, as it could potentially impact the performance of the system in various disease states that would alter pulmonary compliance/resistance. Also, when adding in a pulse dose from the concentrator at the beginning of the breath, the system currently adjusts for volume, but not for inspiratory time (T_i); this results in longer inspiratory times than initially set when in pulse mode. The system must be made to either adjust for this, or to at least have a way of indicating the true resultant T_i. The former option is likely preferential, because the changed T_i could otherwise alter the resultant I:E ratio, whose value can be important in the ventilatory management of a sick patient.

CONCLUSIONS

This study demonstrates functionality for a ventilation system that incorporates closed loop control of oxygenation and oxygen concentrator integration. The system was shown to provide viable amounts of oxygen across a range of clinical settings; and, especially when using coordinated pulse dose ventilation, to do so in a manner that potentially maximizes effect and certainly minimizes resource consumption. Such technology is of particular interest in austere settings such as far-forward military operations and disaster relief scenarios. Further testing and development is needed to eventually create and validate a single device capable of providing the level and type of care whose vision originates with this study.

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AUTHOR CONTRIBUTIONS: MMG – study design, system verification, experimentation/data acquisition, data analysis, and manuscript draft. TCB – initial study design and system troubleshooting. RDB – study design

and interpretation, system concept, and manuscript revision. JAJ – long-term project design/direction and author of initial proposal.

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