REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
16-01-19	Journal	March 2017 - December 2018

4. TITLE AND SUBTITLE
Pulsed Dose Oxygen Delivery During Mechanical Ventilation: Impact on Oxygenation

5a. CONTRACT NUMBER
FA8650-15-2-6605

5b. GRANT NUMBER
FA8650-16-2-6G19

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Thomas Blakeman*; CMSgt Dario Rodriquez, USAF (Ret.)†; Col Jay Johannigman, MC USA*; Richard Branson*

5d. PROJECT NUMBER

5e. TASK NUMBER
16-058

5f. WORK UNIT NUMBER
Legacy RHM

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
*University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267
†Aeromedical Research Department, U.S. Air Force School of Aerospace Medicine, Wright-Patterson AFB, OH 45433

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Air Force Materiel Command
Air Force Research Laboratory
711th Human Performance Wing
Airman Systems Directorate
Airman Biosciences Division
Wright-Patterson AFB, OH 45433

10. SPONSORING/MONITORING AGENCY ACRONYM(S)
711 HPW/RHBA

11. SPONSORING/MONITORING AGENCY REPORT NUMBER(S)
AFRL-RH-WP-JA-2019-0040

12. DISTRIBUTION/AVAILABILITY STATEMENT
Distribution Statement A: Approved for public release.

13. SUPPLEMENTARY NOTES
MILITARY MEDICINE, Vol. 00, 0/0 2018 doi: 10.1093/milmed/usy362

14. ABSTRACT
Adequate oxygenation is one of the primary goals of mechanical ventilation. Maintenance of adequate oxygenation and prevention of hypoxemia are the primary goals for the battlefield casualty, but military operations have unique concerns. In military operations, oxygen is a limited resource. A portable oxygen concentrator has the advantage of operating solely from electrical power and theoretically is a never-exhausting supply of oxygen. Our previous bench work demonstrated that the pulsed dose setting of the concentrator can be used in concert with the ventilator to maximize oxygen delivery. We evaluated this ventilator/concentrator system with closed loop control of oxygen output in a porcine model.

15. SUBJECT TERMS
Positive end-expiratory pressure, oxygen saturation by pulse oximetry

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT:	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON (Monitor)
a. REPORT	b. ABSTRACT	c. THIS PAGE			James Lehman
Unclassified	Unclassified	Unclassified	SAR	8	19b. TELEPHONE NUMBER *(Include Area Code)* N/A

Pulsed Dose Oxygen Delivery During Mechanical Ventilation: Impact on Oxygenation

Thomas Blakeman; CMSgt Dario Rodriquez, USAF (Ret.)†; Col Jay Johannigman, MC USA*; Richard Branson**

ABSTRACT Introduction: Adequate oxygenation is one of the primary goals of mechanical ventilation. Maintenance of adequate oxygenation and prevention of hypoxemia are the primary goals for the battlefield casualty, but military operations have unique concerns. In military operations, oxygen is a limited resource. A portable oxygen concentrator has the advantage of operating solely from electrical power and theoretically is a never-exhausting supply of oxygen. Our previous bench work demonstrated that the pulsed dose setting of the concentrator can be used in concert with the ventilator to maximize oxygen delivery. We evaluated this ventilator/concentrator system with closed loop control of oxygen output in a porcine model. Materials and Methods: The Zoll 731 portable ventilator and Sequal Saros portable oxygen concentrator were used for this study. The ventilator and concentrator were connected via a USB cable to allow communication. The ventilator was modified to allow closed loop control of oxygen based on the oxygen saturation (SpO_2) via the integral pulse oximetry sensor. The ventilator communicates with the concentrator to increase or decrease oxygen bolus size to maintain a target SpO_2 of 94%. Three separate experiments were conducted in this study. Experiments 1 and 2 used oxygen bolus sizes 16–96 mL in 16-mL increments and experiment 3 used 1 mL increments. The oxygen bolus was delivered from the concentrator and injected into the ventilator circuit at the patient connector. Six pigs were used for each experiment. Experiment 1, done without lung injury, was completed to determine the optimum timing during the respiratory cycle for injecting the oxygen bolus. Lung injury for experiments 2 and 3 was induced in the animals by warmed saline lavage via the endotracheal tube until PaO_2/FIO_2 decreased to <100. The pigs were then placed on the ventilator/concentrator system and allowed to adjust the oxygen autonomously to determine if the target SpO_2 could be maintained. PEEP was manually adjusted. Arterial blood gases were drawn to verify the PaO_2 and the SpO_2/SaO_2 correlation. Results: Experiment 1 showed that the O_2 bolus injected into the ventilator circuit 300 ms before breath delivery produced the highest PaO_2. Mean PaO_2/FIO_2 was 500 ± 33 for experiments 2 and 3 before lung lavage and 72 ± 11 after lung lavage ($p < 0.001$), representing severe acute respiratory distress syndrome. Thirty minutes after placing the animals on the ventilator/concentrator system, the bolus size range was 64–96 mL and 16–96 mL after 2 hours ($p < 0.05$). The SpO_2 range was 81–95% after 30 minutes and 94–98% after 2 hours ($p < 0.05$). PEEP range was 5–14 cm H_2O. The SpO_2 to SaO_2 difference was ≤4% throughout the evaluation. Conclusions: The ventilator/concentrator system was able to manage oxygenation of severely injured lungs in a porcine model by injecting oxygen boluses at the front end of the ventilator breath, and appropriate use of PEEP to maximize oxygen delivery at the alveolar level. This proof of concept ventilator system may prove to be of use in situations where high-pressure oxygen is unavailable but electricity is accessible.

BACKGROUND

Achieving adequate oxygenation is a primary goal of mechanical ventilation. This goal is accomplished through the adjustment of inspired oxygen concentration (FIO_2), positive end-expiratory pressure (PEEP), and mean airway pressure (Paw). Titration of these variables is guided by continuous non-invasive monitoring of oxygen saturation by pulse oximetry (SpO_2) and intermittent arterial blood sampling for arterial oxygen (O_2) tension (PaO_2) and measured O_2 saturation (SaO_2). In adults, adequate oxygenation is typically considered an $SaO_2 > 90\%$ and $PaO_2 > 60$ mm Hg. PEEP may also be guided through assessment of pulmonary mechanics, O_2 delivery, intrapulmonary shunt, and cardiac output.

O_2 concentrators are widely used for patients in the home setting that require supplemental O_2 due to chronic lung disease.[1] These concentrators are large devices which are meant to be stationary. In developing and resource constrained countries, concentrators are becoming increasingly popular due to the portability and cost savings compared to pressurized cylinder systems.[2–4] With the development of portable O_2 concentrators (POC) in the early 21st century, the portability of an O_2 source enabled patients receiving long-term O_2 therapy to ambulate easier and more economically than using cylinders.[5]

POC have become the standard for providing home O_2, however other potential uses have emerged. While maintenance of adequate oxygenation and prevention of hypoxemia are the primary goals for the combat casualty, military operations have unique concerns. In civilian U.S. hospitals, under normal conditions, O_2 reserves are plentiful. In military

*University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0558.

†Aeromedical Research Department, U.S. Air Force School of Aerospace Medicine, Wright-Patterson AFB, OH 45433-7913.

doi: 10.1093/milmed/usy362

operations, O_2 is however a limited resource to be conserved. Providing O_2 containers and O_2 generation equipment requires a substantial commitment of weight and space (cube) of the entire logistical footprint necessary to provide medical care during combat operations. Little has been studied regarding the use of POC in austere environments to provide low to moderate levels of O_2 to ventilated patients. Autonomous control of FIO_2 has been accomplished by a number of investigators, primarily in the neonatal population where the oxygenation goals include avoidance of hypoxemia and hyperoxemia. We evaluated a portable ventilator/POC system using autonomous control of O_2 delivery in a porcine model.

METHODS

This study was Institutional Animal Care and Use Committee (IACUC) approved and conducted in the University of Cincinnati Center for Surgical Innovation using eighteen 37–42 kg female Yorkshire pigs (6 for each experiment). Each animal was intubated and sedated using a continuous infusion of propofol to assure no spontaneous respiratory effort and instrumented with a femoral arterial line to facilitate blood pressure monitoring and arterial blood gas (ABG) sampling. Baseline ventilator settings were tidal volume (V_T) of 8–10 ml/kg, PEEP of 5 cm H_2O, and FIO_2 of 100%. Respiratory rate was set to provide a minute ventilation to maintain a pH of 7.35–7.45. This method of baseline ventilator settings was used for each experiment.

System Description

Three different experiments were conducted within this project. Each experiment was conducted using the Zoll 731 series portable ventilator (Zoll Medical Corp., Chelmsford, MA) and a Sequal Saros POC (Chart Industries, Ball Ground, GA) (Fig. 1). A data output port in the Saros was created to enable a connection between the 731 data port so the two devices could electronically communicate. The circuit boards and firmware were modified in both devices in order to allow the 731 to command the Saros to initiate an O_2 bolus. The system utilized a closed loop proportional-integral derivative-type control system that compared the SpO_2 value measured noninvasively from the animal to the target SpO_2 of 94% to determine the size of the O_2 bolus to be given. The bolus size was increased or decreased to maintain the target SpO_2. Additionally, the ventilator will automatically decrease the V_T by the volume of the O_2 bolus delivered from the POC to maintain the set V_T. The Saros O_2 output tubing was connected to a bleed-in port on the ventilator circuit just before the patient connection at the endotracheal tube (ETT). For all experiments, the Saros was operated in bolus mode. The maximum output of the POC was 3 lpm with a bolus range of 16–96 mL in 16 mL increments at an FIO_2 of 93% ± 3%. The system algorithm also responds to hypoxemia by increasing to the maximum O_2 bolus size if SpO_2 is <88% for more than 10 seconds. This ventilator/POC system is unique in that the ventilator was not attached to a high-pressure O_2 source, but instead utilized the ventilator internal compressor using room air to deliver V_T. The system relied on the POC as the sole O_2 source.

Experiment 1

O_2 boluses from the Saros were delivered at the beginning of each breath and were introduced into the lungs by the ventilator compressor. This experiment was designed to determine when best to deliver the bolus to produce the highest partial pressure of O_2 (PaO_2). Each device was connected to a computer that controlled both devices, synchronizing the delivery of the pulse dose at various points relative to breath initiation. The ventilator was set to baseline settings with the exception of FIO_2 which was set at 21% with the O_2 being supplied by the POC. The system was studied in 6 pigs with normal lung conditions and consistent size/weight. Timing of a 96 mL O_2 bolus was set at various points before, simultaneously, and after the initiation of the ventilator breath to determine the best PaO_2 in the porcine

FIGURE 1. Zoll 731 ventilator and Saros POC used in the study.

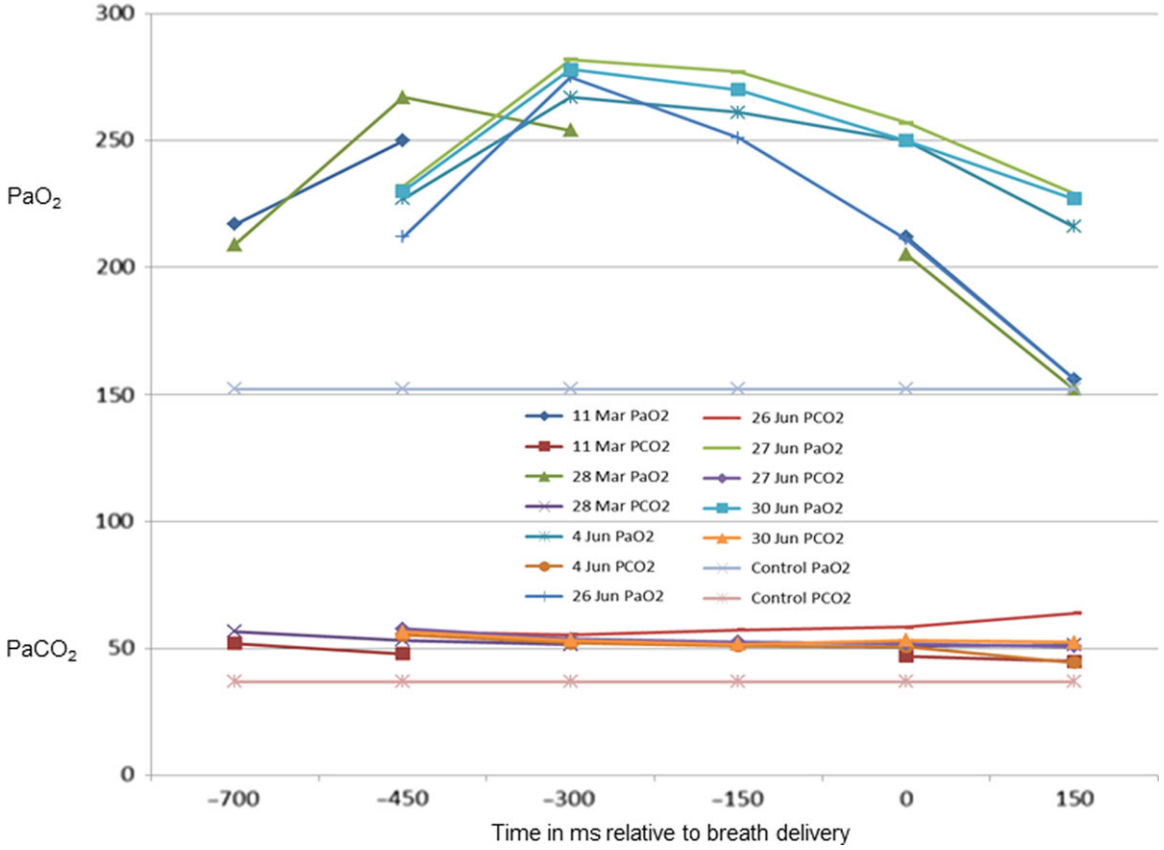

FIGURE 2. Timing in bolus dose relative to VT delivery and corresponding PaO_2 and $PaCO_2$.

model. The timing range for bolus delivery relative to V_T delivery was −4,500 to +150 milliseconds (ms). ABGs were drawn 20 minutes following a change in pulsed dose timing. Adjustments were made to ventilator settings based on arterial blood gas results to ensure adequate minute ventilation.

Experiment 2

This experiment was designed to determine the system's ability to maintain adequate oxygenation in a porcine model of severe ARDS (PaO_2/FIO_2 < 100). Acute lung injury was induced in six female swine weighing approximately 40 kg. The ventilator was set to baseline settings. Warm normal saline (37°C) was instilled into the lungs by gravity using 48" of corrugated tubing connected to the ETT instilling 200–400 mL aliquots until 1 L was instilled or SpO_2 decreased to ≤90% on 100% O_2. The saline was allowed to remain in the lungs for 2–3 minutes between aliquots and 5–10 minutes after 1 L was instilled and then drained by gravity. The animals were allowed to recover for 5–10 minutes to determine the SpO_2 and corresponding level of lung injury. This process was repeated until the SpO_2 after the recovery period remained 90–92% on 100% O_2. The volume of normal saline required to induce a severe lung injury was 3.7 ± 0.6 L. ABGs were drawn at the end of the lavage to verify the level of lung injury. The pigs were then placed on the ventilator/POC closed loop system for 2 hours. Respiratory rate was adjusted as needed to maintain adequate minute ventilation. The concentrator delivered O_2 boluses in 16 mL increments with a target SpO_2 of 94 ± 2%. During the 120 minute period following lung injury, if the O_2 bolus from the POC was at the maximum dose of 96 mL and SpO_2 remained below 80% for >10 minutes, positive end expiratory pressure (PEEP) was increased as needed to increase SpO_2. If SpO_2 remained <80% for more than 30 minutes with the POC at the maximum dose, PEEP was further increased until SpO_2 was ≥88%. PEEP settings were manually adjusted and were not a part of the ventilator closed loop FIO_2 control algorithm. ABGs were drawn every 30 minutes to assess oxygenation and ventilation.

Experiment 3

This experiment used the same procedures as the previous experiment with the exception of an updated concentrator scheme. The POC firmware and software were altered to deliver O_2 bolus sizes in 1 mL increments instead of 16 mL increments as in the previous experiment. The lung injury model and procedures were identical to the experiment 2.

STATISTICAL ANALYSIS

The optimal O_2 bolus timing in experiment 1 was determined by comparing the PaO_2 produced by each timing

scheme with a 96 mL bolus, using a one-way ANOVA followed by two-tailed Student's *t*-test post-test. With experiments 2 and 3, POC bolus size, SpO_2, and PEEP at each time point, utilizing the ventilator/POC system using 1 mL bolus increments were compared to the system utilizing 16 mL increments using a two-tailed Student's *t*-test. A $p < 0.05$ was considered significant.

RESULTS

Experiment 1

Figure 2 shows the timing in bolus dose relative to V_T delivery and the corresponding PaO_2 for six porcine models. O_2 boluses delivered −150 ms and −300 ms before the ventilator breath delivery were significantly higher than those delivered at −450, 0, and +150 ms ($p < 0.05$). Differences in PaO_2 when delivering the O_2 bolus at −150 and −300 ms before ventilator breath delivery were not statistically significant ($p = 0.10$). For experiments 2 and 3 we chose to use −300 ms timing because the mean PaO_2 was higher, albeit the difference was small (276 vs 265 mm Hg)

Experiments 2 and 3

Baseline and post-lung injury PaO_2/FIO_2 in both experiments were not statistically different ($p > 0.5$). After switching from 100% O_2 to the ventilator/POC system, 10 of 12 lung-injured animals' SpO_2 initially decreased to <88% requiring the POC to increase to the highest bolus dose (96 mL). From initial placement on the ventilator/POC system following lung injury, the time required for SpO_2 to increase back to 88% was 19.3 ± 14.9 minutes (range 2–38) in the 1 mL O_2 bolus group, and 19.8 ± 21.7 minutes (range 2–48) in the 16 mL O_2 bolus group. Table I shows the baseline and post-lung injury PaO_2/FIO_2, O_2 bolus size, SpO_2, and PEEP at 30, 60, 90, and 120-minute time points after lung injury. At the 30-minute time point SpO_2 was >80% with all animals. O_2 bolus dose range (Mean ± SD) was 64–96 mL (93 ± 9 mL), SpO_2 range was 81–95% (93 ± 9%), and PEEP range was 5–10 cm H_2O (7 ± 2 cm H_2O). At the end of the 120-minute study period, O_2 bolus dose range was 16–96 mL (46 ± 30 mL), SpO_2 range was 94–98% (95 ± 1%), and PEEP range was 5–14 cm H_2O (10 ± 3 cm H_2O). Mean peak inspiratory pressure (PIP) over all time periods was 20 ± 3 cm H_2O (range 18–28) pre lung injury and 32 ± 5 cm H_2O (Range 22–44) post-lung injury. PIP differences were statistically significant ($p < 0.0001$). Within the group utilizing the concentrator with the 16 mL increment bolus scheme, O_2 bolus size was significantly larger and SpO_2 and PEEP were significantly lower the 30 minute time point as compared to the 120 minute time point ($p < 0.05$). The same was true for the group utilizing the concentrator with the 1 mL increment O_2 bolus scheme. Differences in SpO_2, O_2 bolus dose, and PEEP when comparing the 1 mL increment scheme to the 16 mL increment O_2 bolus dose scheme were not statistically significant ($p > 0.05$) at the 30 minute and 120 minute time points. SpO_2 differences were significantly lower ($p < 0.05$) with the 16 mL scheme at both the 60 and 90 minute time points, although O_2 bolus dose and PEEP differences were not statistically significant at these time points. Figure 3 shows O_2 bolus size, SpO_2 and PEEP settings throughout the 2-hour study period with the ventilator/POC system for animal #3 in table I using 1 mL O_2 bolus increments. Figure 4 shows the same parameters for animal #1 in Table I, with the system using 16 mL O_2 bolus increments.

DISCUSSION

The goals of the study were to evaluate the closed loop communication between the ventilator and POC, determine the optimal timing within the inspiratory cycle in which to deliver the oxygen bolus, and to evaluate the POC using 1 mL O_2 bolus increments versus 16 mL bolus increments. The study findings were: (1) With modifications of the ventilator and POC software and firmware, closed loop control of oxygen delivery was achieved using SpO_2 as the oxygenation feedback parameter to the system; (2) The optimal time

TABLE I. Pre- and Post-Lung Injury $PaO_2/FI$and POC Bolus Sizes, SpO_2, and PEEP at All Time Points

				30 Minute			60 Minute			90 Minute			120 Min		
	Pig #	Baseline P/F	Post Lavage P/F	Bolus (mL)	SpO_2 (%)	PEEP cm H_2O	Bolus (mL)	SpO_2 (%)	PEEP cm H_2O	Bolus (mL)	SpO_2 (%)	PEEP cm H_2O	Bolus (mL)	SpO_2 (%)	PEEP cm H_2O
1 mL Bolus increments	1	490	73	96	85	8	92	97	14	61	99	14	24	94	10
	2	499	82	95	95	5	92	95	5	89	95	8	96	96	10
	3	496	84	94	95	5	82	95	5	58	96	5	26	96	5
	4	555	97	96	91	5	82	97	8	40	97	8	19	95	8
	5	543	64	96	91	5	91	96	10	72	97	10	43	97	10
	6	461	71	96	92	10	65	96	10	47	96	10	40	95	10
16 mL Bolus increments	1	470	78	96	90	5	80	94	8	64	96	10	32	94	10
	2	499	75	96	95	5	16	93	5	16	95	6	16	95	5
	3	516	64	96	91	8	64	94	12	48	95	14	96	95	14
	4	466	60	96	81	8	96	94	10	96	95	14	64	95	14
	5	465	63	96	81	5	80	94	10	96	91	10	80	98	12
	6	545	61	64	95	10	48	95	10	16	94	10	16	95	10

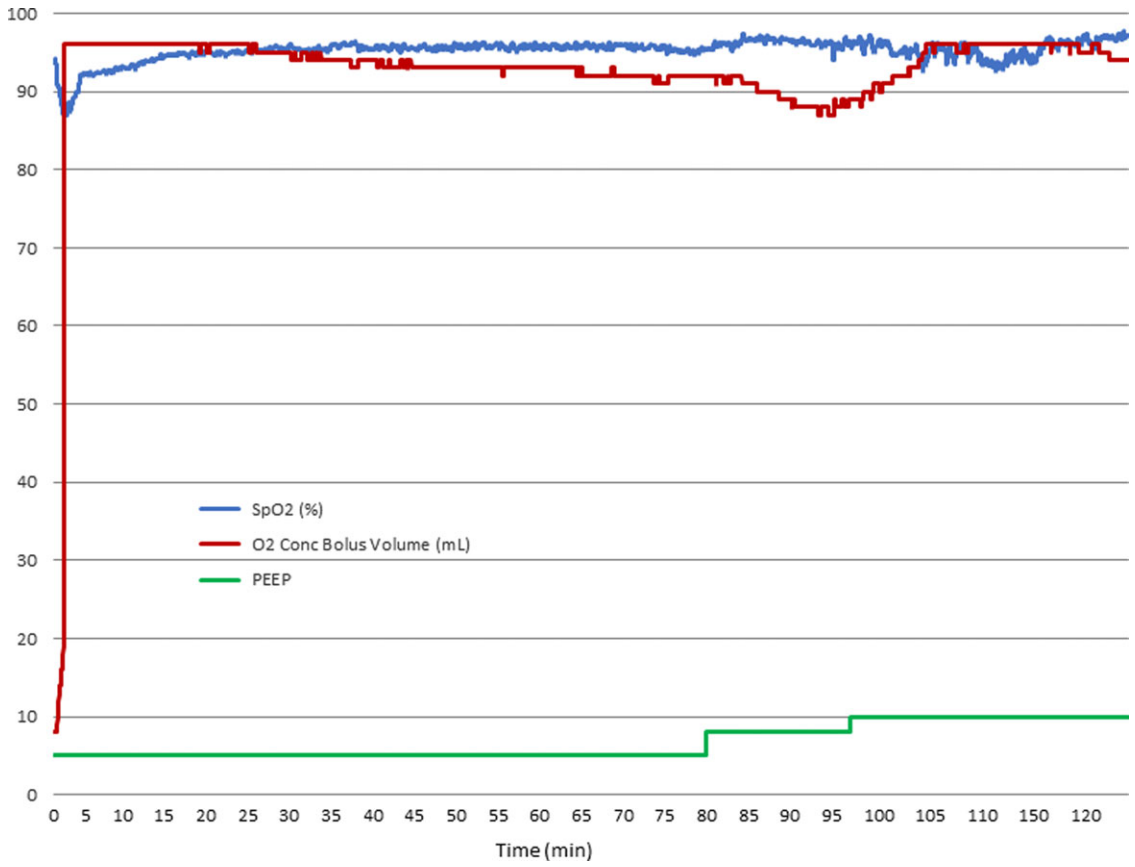

FIGURE 3. Bolus size, SpO_2 and PEEP settings throughout the 2 hours study period with the ventilator/POC system for animal #3 in Table I, using 1 mL bolus increments.

in which to inject the O_2 bolus was 300 ms before ventilator breath initiation; (3) Both 1 mL and 16 mL bolus dose increments provided equivalent levels of oxygenation although the 1 mL bolus scheme appeared more stable due to having less under- and overshoots caused by larger changes in bolus volumes.

To our knowledge, this is the first study to evaluate the use of a ventilator/POC system using closed loop technology. Our study showed that this system was able to manage oxygenation using a POC to provide O_2 in conjunction with the appropriate use of PEEP in a severe ARDS animal model, without manipulation of the POC or ventilator required by the caregiver to adjust oxygenation. Unlike the prior system, the current ventilator/POC system utilized an electronic communication between the ventilator and POC to automatically adjust both ventilator V_T and POC output. In the event that communication between the ventilator and concentrator or the SpO_2 signal is lost, the ventilator/POC system would revert to manual adjustment of the POC bolus or continuous flow oxygen. Frontloading the ventilator breath with 93% ± 3% bolus dose O_2 allows for maximizing the 3 lpm POC output by getting a higher O_2 concentration to the alveoli[1] as opposed to blending the O_2 with air as it enters the ventilator intake (Fig. 5). POC in bolus mode to deliver O_2 uses less power than when in continuous flow mode that conserves battery power and increases efficiency that may be important if a standard electrical power outlet is not initially available.[6,7]

In far forward areas and during transport, the goals of O_2 therapy are to prevent hypoxemia, assure adequate arterial oxygenation, and minimize O_2 usage. Little has been studied regarding the use of POCs in austere environments to provide low to moderate levels of O_2 to ventilated patients although research has shown that POCs are capable of reversing hypoxemia due to hypobaric environments in non-ventilated subjects.[8–10] During aeromedical transport, this ventilator/POC system could serve as a backup system on a fixed wing aircraft where oxygen is plentiful or as the primary system on a rotor-wing aircraft where oxygen is not readily available or in limited quantity. A POC has the advantage of operating solely from electrical power and is theoretically a never-exhausting resource. The POC can be used in a similar fashion to traditional low flow O_2 by adding O_2 to a reservoir bag positioned at the ventilator air intake for O_2 enrichment. Previous work demonstrated that the pulse dosed setting of the concentrator could be used in concert with the ventilator to maximize the O_2 delivered in both animal[11] and bench models.[12,13] With this method, a pulse volume of O_2 was synchronized with the ventilator

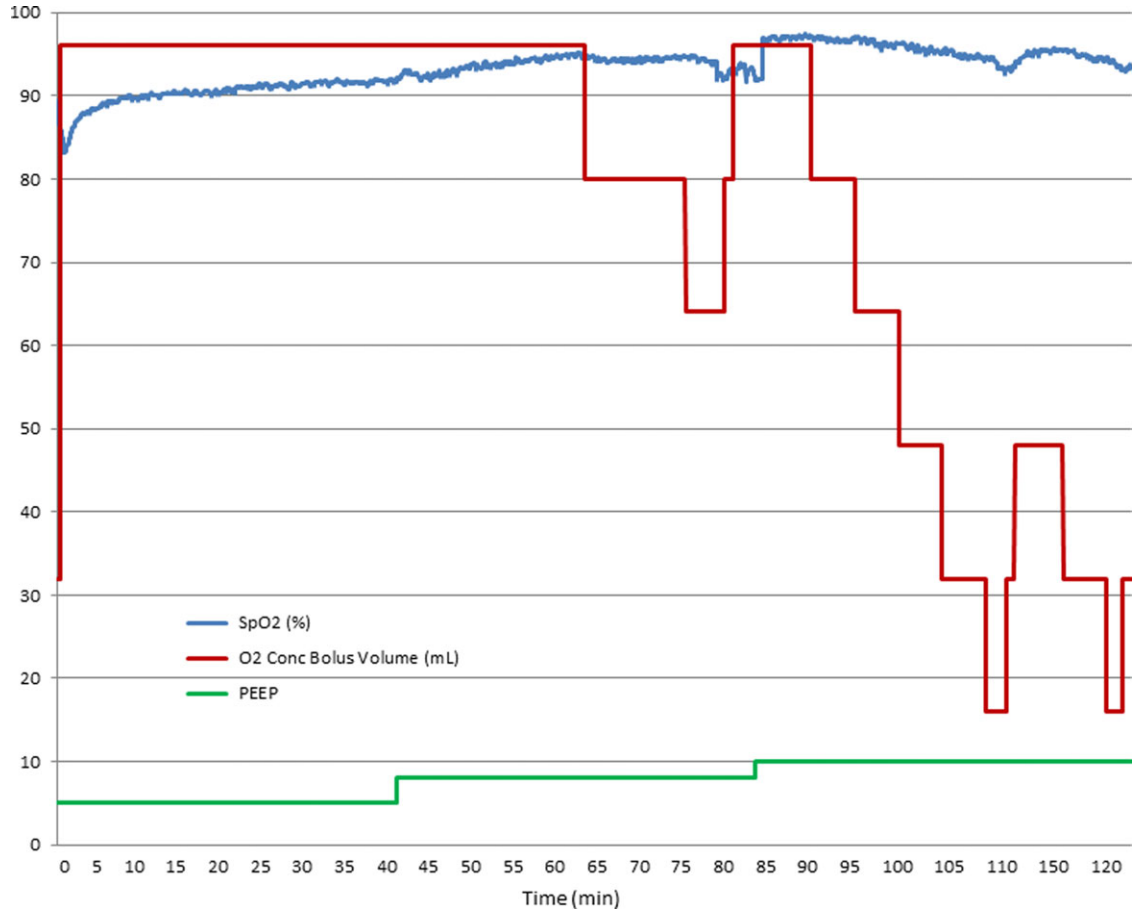

FIGURE 4. Bolus size, SpO2 and PEEP settings throughout the 2 hours study period with the ventilator/POC system for animal #1 in Table I, using 16 mL bolus increments.

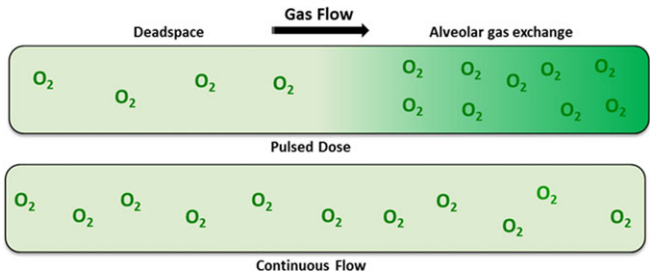

FIGURE 5. Difference in O_2 concentration at the beginning of the ventilator breath with bolus dose vs O_2 concentration with continuous flow O_2.

breath delivery although this required manual adjustment by the caregiver.

This current study showed that the SpO_2 decreased to <88% in 10 of 12 animals when placed on the ventilator/POC system. The reason for this is twofold. First, the lung injury produced a PaO_2/FIO_2 that is consistent with severe ARDS and the animals were receiving 100% O_2 via a ventilator receiving O_2 from a high-pressure gas source. The POC delivers 93% ± 3% O_2, therefore depending on the respiratory rate set on the ventilator there could be as much as 10% decrease in O_2. Studies have shown that in ambulatory oxygen dependent patients that for a given liter flow, the PaO_2 produced while utilizing a POC was significantly lower than the same liter flow from liquid oxygen and compressed oxygen gas sources.[14,15] Second, the design of the ventilator/POC system dictated that bolus O_2 delivery start at the lowest bolus dose and increased as needed in response to the SpO_2 value. As a safety measure, as occurred in nearly every animal in this study, if SpO_2 decreased to <88% for more than 10 seconds, the ventilator/POC algorithm automatically increased the O_2 bolus to the maximum dose (96 mL). Given the degree of lung injury in the animals and the limitations of liter flow and FIO_2 output of the POC, it is unlikely that starting at larger O_2 boluses would have yielded different results. Although this initial decrease in oxygenation occurred, at the 30 minute time point 9 of 12 animals had SpO_2 values ≥90% and at the 60 minute time point the SpO_2 in all animals was ≥93%. Although SpO_2 differences were statistically significantly ($p < 0.05$) when comparing the 1 mL increment bolus to the 16 mL increment O_2 bolus dose at 60 and 90 minute time points, the differences were not considered clinically important since SpO_2 was ≥91%.

Mechanical ventilation in austere environments remains challenging. Due to the logistical difficulties in providing O_2

to remote locations, some areas of operation may not have oxygen at all due to these logistical limitations plus pressurized oxygen cylinders are not used in areas where there is potential to turn an oxygen cylinder into a ballistic missile if hit by artillery fire. Disposal of depleted oxygen cylinders is also problematic in that the cylinders must be stored while awaiting transport to a refill stations and disposal procedures must be followed.[16] Alternately, cylinders may simply be discarded in the area of operation despite the risk of the enemy repurposing the cylinders as weapons. Using a ventilator with a non-explosive source of oxygen, such as a POC, may provide a viable alternative to liquid or compressed oxygen especially in far forward and /or immature in-theater settings.

Limitations

Limitations of the study were the relatively small number of animals and use of 1 ventilator/POC system for the experiments. Additionally, we only tested 5 O_2 bolus timing schemes in experiment 1 so there may be one that is more efficacious that we did not test. The limitation of the POC is the FIO_2 and liter per minute output of the device. As such, the ventilator/POC system would likely not be a 100% solution but may be able to oxygenate most mechanically ventilated casualties.

CONCLUSIONS

Our study shows that either a ventilator/POC closed loop system using a 1 mL or 16 mL increment O_2 bolus from the Saros POC in addition to appropriate use of PEEP can adequately oxygenate swine in a lung injury model of severe ARDS. Although not a 100% solution for providing oxygen for mechanically ventilated patients in austere environments, this system could greatly reduce the logistical burden of providing O_2 via pressurized cylinders or liquid O_2. In contrast to our previous work, the ability of the two devices that make up the system to electronically communicate allows true closed loop control of oxygenation in addition to automatically adjusting ventilator V_T to accommodate POC bolus size without increasing delivered V_T. This could allow a caregiver in an austere environment to focus on other tasks involved in patient care without having to closely monitor and adjust O_2 to achieve adequate oxygenation. The way forward is to further refine the closed loop algorithm to increase functionality of the system and pave the way for future clinical trials.

PREVIOUS PRESENTATION

This study was presented as a poster at MHSRS 2017.

CONFLICT OF INTEREST

Mr. Branson discloses relationships with Mallinckrodt, Bayer, Philips, and Ventec. The remaining authors have no conflicts of interest to disclose.

FUNDING

This study was funded by the United States Air Force Research Laboratory Basic cooperative agreement FA8650-10-2-6140. Task order #FA8650-12-2-6B10.

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