Oxygen Requirement to Reverse Altitude-Induced Hypoxemia with Continuous Flow and Pulsed Dose Oxygen

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BACKGROUND: Hypoxemia secondary to reduced barometric pressure is a complication of ascent to altitude. We designed a study to compare the reversal of hypobaric hypoxemia at 14,000 ft with continuous flow oxygen from a cylinder and pulsed dose oxygen from a portable concentrator.

METHODS: There were 30 healthy volunteers who were randomized to one of three study groups, placed in an altitude chamber, and ascended to 14,000 ft. There were 10 subjects in each study group. Subjects breathed room air for 10 min to induce hypoxemia. Oxygen was then delivered via a nasal cannula from a cylinder at 1, 2, or 3 lpm of continuous flow for 10 min. The subjects again breathed room air at altitude for 10 min and were then placed on pulsed dose oxygen and titrated to obtain the continuous flow S_pO_2 equivalent. S_pO_2, E_tCO_2, RR, HR, Hgb, and tissue oxygenation (S_tO_2) were continuously recorded.

RESULTS: The 1-lpm group's S_pO_2 range was 89–99%. The 2-lpm group's S_pO_2 range was 95–98%, and the 3-lpm group's S_pO_2 range was 95–99%. The 2-lpm and 3-lpm flows were able to correct hypoxemia in every subject. The mean pulsed dose required to achieve an equivalent S_pO_2 ranged from 36.8 ml $\pm$ 18.9 ml in the 1-lpm arm, and 102.4 ml $\pm$ 53.8 in the 3-lpm arm.

CONCLUSIONS: Portable oxygen concentrators using pulsed dose technology corrected hypoxemia in every subject. Oxygen concentrators may be an alternative to liquid oxygen or cylinders for use during aeromedical evacuation.

KEYWORDS: oxygen, hypobaric, concentrator, hypoxemia, aeromedical.

Blakeman TC, Rodriquez D Jr, Gerlach TW, Dorlac WC, Johannigman JA, Branson RD. *Oxygen requirement to reverse altitude-induced hypoxemia with continuous flow and pulsed dose oxygen*. Aerosp Med Hum Perform. 2015; 86(4):351–356.

Hypobaric hypoxia resulting in hypoxemia secondary to reduced barometric pressure is a well-described complication of ascent to altitude.[4,8,13] Even at cabin altitudes encountered on commercial air travel, some people experience decreased oxygen saturations.[11] Current medical operations in support of warfighters in Afghanistan often require ascent to 14,000 ft (4267 m) or more in unpressurized aircraft during evacuation of casualties. While hypobaric hypoxia is no doubt encountered, this issue is not well documented, nor are mitigation strategies for prevention of hypoxemia. The use of unpressurized aircraft for personnel movement at altitudes up to 20,000 ft (6096 m) is possible with new aircraft.

The obvious treatment of hypobaric hypoxemia is supplemental oxygen. Aboard aircraft, oxygen can be delivered using a continuous flow of oxygen from liquid or compressed gas sources or via an oxygen concentrator. An oxygen concentrator uses electricity and pressure swing absorption to separate nitrogen from air and deliver approximately 93% oxygen. The flow from a concentrator is dictated by size and power requirements, with portable devices capable of 1-3 lpm. The on-board oxygen generation system (OBOGS) device carried by some U.S. military aircraft is an oxygen concentrator used by pilots and eliminates the need to carry and maintain compressed gas or liquid oxygen systems.[2,10,12] The advantage of a concentrator

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This manuscript was received for review in October 2014. It was accepted for publication in December 2014.

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DOI: 10.3357/AMHP.4184.2015

over other sources is the inexhaustible oxygen supply in the presence of electricity. The disadvantages of concentrators are weight and the low-flow, low-pressure output.

In home care, oxygen concentrators are used for patients with chronic lung disease at low flows or via a pulsed dose technique. The pulsed dose technique detects patient inspiration and delivers a bolus of oxygen at the beginning of inspiration. This technique has several potential advantages. The gas delivered early in inspiration is destined for alveolar deposition while gas late in inspiration remains in the anatomical dead space, unable to participate in gas exchange. The pulsed dose method also minimizes oxygen use when combined with a liquid or compressed gas source or reduces power consumption when used with a concentrator.

In practice, the manufacturer will list a pulse dose setting (typically labeled as a numerical setting or a pulse volume) that should provide oxygen delivery equivalent to continuous flow from a cylinder. As an example, a pulse dose of 32 ml is intended to be equivalent to a continuous flow of 1 lpm. The actual delivered oxygen concentration to the patient (FDO_2) during low-flow oxygen is based on the oxygen flow and the patient's respiratory pattern. Rapid shallow breathing results in higher actual FDO_2 while large volumes and slower rates result in lower actual FDO_2.

The advent of small, portable oxygen concentrators (POC) approved for air travel (by the Federal Aviation Administration) suggests that these devices might prove useful in aircraft of opportunity for aeromedical evacuation. The devices have not been evaluated in this environment. We designed a study to evaluate the reversal of hypobaric hypoxemia at 14,000 ft (4267 m) with continuous flow oxygen from a cylinder and pulsed dose oxygen from a portable concentrator. The study goal was to determine the pulse dose required to achieve an equivalent S_pO_2 when administering oxygen liter flows of 1-3 lpm.

METHODS

Subjects

The study was approved by the University of Cincinnati Medical Center Institutional Review Board, the Wright Patterson Air Force Base Institutional Review Board, and the Surgeon General's Human Research Protections Office. Informed consent was obtained from each subject prior to any study related procedures. All subjects held current altitude chamber certifications, were >18 yr of age, and were judged physically fit to fly. All subjects were examined by the flight physician and physician's assistant prior to and after each flight. There were a total of 30 subjects who were randomized to one of the three study groups, resulting in 10 subjects per group.

The subjects were placed in the altitude chamber in a seated, upright position. The flight plan began at local atmospheric pressure (746-753 mmHg) and included an initial increase to 5000 ft (1524 m) of simulated altitude (mmHg) at 2500 ft · min^{-1} (762 m · min^{-1}) for an ear and sinus safety check. Participants who had no pain or pressure consequences remained in the study and were returned to sea level. The flight plan to 14,000 ft (4267 m) of simulated altitude (mmHg) was accomplished at 2500 ft · min^{-1} and lasted approximately 75 min. All flights included 1-2 subjects, 1-2 investigators, an inside observer, and a flight surgeon. The chamber was staffed by two external operators and two external observers.

Equipment

There were five periods of study and data collection (**Fig. 1**). The baseline period occurred during 10 min at local atmospheric pressure. After reaching 14,000 ft (4267 m), the subjects breathed room air for 10 min. If at any time oxygen saturation of subjects fell below 82% for longer than 30 consecutive seconds, oxygen was delivered via a nasal cannula. At the end of 10 min at 14,000 ft patients were placed on compressed oxygen from a cylinder at 1, 2, or 3 lpm via a nasal cannula based on a computer generated random numbers table. This continuous flow of oxygen was accomplished for 10 min. Subjects were then returned to breathing atmospheric air at 14,000 ft without oxygen supplementation for 10 min. After stabilization, subjects were placed on pulsed dose oxygen from a POC

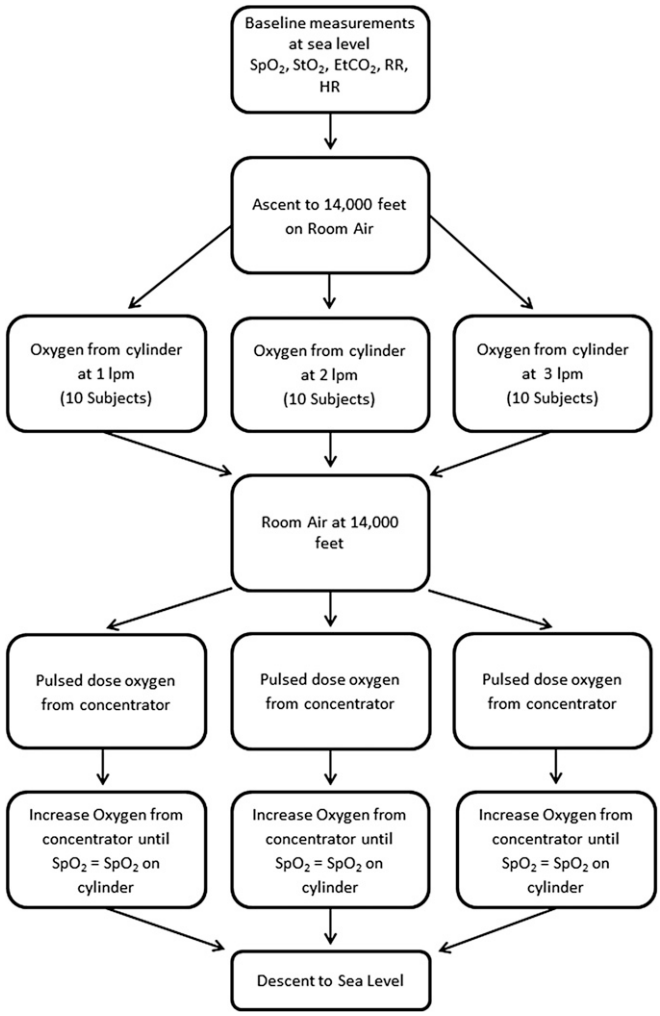

Fig. 1. Study flow diagram.

(Eclipse 3, Sequal Technologies, Ball Ground, GA). If the S_pO_2 during pulsed dose oxygen delivery did not meet the S_pO_2 achieved during the continuous flow period, investigators titrated the pulsed dose until the S_pO_2 was equal to the S_pO_2 in continuous flow mode. Subjects were then returned to atmospheric pressure and ambient oxygen. The dose reported by the POC manufacturer to be equivalent to the continuous flow of compressed oxygen was: 1 lpm = 32 ml bolus, 2 lpm = 64 ml bolus, 3 lpm = 96 ml bolus.

Procedure

Upon entry to the altitude chamber, subjects were connected to commercially available monitoring devices. This included a respiratory monitor (Capnostream 20, Oridion Medical, Needham, MA) which monitored pulse oximetry and pulse rate via a finger sensor and used a nasal cannula (Smart Capnoline, Oridion, Needham, MA) for monitoring end-tidal carbon dioxide ($P_{ET}CO_2$) and respiratory rate. A second pulse co-oximeter (Masimo Radical 7, Masimo, Irvine, CA) was placed on the opposite hand via a finger sensor. This oximeter was equipped with the ability to monitor heart rate, S_pO_2, and hemoglobin (Hgb) noninvasively. Subjects were also monitored via a tissue oxygen sensor (InSpectra Sto_2, Hutchinson Technology Inc., Hutchinson, MN). The tissue oxygen sensor was placed on the thenar eminence of the thumb. Tissue oxygen saturation (S_tO_2) was monitored continuously. All devices recorded data continuously to magnetic memory for later analysis. During the study, the investigators continuously monitored subjects and manually recorded data every 5 min to a case report form.

Statistical Analysis

Endpoint measurements of Hgb, $P_{ET}CO_2$, heart rate, respiratory rate, S_pO_2, and S_tO_2 were compared between study periods using paired *t*-tests. *P*-values of 0.05 or less were used to determine statistical significance.

RESULTS

S_pO_2 varied both between and within study groups. The 1-lpm group had the widest S_pO_2 range: 89–99% (mean 93.4% ± 3.1), and this setting was not able to correct hypoxemia ($S_pO_2 \geq$ 90%) in every subject. The 2-lpm group's S_pO_2 range was 95–98% (mean 96.8% ± 0.9). The 3-lpm group range was 95–99% (mean 97.7% ± 1.3). Both the 2-lpm and 3-lpm settings were able to correct hypoxemia in every subject. The mean pulse dose required to achieve the equivalent S_pO_2 from the cylinder at altitude was 36.8 ± 18.9 ml (range 16-80 ml) in the 1-lpm group, 101.6 ± 50.9 ml (range 48-192 ml) in the 2-lpm group, and 102.4 ± 53.8 ml (range 48-192 ml) in the 3-lpm group. The differences in final pulse dose setting after titration to achieve equivalent S_pO_2 with continuous flow from the cylinder was statistically significant ($P < 0.05$) in all three study groups. **Tables I-III** show the measured parameters in each of the study groups at each study period.

Comparing sea level and 14,000 ft (4267 m) on room air, S_pO_2 differences were statistically significant ($P < 0.0001$) in all three study groups (**Table IV**), as were heart rate differences ($P < 0.05$). Respiratory rate was significantly different ($P < 0.05$) in the 3-lpm group, but not at the other two flow levels. $P_{ET}CO_2$ and Hgb were statistically different in the 1-lpm and 2-lpm groups, but not the 3-lpm group. S_tO_2 was significantly different in the 2-lpm ($P < 0.01$) and 3-lpm ($P < 0.05$) groups, but not the 1-lpm group. Comparing 14,000 ft on the oxygen cylinder and the ending dose on the concentrator (Table IV), none of the differences in measured variables reached statistical significance with the exception of $P_{ET}CO_2$ in the 2-lpm group ($P < 0.001$).

An incidental finding was noted during data analysis. Hgb measured noninvasively by the Masimo oximeter decreased when S_pO_2 decreased at 14,000 ft (4267 m) on room air. The Hgb decrease was statistically significant ($P < 0.05$) in the 1-lpm and 2-lpm study groups. The Hgb decrease in the 3-lpm group approximated ($P = 0.059$) but failed to reach statistical significance. The mean decrease in measured Hgb was 14.9 ± 1.5 at sea level to 13.8 ± 2.1 at 14,000 ft on room air across all three study groups.

DISCUSSION

The main study findings demonstrate that hypoxemia at an altitude of 14,000 ft can be reversed using both continuous flow oxygen from a cylinder and pulse dosed oxygen delivery from a POC via nasal cannula. The increase in subjects' tidal volume (V_T) at altitude required that the pulse dose setting be increased by 6–37% compared to the manufacturers' suggested setting for an equivalent to continuous flow.

Table I. Measured Parameters in the 1-lpm Group.

	SEA LEVEL	14,000 ft	14,000 ft CYLINDER	14,000 ft	FINAL PULSE DOSE
	MEAN ± SD (MIN–MAX)				
S_pO_2	97.0 ± 1.5 (95–100)	84.3 ± 3.6 (82–92)	93.4 ± 3.1 (89–99)	85.0 ± 4.1 (82–95)	94.3 ± 2.8 (91–99)
HR	72.4 ± 9.2 (61–88)	78.7 ± 12.1 (58–100)	69.4 ± 10.8 (52–88)	76.8 ± 11.1 (63–99)	68.0 ± 11.0 (55–89)
RR	14.4 ± 3.1 (11–20)	13.8 ± 3.3 (9–19)	15.0 ± 2.5 (11–20)	13.1 ± 2.8 (10–20)	14.1 ± 4.6 (9–24)
$P_{ET}CO_2$	39.9 ± 3.1 (36–46)	36.0 ± 2.9 (30–40)	36.8 ± 3.6 (29–41)	37.1 ± 2.6 (33–41)	34.7 ± 3.6 (29–39)
S_tO_2	76.1 ± 6.2 (66–85)	72.5 ± 5.9 (62–82)	76.4 ± 5.6 (66–83)	72.6 ± 5.2 (65–81)	74.2 ± 5.5 (66–82)
Hgb	14.8 ± 1.7 (12.1–18)	13.8 ± 2.1 (11.1–17.9)	14.4 ± 1.2 (12.4–16.6)	13.6 ± 0.8 (12.7–15.2)	14.3 ± 1.2 (12.3–16.3)
Pulse dose					36.8 ± 18.9 (16–80)

Table II. Measured Parameters in the 2-lpm Group.

	SEA LEVEL	14,000 ft	14,000 ft CYLINDER	14,000 ft	FINAL PULSE DOSE
	MEAN ± SD (MIN–MAX)				
S_pO_2	97.4 ± 1.3 (96–99)	83.0 ± 1.3 (82–86)	96.9 ± 0.9 (95–98)	83.7 ± 1.8 (82–86)	97.1 ± 0.7 (96–98)
HR	74.2 ± 10.6 (54–91)	80.1 ± 9.1 (66–95)	69.4 ± 9.6 (50–84)	77.0 ± 7.4 (67–85)	68.4 ± 7.7 (53–79)
RR	14.7 ± 5.1 (8–22)	12.7 ± 4.2 (9–23)	10.4 ± 2.8 (7–15)	11.5 ± 3.0 (7–17)	13.1 ± 3.0 (8–17)
$P_{ET}CO_2$	41.7 ± 2.6 (37–45)	38.5 ± 4.0 (34–48)	31.9 ± 7.2 (18–39)	38.8 ± 3.6 (33–47)	39.7 ± 5.4 (30–50)
S_tO_2	78.6 ± 6.3 (69–90)	71.8 ± 4.7 (61–77)	77.7 ± 7.2 (64–90)	73.3 ± 5.3 (63–82)	76.7 ± 5.4 (64–85)
Hgb	14.5 ± 1.6 (12.7–17.9)	13.3 ± 2.1 (9.7–16.5)	14.6 ± 1.0 (12.8–16.1)	13.9 ± 1.8 (11.2–16.6)	14.8 ± 1.4 (12.9–16.9)
Pulse dose					101.6 ± 50.9 (48–192)

In the current military conflict, during aeromedical evacuation, patients encounter hypobaric conditions during flight. During fixed wing aeromedical transport, air frames typically pressurize the cabin to a barometric pressure equivalent to an altitude of approximately 8000 ft (2438 m), equivalent to a barometric pressure of 564 mmHg. Casualties transported by rotor wing aircraft in unpressurized cabins may be exposed to greater elevations. Current operations in Afghanistan are carried out at a base camp approximately 4895 ft (1492 m) above sea level. As casualties are evacuated over mountainous terrain, altitudes of 14,000 ft (4267 m) can be encountered. At 14,000 ft the barometric pressure falls to 447 mmHg, which results in a decrease in the partial pressure of inspired oxygen (P_IO_2) to 94 mmHg in the atmosphere and 44 mmHg at the alveolar level.[13] With the decrease in the atmospheric oxygen pressure at this altitude, hypoxemia can occur in critically ill/wounded patients. Hypoxemia is known to increase the risk of mortality in patients with head injuries[6,7,9] and sustained hypoxia may impair caregivers' ability to adequately tend to those being transported.

Under normal hospital conditions oxygen is abundant. Under battlefield conditions and other hostile environments, oxygen is a scarce resource. Supplying oxygen in a far forward environment, however, represents a significant logistical challenge. Compressed gas cylinders at 2200 psig containing 644 L of gaseous oxygen are currently used during rotor-wing transport of casualties. Cylinders are heavy and represent a fire and projectile risk, and can also be repurposed by the enemy. When an oxygen cylinder is empty it ceases to be useful.

An alternative to compressed oxygen is a portable oxygen concentrator.[17,20,22] An oxygen concentrator draws room air through a sieve bed of Zeolite under pressure. The Zeolite absorbs nitrogen, allowing concentrated oxygen to be delivered. These devices are predominantly used in home care for patients with chronic respiratory disease. Portable devices typically can produce 3 lpm of 93% oxygen. Larger devices often exceeding 50 lb can produce 15 lpm and room sized devices can supply a small hospital. In the presence of electrical power, an oxygen concentrator can produce oxygen until power is lost. A concentrator has many advantages over a compressed gas cylinder. There is no explosive risk as the device is not under pressure and it provides an infinite source of oxygen in the presence of electricity. The oxygen purity leaving the concentrator (93%) and volume of oxygen per pulse is equivalent. The use of pulse dose technology allows bolus volumes from 16–192 ml with this device while preventing oxygen waste, consuming less electrical power, and providing longer battery life.

Several publications have shown the value of POCs for use by COPD patients at rest, during exertion,[14,18,23] and while sleeping.[5] Bolus dosing of oxygen from a concentrator has been shown to more efficient, economical, and as efficacious as traditional cylinder oxygen for patients receiving long-term oxygen therapy.[3,15] These POCs have a smaller footprint, use less power, and enable users' greater mobility than stationary concentrators, are less cumbersome and do not require refilling as do oxygen cylinders. The use of medical devices in the aeromedical transport arena requires many of these same characteristics. POCs need to be small, lightweight, portable, run from battery power if needed, and provide enough oxygen to reverse mild hypoxemia. The POC used in this study was able to reverse hypobaric hypoxemia in all of the subjects, albeit increases in pulse dose volume were required in selected subjects in order to attain an equivalent S_pO_2 compared to continuous flow from the cylinder. Individual subject physiological response to hypoxemia may have contributed to the need

Table III. Measured Parameters in the 3-lpm Group.

	SEA LEVEL	14,000 ft	14,000 ft CYLINDER	14,000 ft	FINAL PULSE DOSE
	MEAN ± SD (MIN–MAX)				
S_pO_2	97.6 ± 1.1 (96–100)	83.2 ± 0.9 (82–84)	97.7 ± 1.3 (95–99)	86.0 ± 3.4 (82–94)	97.6 ± 1.3 (95–99)
HR	72.1 ± 8.6 (61–82)	81.1 ± 11.3 (64–103)	66.5 ± 8.1 (54–79)	74.5 ± 7.2 (66–87)	68.5 ± 8.2 (58–82)
RR	16.7 ± 3.8 (13–23)	12.3 ± 2.7 (8–15)	12.3 ± 4.1 (7–18)	11.4 ± 2.9 (7–17)	14.3 ± 5.8 (5–22)
$P_{ET}CO_2$	39.4 ± 1.8 (37–42)	38.8 ± 3.6 (35–47)	33.7 ± 7.5 (23–46)	39.1 ± 4.9 (32–50)	38.7 ± 5.9 (28–47)
S_tO_2	76.9 ± 6.7 (64–86)	72.3 ± 5.2 (65–80)	77.7 ± 4.9 (67–86)	75.3 ± 3.9 (69–81)	78.8 ± 5.9 (71–87)
Hgb	15.3 ± 1.2 (13.4–16.9)	14.4 ± 2.3 (10.7–16.7)	15.0 ± 1.0 (13.6–16.7)	14.5 ± 1.7 (12.8–17.1)	14.9 ± 1.2 (13.2–16.8)
Pulse dose					102.4 ± 53.8 (48–192)

Table IV. S_pO_2 Differences on Room Air at 14,000 ft as Compared to Sea Level, and S_pO_2 Differences at 14,000 ft on the Concentrator Ending Dose as Compared to the Oxygen Cylinder in Each of the Three Study Groups.

	MEAN S_pO_2 DIFFERENCE ON ROOM AIR: 14,000 ft: SEA LEVEL				MEAN S_pO_2 DIFFERENCE AT 14,000 ft: ENDING CONCENTRATOR DOSE—CYLINDER			
STUDY GROUP	**MEAN DIFFERENCE**	**STD. ERROR**	***t*-VALUE**	***P*-VALUE**	**MEAN DIFFERENCE**	**STD. ERROR**	***t*-VALUE**	***P*-VALUE**
1 lpm	−12.7	0.94	−13.5	<0.0001	0.9	0.43	2.1	0.07
2 lpm	−14.4	0.48	−30.3	<0.0001	0.2	0.29	0.7	0.51
3 lpm	−14.4	0.48	−30.0	<0.0001	−0.10	0.18	−0.6	0.59

to increase pulse dose. The normal physiological response to acute hypoxemia is an increase in cardiac output through increasing heart rate[16,24,25] and a decrease in alveolar CO_2 via hyperventilation.[1,19] **Fig. 2** shows a sample flight with the changes in heart rate, respiratory rate, and $P_{ET}CO_2$ in response to hypoxemia.

Differences in S_pO_2 among subjects in the same study group in bolus mode may be attributed to the breathing pattern. As compared to the continuous flow rate in the same study group, $P_{ET}CO_2$ was significantly lower ($P < 0.05$) during bolus mode, suggesting hyperventilation was achieved by increasing V_T rather than respiratory rate. The reason for the significant difference in $P_{ET}CO_2$ on the oxygen cylinder versus the final dose on the concentrator in the 2-lpm study group is unclear. Differences in individual breathing patterns among study subjects resulting in a wide $P_{ET}CO_2$ range (18-39 mmHg) on the oxygen cylinder (versus 30-50 mmHg on the concentrator at final pulse dose) provides a likely explanation. Differences in respiratory rate were not statistically significant between the continuous flow and bolus mode in any of the study groups. Increasing V_T decreases actual FDO_2 by diluting the oxygen bolus being delivered. Another possible explanation for the S_pO_2 difference is the concentrator delivers 93% ± 3% oxygen[21] as compared to 100% from the cylinder. The lower F_IO_2 coupled with larger V_T may explain the lower S_pO_2 in bolus mode. As a result, the bolus dose had to be increased above the reported bolus dose equivalent in 25 of 30 subjects to achieve an S_pO_2 equal to that achieved by continuous flow delivery ($P < 0.5$). Although increases in bolus volumes were required, the dose required to reach the S_pO_2 equivalent while breathing continuous flow oxygen was well within the concentrator's capability. The decrease in Hgb measurements with hypoxemia likely represents an error created by the rapid S_pO_2 change in the Masimo software, which deserves further investigation, but is beyond the scope of this study.

The limitations of this study are that it took place in a controlled environment (altitude chamber) using healthy volunteers. We do not know if ill/injured patients would respond in the same fashion. Additionally, we did not have a method to measure subjects' V_T, so we had to assume that a decrease in $P_{ET}CO_2$ with stable respiratory rate was due to increased V_T. The fall in respiratory rate and decrease in $P_{ET}CO_2$ predicts that tidal volume was increased, as does observation of the subjects.

In conclusion, at an altitude of 14,000 ft (4267 m), 1-3 lpm continuous flow oxygen from a cylinder corrected hypoxemia in all but one subject. This subject was randomized to the 1-lpm study group and achieved a maximum S_pO_2 of 89%. Although

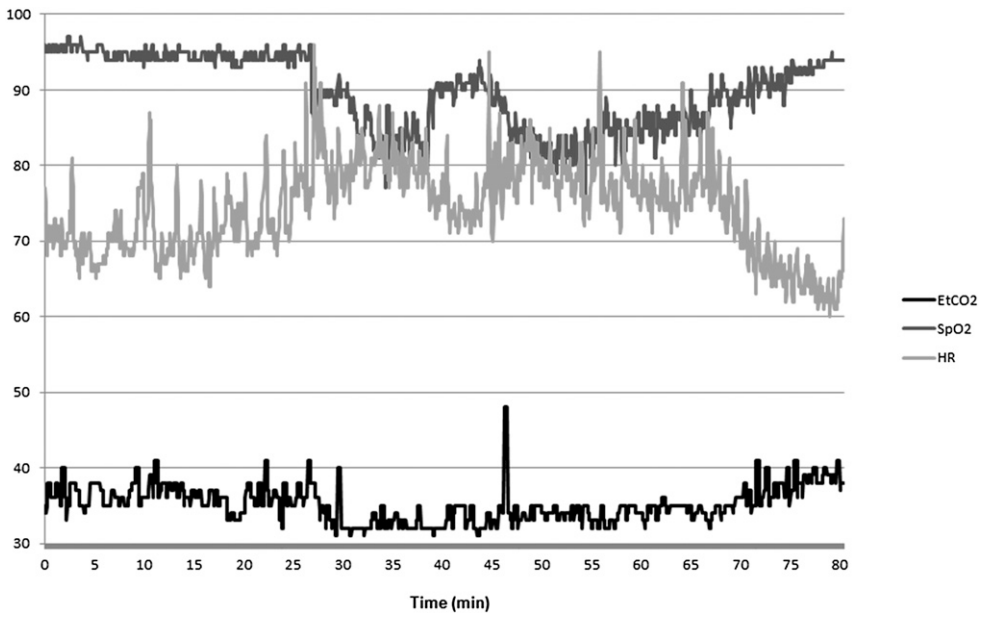

Fig. 2. Sample flight showing physiological changes in response to hypoxemia.

using the concentrator in the 2-lpm and 3-lpm groups had more subjects with $S_pO_2 < 90\%$, the increased pulse dose required to obtain an S_pO_2 equivalent to continuous flow was well within the device's capability. Oxygen concentrators may be an alternative to liquid oxygen or cylinders for use during aeromedical evacuation. The POC used in this study is small, light, highly portable, has a wide range of bolus volumes, and, as long as electricity is available, can produce infinite oxygen.

ACKNOWLEDGMENTS

Funding for this project was from the United States Air Force 711th HPW.

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