Arterial Oxygen Saturation, Pulse Oximetry, and Cerebral and Tissue Oximetry in Hypobaric Hypoxia

William Ottestad; Jan Ivar Kåsin; Lars Øivind Høiseth

INTRODUCTION: Clinical accuracy of pulse oximeters (giving S_pO_2) is routinely tested down to an S_aO_2 of 70%, but lower oxygen saturations are often experienced during hypobaric hypoxia. Cerebral (S_cO_2) and peripheral tissue (S_tO_2) oxygen saturations can be measured using near infra-red spectroscopy. In a project simulating oxygen system failure during high altitude-high opening parachuting (HAHO), S_aO_2, S_pO_2, S_cO_2, and forearm S_tO_2 were measured. The aim of the present analysis was to explore the agreement between S_aO_2 and the three noninvasive measurements of hypoxemia (S_pO_2, S_cO_2, and S_tO_2).

METHODS: Healthy volunteers from the Norwegian Special Operations Commando were studied in a hypobaric chamber as supplemental oxygen was removed at 301 hPa ambient pressure (30,000 ft) and recompressed at 25 hPa · min^{-1} (1000 ft · min^{-1}) to ground level simulating a HAHO parachute flight. S_aO_2 was compared with S_pO_2, S_cO_2, and S_tO_2 in scatterplots and Bland-Altman plots, calculating bias and limits of agreement (LOA).

RESULTS: The bias ± LOA were: S_aO_2 vs. S_pO_2: −5.8% ± 16, S_aO_2 vs. S_cO_2: −3.4% ± 11, and S_aO_2 vs. S_tO_2: 17% ± 30. The bias for S_aO_2 vs. S_pO_2 was dependent on the range of values, and correcting for this with a sloped bias line reduced the LOA to ± 8.2%.

DISCUSSION: There were wide limits of agreement between S_aO_2 and S_pO_2. S_aO_2 and S_cO_2 agreed better, whereas S_aO_2 and forearm S_tO_2 had wide LOA. The agreement between S_aO_2 and S_pO_2 improved when correcting for the underestimation of S_pO_2 at low values. There is a poor agreement between S_pO_2 and the gold standard S_aO_2 during extreme hypobaric hypoxemia.

KEYWORDS: atmospheric pressure, blood gas analysis, hypoxia, oximetry.

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In-flight loss of consciousness due to hypobaric hypoxia is a serious threat to aviators, and in-flight hypoxia has been reported to be common among military aircrew.[4] In order to demonstrate the physiological effects of hypoxia and increase hypoxia awareness, aircrew members undergo mandatory and regular training in hypobaric chambers. Hypobaric chamber training exposes personnel to acute profound hypoxia. In order to avoid hypoxic syncope and assure timely administration of oxygen, estimating arterial oxygen saturation with pulse oximetry (S_pO_2) is performed in most institutions during hypobaric chamber training. However, in research situations when aiming to explore the effects of decompression and hypobaric hypoxia, pulse oximetry may not be a reliable tool to accurately reflect the degree of hypoxemia.

High-altitude insertion of military parachutists is carried out at altitudes between 6096 m (20,000 ft) and 10,668 m (35,000 ft). To operate at these altitudes requires supplemental oxygen to prevent hypoxia, however, there remains a substantial risk of acute hypoxia in the event of oxygen equipment failure. We recently published a study on acute hypoxia in a simulated high-altitude airdrop scenario due to oxygen system failure wherein repeated arterial blood gas analyses were performed and arterial oxygen saturation (S_aO_2) measured. The data presented in the current manuscript are from the same experiment. We also measured S_pO_2 and cerebral (S_cO_2) and forearm (S_tO_2) tissue oxygen saturations by near-infrared spectroscopy (NIRS) using commercially available devices specified in the Methods section of the present manuscript.[8]

From the Norwegian Special Operations Commando; Air Ambulance Department, and Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital; and Norwegian Defense Medical Services, Institute of Aviation Medicine, Oslo, Norway.

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Address correspondence to: Lars Øivind Høiseth, M.D., Ph.D., Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital, Pb 4950 Nydalen, 0424 Oslo, Norway; lars.oivind.hoiseth@hotmail.com.

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Measuring S_aO_2 requires an indwelling arterial catheter or an arterial puncture. Estimating S_aO_2 by pulse oximetry (S_pO_2) is therefore preferred in most clinical and experimental circumstances, as monitoring can be achieved continuously and non-invasively. S_pO_2 is based on the pulsatile component in the absorption of red and infrared light and the different absorption spectra of oxygenated and deoxygenated hemoglobin.[7] Near-infrared spectroscopy utilizes some of the same basic principles, but does not extract the pulsatile component and thus estimates the tissue oxygen saturation of the arterial, capillary and venous blood in the sample volume.[10] The aim of the present analysis was to explore the agreement between S_aO_2 and S_pO_2, S_cO_2 and S_tO_2 during profound hypobaric hypoxia over a wide range of P_aO_2-values.

METHODS

Subjects

The study protocol was approved by the Regional Committees for Medical and Health Research Ethics (REC South East, reference 2014/469). Each subject provided written informed consent before participating. Nine healthy men were recruited among personnel qualified for performing HAHO-procedures in the Norwegian Army Special Operations Commando.

Equipment

After performing Allen´s test and verification by ultrasound of a patent ipsilateral ulnar artery, a 20-gauge arterial catheter was placed in the left radial artery and locked with heparin 100 IE/ml. A LNOP DC-I (Masimo Corp., Irvine, CA) finger probe of a Masimo Radical 7 pulse oximeter, version 7.3.1.1 (Masimo Corp.) was placed on the left index finger. NIRS sensors (Adult SomaSensor; Covidien, Mansfield, MA) were attached to left and right forehead and on the volar aspect of the left forearm, approximately 3 cm distal to the elbow crease. The NIRS sensors were attached to an Invos 5100C cerebral/somatic oximeter (Somanetics, Troy, MI). S_cO_2 was averaged from the left and right measurements. S_cO_2 and S_tO_2 at the end of the run (ambient pressure) were used as baselines.

The averaging time of the Masimo pulse oximeter was set to a minimum (2 s), and data extracted at 0.5 Hz using the TrendCom software (Masimo Corp.). Data were extracted from the Invos oximeter by its serial output (one value every 7–8 s). Blood gas samples were analyzed in a Radiometer 133 ABL 90 FLEX, blood gas machine (Radiometer, Brønshøj, Denmark).

Procedure

The subjects were breathing 100% oxygen (denitrogenation) 40 min at ground level before reducing pressure to 753 hPa, corresponding to an altitude of 2438 m (8000 ft), which was kept for an additional 20 min. Pressure was then reduced to 301 hPa, corresponding to an altitude of 9144 m (30,000 ft), still breathing 100% oxygen. Immediately before removal of oxygen supply, the subjects performed 30 squats in order to simulate the workload associated with exiting the aircraft in a military airdrop scenario. Supplemental oxygen was removed at the start of chamber recompression (simulated descent to ground in free fall and under canopy), and the subjects breathed ambient air throughout the flight profile. The flight profile is illustrated in **Fig. 1**.

Arterial blood gas samples were drawn every 20 s for the first minute, every 30 s the next 9 min, every min the next 10 min and every 5 min the last 10 min. Samples were immediately put on ice and brought out through the chamber lock in batches every 4 min for analysis within 10 min of sampling. According to the manufacturer's user manual, the ABL 90 blood gas machine is validated for P_aO_2 values as low as 1.9 kPa. S_pO_2, S_cO_2, and S_tO_2 were sampled continuously.

Statistical Analysis

Data from the first 3 min of the run were discarded, as they represented very rapid changes making synchronization difficult, as shown in **Fig. 2**. Analyses are therefore performed on data starting 3.5 min from start of the hypoxic exposure. Blood gas analyses are matched with S_pO_2, S_cO_2, and S_tO_2 values

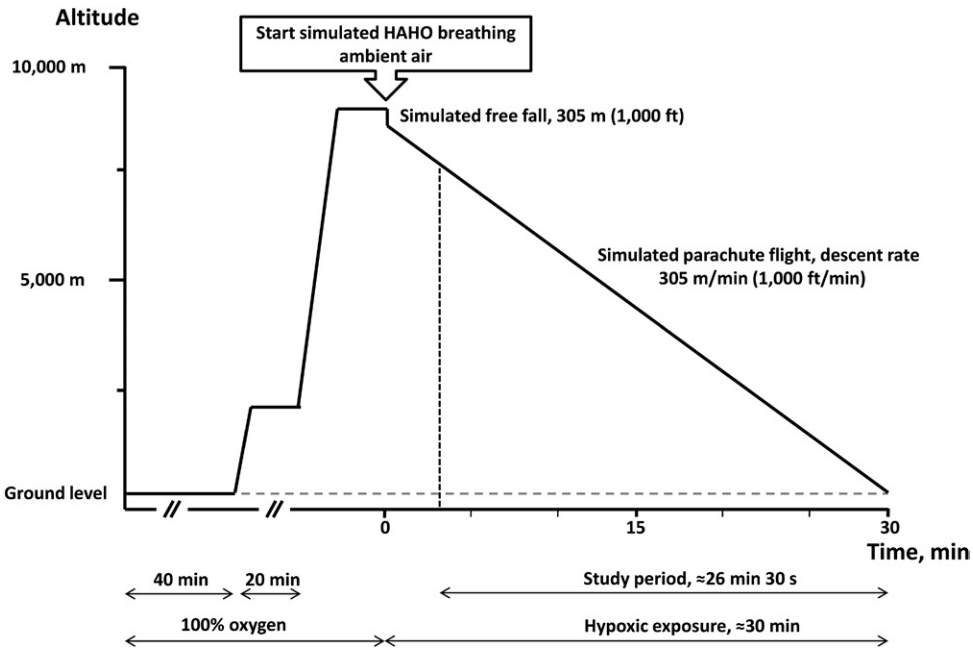

Fig. 1. The pressure profile of the denitrogenation procedure and simulated parachute descent. The first three minutes breathing ambient air after the start of simulated HAHO were not used in the present analysis. HAHO = high altitude high opening.

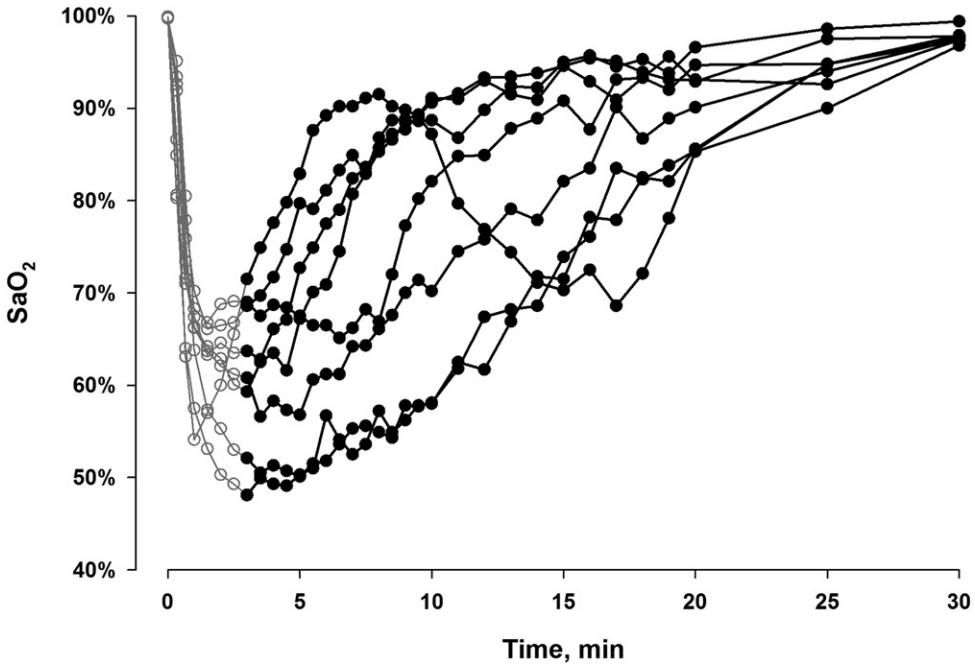

Fig. 2. Lineplot of S_aO_2 through the simulated parachute descent with circles/dots representing blood gas analyses. During the first three minutes (gray circles and lines) there were rapid changes, making synchronization difficult. The analyses are therefore performed on the measurements starting at 3.5 min, presented as black dots and lines. S_aO_2, arterial oxygen saturation from blood gas analysis.

averaged over 15 s starting at the time the blood gas was drawn to account for the delay from signal detection and processing to output of the devices.

S_aO_2 was compared to S_pO_2, S_cO_2, and S_tO_2 in scatterplots and Bland-Altman (difference vs. mean) plots. Although Bland-Altman plots are intended to compare two measurement methods of the same variable, S_aO_2 was also compared to S_cO_2 and S_tO_2 using this approach. Linear mixed models with subjects as random effects were used due to repeated measurements within subjects. In the Bland-Altman plots, limits of agreement were calculated as $\pm$ 1.96 $\times$ $\sqrt{}$(between-subject variance + within-subject variance).[3] The classic Bland-Altman plot assumes that the difference between methods is stable across the range of measurements. To account for violations of this assumption, bias and limits of agreement (LOA) were also calculated as a function of the mean of the two measurements (sloped bias $\pm$ LOA-lines).[2] Analyses were performed in R 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria) in RStudio 1.0.143 (RStudio Inc., Boston, MA). No separate power analysis was performed for the analyses in the present manuscript.

RESULTS

Nine subjects were recruited: age 31 (27–48) yr, weight 85 (75–95) kg, height 183 (174–193) cm [median (range)]. One subject was given supplemental oxygen after experiencing loss of useful consciousness after 4 min at a pressure of 370 hPa [corresponding to 7740 m (25,400 ft)] and was excluded from the analyses. All the other subjects completed the protocol. In one subject, forearm S_tO_2 was not recorded due to accidental disconnection during the squats.

S_aO_2 through the experiment is shown in Fig. 2. Scatterplots and Bland-Altman plots are presented in **Fig. 3**. Conventional bias $\pm$ LOA between S_aO_2 and the other measurements were S_pO_2 -5.8 $\pm$ 16%, S_cO_2 -3.4 $\pm$ 11% and S_tO_2 17 $\pm$ 30%. The bias between S_aO_2 and S_pO_2 was obviously dependent on their average, and adding a slope to the bias line approximately halved the LOA to $\pm$ 8.2%. Although having statistically significant bias slopes, the LOAs of S_aO_2 vs. S_cO_2 or S_aO_2 vs. S_tO_2 were not reduced by sloping the bias.

DISCUSSION

The main findings of this analysis were the relatively wide LOA between S_aO_2 and S_pO_2 and that S_pO_2 tended to underestimate oxygen saturation at low values of S_aO_2. Furthermore, S_cO_2 seemed to agree rather well with S_aO_2, even at low S_aO_2 values.

Testing for clinical accuracy of pulse oximeters is routinely performed down to an S_aO_2 of 70%.[12] Measuring lower saturations is often of marginal interest in most adult clinical use, as every value below 70% is unacceptably low. In some selected clinical conditions, e.g., during cardiopulmonary resuscitation and severe respiratory failure, it may however be of interest. Furthermore, it may be important in selected experimental conditions, e.g., when exposing personnel to hypobaric hypoxia. The wide limits of agreement between S_aO_2 and S_pO_2 were narrowed (nearly halved) by accounting for the systematic tendency of S_pO_2 to underestimate oxygen saturation by applying a regression-based sloped bias line. Conventional limits of agreement would otherwise be too dependent on the range of oxygen saturations studied, widening when adding lower oxygen saturations. With this correction, the LOA between S_aO_2 vs. S_pO_2 were not wider than the LOA of S_aO_2 vs. S_cO_2.

S_cO_2 seemed to have a small bias to S_aO_2 which was stable over the range of oxygen saturations studied and thus seemed to reflect S_aO_2 well over the entire range of P_aO_2 values (approximately 3 to 15 kPa). Although the slope of the bias line was statistically significant, the effect was so small that the clinical significance is probably negligible. S_cO_2 is believed to mainly reflect oxygen saturation of hemoglobin in small arteries, capillaries and veins in brain tissue.[10] The contribution of other chromophores is debatable.[10] As S_cO_2 is meant to reflect oxygenation of cerebral tissue, absolute values have been compared to an estimate based on arterial and venous (jugular bulb)

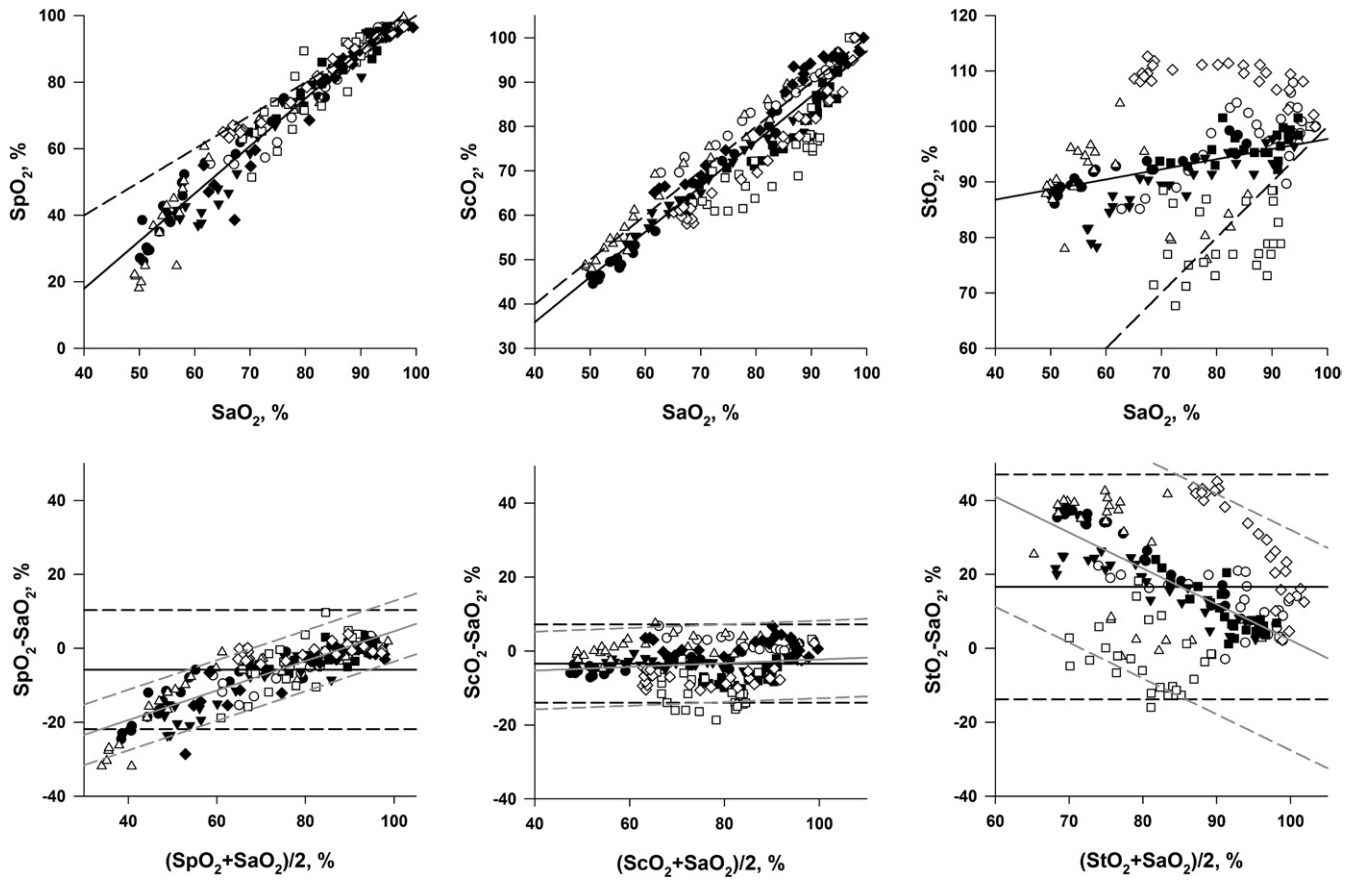

Fig. 3. Scatterplots (top row) and Bland-Altman plots (bottom row) of S_aO_2 vs. S_pO_2, S_cO_2 and S_tO_2. In the scatterplots, the dashed line is the line of identity (y = x) whereas the solid line is the regression line. In the Bland-Altman plots, the solid line is the bias whereas the dashed lines are the limits of agreement (LOA). Conventional bias ± LOA are in black, regression-based (sloped) bias ± LOA are in gray. Different subjects have different symbols. The bias ± LOA were: S_aO_2 vs. S_pO_2 -5.8 ± 16 (conventional) and -35 + 0.4 x ± 8.2 (sloped); S_aO_2 vs. S_cO_2 -3.4 ± 11 (conventional) and -7.3 + 0.05 x ±11 (sloped); S_aO_2 vs. S_tO_2 17 ± 30 (conventional) and 99 - 0.97 x ± 30 (sloped). S_aO_2, arterial oxygen saturation from blood gas analysis; S_pO_2, arterial oxygen saturation from pulse oximetry; S_cO_2, cerebral oxygen saturation; S_tO_2, tissue (forearm) oxygen saturation.

blood, with venous blood being quantitatively dominant (70–75%).[6,9] As we did not measure venous saturation, we only compared S_cO_2 relative to baseline to S_aO_2. In our experience, S_cO_2 measurements using NIRS are relatively easy to perform and seem resistant to, e.g., motion artifacts. Further, it interferes little with manual labor or movement. It may therefore be of value during research and training, and could potentially be implemented in headgear to detect hypoxia in aviators. Additionally, S_cO_2 may be useful in clinical scenarios with extreme hypoxemia and shock. During cardiac arrest or other shock-states a peripheral pulse signal is often absent and pulse oximetry fails to produce reliable data,[11] however S_cO_2 is of potential value in this clinical situation.[14]

Forearm S_tO_2 did not agree well with S_aO_2. As the measurement technique is the same as for S_cO_2, the difference for S_cO_2 probably reflects the nature of the tissue measured, and not the measurement technique itself. The sampling volume mainly consists of skeletal muscle, which was inactive during the present experiment. Isocapnic hypoxia increases forearm vascular conductance, partially opposed by sympathetic vasoconstriction.[13] Forearm S_tO_2 is reduced by both hypovolemia and pain,[1,5] probably due to sympathetically mediated reductions in regional blood flow. Our results indicate that forearm S_tO_2 is not a reliable measure of S_aO_2 during hypobaric hypoxia.

Absolute S_cO_2 and S_tO_2 values at the end of the run were used as baseline as these were close in time to the exposure. By sampling baseline data at the end of the hypobaric exposure, there is a risk of a carry-over effect. However, if baseline data had been sampled before denitrogenation, this would have been approximately 1 h prior to the start of the exposure.

Arterial blood sampling was performed with great accuracy (within 1–2 s of the time stated). There is, however, an uncertainty regarding the time resolution and delay of the pulse oximeter and tissue oximeter. Values averaged over 15 s starting at the time of the arterial blood sampling were used for both measurements and compared to the blood gas analyses. This assumes that the delays in the instruments were approximately 7–8 s from measurement through processing to output. Calculated in a linear mixed effects model (subjects as random effect, random intercept), the effect of time on S_pO_2 was 2.1%/min (95% CI 1.8 to 2.3) and S_cO_2 1.1%/min (95%CI 1.0 to 1.2). The estimate of the effect of deviating by 1 min was therefore ≈2% for S_pO_2 and ≈1% for S_cO_2.

We used commercially available oximeters in our experiments. Each device has its own algorithm, and the results may, therefore, not apply to devices with different software and from different manufacturers.

The linear mixed regression model used to calculate the LOAs assume that the observations within subjects are independent, which they are not as they are sampled consecutively. Imposing an AR(1) covariance structure increased the LOAs of S_aO_2 vs. S_tO_2 to $\pm$ 43% (from $\pm$ 30%), but did not seem to make clinically important changes to the other estimates (results not shown). We, therefore, believe the more parsimonious model used in our calculations is adequate.

In summary, there are wide LOAs between S_aO_2 and S_pO_2 during profound hypobaric hypoxia due to a systematic underestimation of S_pO_2 at low values. S_pO_2 measurements should be interpreted with caution in research situations. S_cO_2 appears to agree better with S_aO_2 and might be a valuable tool for evaluation of hypoxemia in research situations and for monitoring during hypobaric chamber training.

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Authors and affiliations: William Ottestad, M.D., Norwegian Special Operations Commando (NORSOC) and Air Ambulance Department, Oslo University Hospital; Jan Ivar Kåsin, Ph.D., Norwegian Defense Medical Services, Institute of Aviation Medicine; and Lars Øivind Høiseth, M.D., Ph.D., Department of Anesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway.

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