UCSF HYPOXIA LAB
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THE OpenOximetry.org PROJECT

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UCSF IRB: 21-35637
WHO Protocol ID: ERC.0004026

Protocol: Basic pulse oximeter hypoxemia (lab) performance study

Citation: UCSF Hypoxia Lab, Protocol for basic pulse oximeter hypoxia performance study. May 2024. https://openoximetry.org/study-protocols/

Abstract/Description

Pulse oximeters were introduced clinically around 1982 and are routine in most clinical settings including surgery, recovery, intensive care, and other special applications where patients may be at risk of inadequate oxygenation or ventilation. There are numerous manufacturers of these devices. The instruments intended for clinical use are required by the US FDA and multiple other bodies to be tested per ISO 80601-2-61 over the range of SpO2 70-100%. The instruments are calibrated by design at the factory and generally do not need or permit recalibration.

This study protocol was started in 1986 to determine the performance of pulse oximeters and to help generate data to improve performance and safety. More than 3000 subjects have been studied, using more than 100 different manufacturers' devices. Because of continuing improvements in pulse oximeter design, continuing introduction of new products to the market, and ongoing challenges in performance, the testing is still needed to ensure and improve safety and performance of pulse oximeters.

Update history

October 24, 2024 - Updated sampling to more accurately describe practice of blood gas sample analysis
September 26, 2024 - Updated Section 4 to specify that all fingers on either hand, including in the presence of an arterial line, are used to test pulse oximeter performance. Also updated our timing for achieving plateau stability
June 10, 2024 - Removed methylene blue as an exclusion criteria
May 28, 2024 - Updated Step 1 of the protocol to include our recruitment practices (i.e. use of the UCSF Clinical and Translational Science Institute (CTSI) Participant Recruitment Program (PRP), TrialFacts as well as other general recruitment strategies). Other minor edits to the steps were made to reflect the current practices of the Hypoxia Lab in terms of arterial line insertion, blood sampling, assessing participants' vital signs, control of the gas mixtures, etc.
May 23, 2024 - Updated protocol for running arterial blood samples on ABL machines (see bullet point 8 of steps). Also, added the Nihon Kohden and Philips IntelliVue as reference devices.
May 17, 2024 - Added that we quantify skin color on areas of the skin free of any product, including sunscreen, makeup, etc.
April 3, 2024 - Added the **WHO Protocol ID:** ERC.0004026 to page 1
February 5, 2024 - Included that we record observed skin tone of subjects on the day that they complete the study.
January 29, 2024 - Updated step 4 to say that we record averaging time for reference devices and any changes to the settings. Also, specified the averaging time settings for the references in the materials section.
January 25, 2024 - Updated exclusion criteria with the methylene blue exclusion

Guidelines

This protocol was designed by the UCSF Hypoxia Lab and was the original model for the FDA and later ISO80601-2-61 requirements and standards for pulse oximetry performance. We continuously update this protocol with the intention of meeting and exceeding requirements by ISO 14155, ISO 80601-2-61 and FDA 510k as they evolve.

Before starting

Ensure IRB approval, consent, forms meet ISO15155 and are approved by IRB. Ensure safety protocols, trained personnel (anesthesia and/or critical care) and access to emergency resuscitation equipment are immediately present, checked and functioning. All equipment must be calibrated in accordance with manufacturers' specifications. This includes oxygen and CO2 gas analyzers as well as blood gas analyzers and of course emergency equipment. Ambient temperature, humidity and barometric pressure must be measured and accounted for.

Safety warnings

This protocol involves placing arterial catheters and administering hypoxic gas mixtures. This protocol should only be implemented by personnel with relevant experience and training, safety equipment and safety protocols.

Materials

1x Mass spectrophotometer CO2
1x Mass spectrophotometer O2
2-3x Hemoximeter(s) (ABL90, Radiometer - or equivalent)
22g arterial cannulas and associated transducers
Multimodal automated vitals sign monitor with alarms (BP, ECG, HR, RR, SpO2, ABP)
Reference pulse oximeters
    Nellcor PM1000N, set to default averaging time
    Masimo Radical-97 (x2), set to default averaging time
    Nihon Kohden, set to default averaging time
    Philips A01 Philips FAST SpO2 Module, set to default averaging time
National Instruments Labview software
National Instruments Labview digital to analog converters
Computer
Gas flow control system for nitrogen, air, oxygen and carbon dioxide
Heparinized 3mL syringes
Colorimeters/melaninometers/spectrophotometers

Study Design

1. Subject recruitment & diversity
    a. 10-14 healthy adult (18-50yo) volunteer paid participants are recruited to ensure adequate diversity and data sample size. This was the default for most studies up until 2022. Starting in 2022, we aimed to recruit at least 24 participants per study cohort and in some cases >100 depending on study design
    b. We typically recruit 10-20% more subjects than is required to power the study, to account for data loss due to participant drop out or data quality, among other factors.
    c. Participant data is recorded including baseline vital signs, weight, skin color and finger diameters
    d. Skin color
        i. Skin color assessment is performed by one or more clinical research coordinators and/or the study physician assigning for each subject a skin color category using two visual-analogue printed color scales - perceived Fitzpatrick Scale (pFP) and Monk Skin Tone (MST) Scale. The assessed portion of skin is cleaned of any product, including sunscreen, makeup, et cetera. When using the pFP or MST, the color scale next to the patient's skin (forehead, ear, nose, arm, and fingers). Skin color is also assessed by measuring color with a Konica Minolta 700d skin spectrophotometer that reports color in the LAB colorspace (and is used to calculate individual typology angle (ITA) - a surrogate for skin melanin content). The spectrophotometer is applied to the skin in a manner that uses minimal force to ensure circumferential contact. The device shines visible light onto a non-identifiable 3mm section of skin, and measures the color of reflected light. Skin color observed on the day of the study should be recorded for each new data entry. We aim to recruit ~30% of study participants per device tested in each of 3 bins of skin color defined by the Monk Skin Tone Scale (ABC, DEFG, HIJ). Given known limitations in subjective skin color scales, we will also objectively measure ITA and ensure 30% of participants have an ITA<-30, a previously established cutoff for dark skin pigment. We also aim to ensure half of subjects in the ‘dark pigment’ category have an ITA < -50. Both ITA and MST are done on the forehead and at the site of pulse oximeter placement. We collect data using skin melaninometry, colorimetry and spectrophotometry to quantify skin color on areas of the skin free of any product, including sunscreen, makeup, et cetera. Protocol updates are in progress to better define and recruit adequate diversity for this study protocol (See Skin Color Quantification Protocol separately).

e. We collaborate with the UCSF Clinical and Translational Science Institute (CTSI) Participant Recruitment Program (PRP) to ensure best practices. This includes optimizing study recruitment materials and strategies. Through the PRP, the study is being advertised via social media (Facebook ad posts, Craigslist, etc.) and through the electronic health record system at UCSF. We also utilize a specialized recruitment service vendor. For equity among interested participants, information is sent both electronically and through paper mail. Subjects new to the study will also be recruited via flyers posted on university campuses in the San Francisco Bay Area or emailed electronically to student based affinity groups. Some subjects may also be recruited via word of mouth from previous study subjects.
f. Inclusion criteria:
    i. The subject is aged ≥ 18 and < 50.
    ii. The subject is in good general health with no evidence of any medical problems.
    iii. The subject is fluent in both written and spoken English (we are actively working to expand access to this study to subjects who prefer other languages).
    iv. The subject has provided informed consent and is willing to comply with the study procedures.
g. Exclusion criteria:
    i. The subject has a BMI > 35.
    ii. The subject has a known history of heart disease, lung disease, kidney disease or liver disease.
    iii. Diagnosis of asthma, sleep apnea, or use of CPAP.
    iv. Subject has diabetes.
    v. Subject has a clotting disorder.
    vi. The subject a hemoglobinopathy or history of anemia, per subject report or the first blood sample, that in the opinion of the investigator, would make them unsuitable for study participation.
    vii. The subject has any other serious systemic illness.
    viii. The subject is a current smoker.
    ix. Any injury, deformity, or abnormality at the sensor sites that in the opinion of the investigators' would interfere with the sensors working correctly.
    x. The subject has a history of fainting or vasovagal response.
    xi. The subject has a history of sensitivity to local anesthesia.
    xii. The subject has a diagnosis of Raynaud's disease.
    xiii. The subject has unacceptable collateral circulation based on an exam by the investigator (Allen's test).
    xiv. The subject is pregnant, lactating or trying to get pregnant.

xv. The subject is unable or unwilling to provide informed consent, or is unable or unwilling to comply with study procedures.
xvi. The subject has any other condition, which in the opinion of the investigators' would make them unsuitable for the study.
xvii. Subjects are screened for COVID-19 before coming in for testing. Fully vaccinated subjects are recruited for this study. Subjects will be asked if they have any symptoms related to COVID-19 and if they have any symptoms or are sick they cannot participate and a temperature will be taken before the study.

2. Arterial catheter insertion
    a. After ensuring subjects do not have drug allergies, the study physician uses local anesthesia (1mL of 1% lidocaine injected subcutaneously via 25-gauge needle) and sterile technique, to place a 22-gauge catheter in one radial artery. An Allen's test and/or sonographic identification of patent ulnar and radial arteries are performed prior to catheter insertion in order to maximize safety.
3. Monitoring
    a. Oxygen saturation (SpO2), heart rate, blood pressure, respiratory rate and temperature are recorded at baseline. Heart rate, ECG, SpO2, blood pressure and respiratory rate are recorded throughout the study either at time intervals or continuously in accordance with ISO80601-2-61.
4. SpO2 probe placement site selection
    a. Probes are placed on sites selected by randomization or sponsor preference, with at least one device capable of measuring pulsatility amplitude (i.e., sometimes commonly referred to as perfusion index) on the same hand and/or adjacent digit. All fingers, including the thumb and pinky, are used to test the performance of pulse oximeters, and, in some cases, placement occurs on the same side as the arterial line. One or both of the lab's FDA 510(k)/CE reference oximeters are always used for all studies.
        i. After Fall 2022 UCSF Hypoxia Lab is using Nellcor PM1000N with the DS-100A1 Adult Reusable SpO2 Sensor and Masimo Radical-97 with the RD Set DCI Adult Reusable Sensor 3ft purchased in Fall 2022. Depending on study design, the Masimo Adult Reusable Ear Sensor or Nellcor Max-Fast Forehead Sensor may also be used.
        ii. Prior to Fall 2022 UCSF Hypoxia Lab reference pulse oximeters were Nellcor N-595 and Masimo Rad 7 non-color, non-touch screen.
    b. Adjacent finger pulse oximeter probes are optically isolated from each other using a custom isolation divider made of molded kydex and a modified Masimo disposable optical light shield (Image 1). Averaging time for devices is also recorded on the day of the study, if changes to the settings are made. In general, devices are kept on default averaging time settings, unless otherwise noted.

5. Patient positioning
    a. Subjects lie semi-supine and breathe through a mouthpiece while the nose is obstructed by a nose clip. A viral filter is placed in the breathing circuit to prevent cross contamination between subjects and/or study personnel. Subjects are instructed to increase minute ventilation during all runs, breathing at ~20 breaths per minute with 2-3 times deeper breaths than baseline to speed alveolar gas equilibration and provide frequent end tidal samples for analysis by mass spectrometry and computer calculation of saturation. 1-4% CO_2 is added to inspired air to prevent significant hypocapnia. A pneumotach is sometimes used to measure minute ventilation and respiratory rate. This flow sensor is used in accordance with its manufacturer approved labeling as a component of the breathing circuit.
    b. When pulse oximeters are tested on the extremities, those extremities are at or more commonly below the level of the phlebostatic axis. Depending on study objectives, if multiple devices are being tested on adjacent digits, then shielding may be placed between devices to prevent device-to-device visible and IR light contamination. Shielding from ambient laboratory lighting is not routinely done.
    c. By default we do not warm the hands or fingers of study participants. For devices tested as part of the OpenOximetry.org project, hand warming was not routinely performed unless the study was shared with a sponsoring manufacturer who requested warming be done. Warming was performed with a commercially available consumer grade heating pad placed under or around the hand.
6. Controlling hypoxemia
    a. (Figure - Desaturation Step Protocols) The study investigator (anesthesiologists and/or critical care physician MD) controls the delivered oxygen concentration by adjusting nitrogen, oxygen, carbon dioxide and room air flow meters via a custom breathing circuit setup to deliver a desired oxygen concentration. Gas concentrations are adjusted to achieve different steady state levels of hypoxemia from 70-100% (due to variability in subject physiology and device performance accuracy this may sometimes result in saturations in the 65-70% range). A computer program displays a breath by breath, calculated arterial oxygen saturation, (cSaO2) of the study subject. The cSaO2 is computed from end-expired PO2 and PCO2 as determined by mass spectrometer gas analysis (AEI Technologies, S3A - 0.01% accuracy, calibrated daily). This information permits the inspired gas mixture of air, plus CO2 and nitrogen, to be adjusted by an operator watching the value computed after each expiration on an analog meter (of note this cSaO2 is not used in place of measured SaO2 by hemoximetry). This computer-estimated saturation is adjusted by the operator to one of 6 levels of predicted saturation. The calculated oxygen saturation and gas flows are held constant, and SpO2 values are allowed to reach a steady plateau.

7. Plateau Stability
    a. The time period for stability is at least 60 seconds but typically 60-180 seconds prior to sampling at each plateau (of note, in patients with lower perfusion, the plateau may be held for longer ~120-240 seconds to ensure adequate SpO2 stabilization). The 6 target plateaus are achieved in two separate desaturation 'runs' as outlined in the supplementary figure. Each "run" lasts ~15 min. Plateaus are typically sought to be evenly distributed among the three SaO2 decades of 70% to 80%, 80% to 90% and 90% to 100%.
    b. A calculated saturation (ScO2) based on end tidal O2, end tidal CO2, assumed A-a gradient, and p50, is used in addition to SaO2 and SpO2 data from reference devices to estimate plateau stability in real time. Study investigator visually inspects ScO2 and reference device SpO2 curves in real time to ensure stable plateaus prior to and during sampling. A custom configuration of labview interprets ScO2 and SpO2 of reference devices in real time to calculate slope for the past 20 seconds and predict SpO2 change over the next 1 minute. A green light is displayed to indicate if predicted SpO2 change is < 2% *and* ScO2 change is < 2%. A red light is otherwise displayed. Generally, these indicators are used to determine sampling along with the discretion of the study investigator
    c. SaO2 from ABLs is also analyzed in real time in Labview, and a red indicator is displayed if SaO2 changes by more than 1.5% between samples, indicating instability
8. Blood sampling
    a. During controlled hypoxemia, up to 30 1.5-2 mL arterial blood samples from each subject (<70mL total) are obtained at different steady-state levels of hypoxemia from 70-100%. Prior to the study sample being drawn, a discard sample (~0.5 - 1mL) of ~2-3x the circuit dead space is drawn. Blood samples are withdrawn in <5 seconds into a 3mL heparinized syringe. Samples are visually inspected, air bubbles are expelled through a vented tip cap, and the syringe is gently mixed (by inverting and rolling). Syringes contain lyophilized balanced Li-heparin with a goal of 20IU/mL blood (liquid heparin may impact/dilute results including pO2). Samples are drawn after stability as measured by reference oximeter SpO2 (Nellcor PM1000N with DS-100A1 Adult Reusable SpO2 Sensor, Masimo Radical 97 with RD Set DCI Adult Reusable Sensor 3ft) and calculated saturation as outlined above. Blood samples obtained from the arterial line are immediately analyzed by co-oximetry (Radiometer ABL90 Flex Plus) to determine true functional saturation (SaO2) value. If sample is not run immediately (e.g., running the sample on a third ABL90 to confirm results) then it is gently mixed via vortex prior to analyzing. Readings from the test pulse oximeters are recorded and compared to these functional saturation (SaO2) "gold-standard" blood values. (Note: Some manufacturers and labs have been known to use

fractional saturation O2Hb instead of functional saturation for calibration). Up to three blood gas analyzer machines are used in parallel to confirm readings (ABL90 Flex plus, Radiometer). A single blood sample is initially run on two of the ABLs; if there is >0.5% difference in the SaO2 values, the sample is run a third time on an additional ABL it was not originally run on. Amongst the three, if two of the SaO2 values are not within 0.5% of each other, then that data point is excluded during data cleaning. If two SaO2 values are within 0.5% then the average of those two results are recorded as the sample's SaO2.

9. Return to baseline
    a. Inspired oxygen is abruptly changed when blood sampling is completed, either to a lower level or, at the final plateau of each run, to 100% oxygen. At the end of the study, the arterial line is removed and pressure is applied to the site for 10 minutes or until hemostasis. Vital signs are repeated at the end of each study. Subjects are monitored in the lab for at least 15 minutes after each study to ensure hemostasis and absence of symptoms.
    b. Coban wrap is applied to subject wrist and subjects are instructed to remove after an hour. Subjects are advised to avoid strenuous exercise or weight lifting for the rest of the day.
10. Carbon dioxide (CO_2) control
    a. For most pulse oximeter hypoxia studies, CO2 is delivered into the circuit by the investigator to maintain normal end tidal and arterial CO_2 to prevent symptomatic hypocapnia and promote regular respiratory pattern. For some studies, hyper- and hypocapnia are targeted and controlled as follows. To reduce PCO_2, subjects voluntarily hyperventilate during the test, to an end tidal PCO2 goal of 25 mmHg. The study doctor observes end-tidal PCO_2 values on a breath-by-breath basis using a CO2 gas analyzer (AEI Technologies, CD-3A and P61-B - calibrated daily, Accuracy: ± 0.02% CO2 0 – 7% CO2) and directs to the subjects breathing to achieve a PCO_2 of the desired level. For higher PCO_2 values, CO_2 is metered into the breathing circuit to increase end tidal PCO_2 by 10-15 mmHg from baseline. These interventions each last 6-8 minutes.
11. Pulsatility/Perfusion assessment
    a. By default we do not alter pulsatility or perfusion of participants. For some studies, peripheral vascular perfusion is modified by 1) elevation of the hand plus systemic hypotension with nitroprusside if needed; 2) clamp compression of the brachial artery (often avoided due to potential venous compression); 3) brachial cuff inflation (often avoided due to venous compression); 4) intraarterial norepinephrine or phenylephrine (NE); 5) cooling/warming the room or patient's extremity (with forced air cooler and liquid cooling systems) 6) by placing their hand in an ice bucket or controlled cooling device. Perfusion is measured using a Nellcor PM1000N pulsatility amplitude signal output, Masimo Radical-97

perfusion index, and a custom raw PPG device as ‘reference’ perfusion devices (expanded protocol on perfusion is coming soon). One reference device is placed on each hand so that pulsatility data are available for at least each hand. Prior to initiation of each study, perfusion dates are recorded with one reference device for all fingers on both hands. When testing study devices that do not measure perfusion, a reference device is placed on the same hand, and when possible on an adjacent finger to approximate perfusion for the study device digit. This technique has limitations that are currently being optimized.

12. Motion
    a. By default for most studies subjects are asked to remain as motionless as possible. For some studies, affixing the subject’s arm to a motion machine and rhythmically moving the arm in a repeatable and controlled manner during the study is used to evaluate impact of motion on performance (expanded protocol on motion is coming soon). Depending on study objectives, other methods may be used to induce or simulate motion, though this is not part of the standard protocol.
13. Data Recording & Cleaning
    a. Hemoximeter (SaO2) data from the ABLs, SpO2 data from reference oximeters, ECG waveform (Philips Intellivue MX 750), arterial line waveform (Philips Intellivue MX 750), RR (Philips Intellivue MX 750), EtO2 (AEI Technologies), S3A, EtCO2 (AEI Technologies, CD-3A and P61-B) are routed directly into custom configuration of Labview (National Instruments, Austin, Tx)
    b. Data are used to estimate calculated oxygen saturation (ScO2) (as described above) at 1hz
    c. SaO2 and SpO2 data from the reference devices (Nellcor PM1000N and Masimo Rad-97) are cleaned using an algorithm that checks for plateau stability. Data points are flagged if their difference from both the previous and next readings exceeds a predefined threshold. If the data point is the first or last in the session, the difference from the subsequent or preceding reading, respectively, will be checked. The threshold for flagging SaO2 data points is 1.5, while the threshold for SpO2 data from the references is 2. Any data point flagged for either SaO2 or SpO2 from Nellcor PM1000N will be excluded from the analysis and undergoes manual review.
    d. Finally, sessions will be flagged for review if they contain at least one data point from devices under test that meets any of the following criteria: 1) an absolute bias greater than 20, 2) a bias difference of ≥5 compared to both the previous and next samples, or 3) an SaO2 value of 80% or higher with an absolute bias greater than 10. Flagged sessions will be reviewed manually by the Principal Investigator, and data points will be excluded based on their

instructions. These criteria were determined after manual analysis of >600 sessions (>10,000 data points).

e. For some studies, sponsors may request to record the subject's face during the desaturation study. These recordings will be used to determine if blood oxygen saturation can be determined through facial recordings. These recordings will be kept by the sponsor for a period of 2 years after completion of the study. Timestamps will be used to correlate to the subject number.
f. For some studies, the protocol may video record the hands and/or wrists through the study period. This is to record data from pulse oximeters with displays on the wrist and hands (i.e. to record the data output directly from the display). This information would be kept by sponsors/investigators for the length of the IRB approved period. The subject faces would not be recorded at any point for this purpose. Timestamps from the video recording will be used to correlate video recordings to the subject number.

Device Calibration

1. Konica Minolta
    a. Device undergoes yearly factory calibration.
    b. Before data collection, the device is turned on and, when prompted, zero calibration is completed with the zero calibration cap/cylinder purchased from Konica Minolta. White calibration is then completed with the white calibration cap when prompted by software.
2. Radiometer ABL90 FLEX - completed the day before each study
    a. Test is completed to calculate machine's hemolyzer frequency and ensure ensure it is within acceptable range
    b. Calibration performed
    c. Iternal quality controls 1, 2 & 3 performed
    d. Ampule (external) quality controls 1, 2 & 3 performed
    e. tHb calibration performed
    f. If at any point calibrations or QCs do not pass, consumables are changed and/or a Radiometer representative is contacted to fix the issue. ABLs are only used once they pass all calibrations and QCs.

Image 1u

Study participant, UCSF Hypoxia Research Lab, finger shielding of adjacent devices with kydex plastic mold, lined with Masimo finger shield sleeves (Note: top left open for data recording; for handheld and tabletop devices, full circumference finger shields may be used).

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