Accuracy of pulse oximeters with profound hypoxia
Test protocol

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Aims
The aim of this project is to test the accuracy of pulse oximeters during mild, moderate and severe hypoxia; i.e. a range of arterial HbO_2 saturations from 100 to down to 70%. This is done by comparing the reading of the pulse oximeter during brief, steady state hypoxia with a gold-standard measurement of blood oxyhemoglobin saturation (arterial blood sample processed in a laboratory hemoximeter). The data obtained is submitted by pulse oximeter manufacturers to the FDA for device approval, or may be used for engineering or calibration purposes.

Subjects
A typical study will include at least 10 subjects (up to 14 if needed to reach the 200 necessary data points to meet the ISO 80601-2-61:2017).

Per FDA guidance, at least 2, or 15% of the subjects will have dark skin. Equal numbers of men and women will be enrolled.

Inclusion Criteria
1. The subject is male or female, aged ≥18 and <50.
2. The subject is in good general health with no evidence of any medical problems.
3. The subject is fluent in both written and spoken English.
4. The subject has provided informed consent and is willing to comply with the study procedures.

Exclusion criteria:
1. The subject is obese (BMI>30).
2. The subject has a known history of heart disease, lung disease, kidney or liver disease.
3. Diagnosis of asthma, sleep apnea, or use of CPAP.
4. Subject has diabetes.
5. Subject has a clotting disorder.

6. 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.
7. The subject has any other serious systemic illness.
8. The subject is a current smoker.
9. Any injury, deformity, or abnormality at the sensor sites that in the opinion of the investigators' would interfere with the sensors working correctly.
10. The subject has a history of fainting or vasovagal response.
11. The subject has a history of sensitivity to local anesthesia.
12. The subject has a diagnosis of Raynaud's disease.
13. The subject has unacceptable collateral circulation based on exam by the investigator (Allen's test).
14. The subject is pregnant, lactating or trying to get pregnant.
15. The subject is unable or unwilling to provide informed consent, or is unable or unwilling to comply with study procedures.
16. The subject has any other condition, which in the opinion of the investigators' would make them unsuitable for the study.

Procedures

After injection of a local anesthetic, a 22-gauge catheter is inserted in one radial artery. Pulse oximeters are attached to fingers, ears or flat body surfaces. Subjects are in a comfortable semi-recumbent position. Subjects then breathe air mixtures containing reduced amounts of oxygen to produce the desired level of hypoxemia. Stable, safe and controlled hypoxia is breath-by breath by breath respiratory gas analysis and a computer program that permits the inspired gas mixture to be adjusted to achieve a level of lung alveolar gas that will achieve the desired degree of saturation.

Typically, saturation levels involve one period with air breathing and then at one of 6 levels with reduced oxygen, e.g. 94%, 90%, 85%, 80%, 75% and 70% saturation. Each level of saturation is held for 30-60 seconds. At appropriate intervals and when oxygen levels are stable, arterial blood samples are obtained from the radial arterial catheter. The operator then changes the inspired oxygen concentration to attain the next desired stead-state level of hypoxia. A "run" consists of several stable steady-state hypoxia levels and together takes 10-15 minutes. Each run is terminated by a breath of 100% O_2 followed by room air. Two runs together enable obtaining a total of 20-25 blood samples, 2 samples at each plateau. Saturation of each arterial blood sample is determined by direct oximetry in a Radiometer ABL-90 multi-wavelength oximeter. The precise target levels of saturation can be adjusted to suit the sponsor, but typical testing is done to satisfy ISO and FDA standards for testing, which is 70% to 100%.

The study takes about 1 hour of each subject's time. Analysis of the data requires several days. We encourage manufacturer's representatives to be present for these tests, and to mount the probes. An extra charge is made if no representative is present, requiring us to mount the probes and record data.

Sponsor Pulse oximeter study data

Data from test pulse oximeters for comparison to blood values can be obtained in several ways. In every case, the goal is to obtain a reading from the oximeter that corresponds to the

associated blood sample or a reference oximeter. Because of circulation delays and instrument averaging time, we attempt to create steady state conditions at each level of oxygenation. Therefore, a means should be provided to record the instrument reading at each blood sample. This instrument reading may be obtained with several different approaches. Some instruments have no digital or analog output and the instrument reading may be recorded manually or recorded by a video of the instrument display. Other instruments may have an analog output. The laboratory can record analog data by use of LabView. Digital recording of output can also be obtained via LabView but his requires information from the sponsor concerning the structure of the digital signal. Consultation with us is recommended.

If a manufacturer prefers to collect and analyze the data, the continuous digital signal of each oximeter should be read, for comparison with the blood sample, 9 seconds before the record shows a sudden fall or rise in oxygen saturation, not at the time of blood sampling. This procedure accounts for the delays of finger circulation and uses the estimated delay from the lung to the sample site. There is no useful correlation between the actual time of blood sampling and the oximeter recording because of the variability of tissue blood flow lag. As mentioned, steady-state hypoxia avoids the concern that oximeter reading is not aligned with a blood sample reading.

Statistics

The number of subjects and the number of comparisons (paired pulse oximeter readings and arterial saturation values) is determined by current FDA guidance requirements [2]. This is a minimum of 200 data points and 10 subjects. In the course of this type of study, some subjects may drop out, some readings can be lost due to motion or other interference and occasionally some do not consent.

The following demographic data will be collected on the subjects:

- gender (male, female, other)
- age
- skin tone (dark, medium, light)
- height (cm)
- weight (kg)
- wrist circumference (cm)
- dominant hand (left or right)

Data Analysis

In all cases, the blood analysis data are provided, including the SaO2, MetHb, COHb and Hgb concentration.

The data analysis report will consist of the following:

- A Table of the oximeter readings versus corresponding blood SaO2 values.
- Graphic plots of the bias between the oximeter reading and the SaO2 measured by the hemoximeter (on the blood sample, i.e Modified Bland -Altman plots for each instrument or instrument probe combination.
- Regression equations for the bias of each instrument.
- Tables of the mean error or bias, its standard deviation, standard error, 95% confidence interval, maximum and minimum and root mean square error, all computed both overall and by several sub-ranges of desaturation.

- A table of the demographics of the subject population is provided.

Subject Safety

Pulse oximeters are typically considered non-significant risk medical devices. The LED light energy utilized in typical test measurements is within the same range as other cleared marketed devices and introduces no further risks. An LED light emits light that passes through the tissue. A light detector then measures how much light was absorbed by the tissue. Based on the ratio of absorbance of different wavelengths of light, the device calculates the oxygen saturation.

Risks

Breathing a very low oxygen mixture may cause dizziness and might cause loss of consciousness for a few seconds. It may make one feel very short of breath during the test and for a few seconds afterwards. There is a remote possibility that if the subject loses consciousness he/she might have muscular twitching or convulsions. This study will not seek to reach saturations below 70%. Hypoxia may cause tachycardia and increased blood pressure during the test, and might cause headache. In all the years of conducting the study no subject has mentioned headache. Much more severe and prolonged lack of oxygen could cause brain injury or death, but the duration and depth of hypoxia is limited by the test protocol to short intervals. The needle catheter used to take blood may hurt when it is inserted despite the use of local anesthesia, and there may be a black and blue spot afterward. It is remotely possible the artery might be damaged or clot, or a tendon sheath near it be injured by the needle, resulting in some soreness. These risks are unlikely because none of the enrolled 2000+ subjects has ever had a serious complication. Hyperventilating during the part of the study requiring reduced PCO2 may make subjects lightheaded or dizzy. Breathing air with added CO2 may make subjects feel short of breath and cause a headache. Some subjects feel faint when they arrive for the study, apparently related to the thought of having an arterial line. These subjects were excluded from the study and suffered no further discomfort.

Risk Mitigations

Subjects are all monitored with accurate reference oximeters and continuous end-tidal gas analysis to prevent the risk of more profound hypoxia than desired. Investigators are experienced anesthesiologists adept at assessing breathing and in maintaining appropriate airway conditions. The study room is set up like an OR with all resuscitation equipment immediately available.

Informed Consent

Written informed consent is obtained before any study interventions. In discussions with the study coordinator before the day of the study, potential subjects will be offered the consent form to review. On the day of the study subjects are given the consent form which they read and sign if they wish to participate. A study doctor is present to answer questions.

Only subjects clearly able to understand and read English will be enrolled. Subjects will be asked if they have any questions and are told they can withdraw at any time.

Data Storage

Identifiable subject information is always stored securely following all applicable rules and regulations. Consent forms and other study related documents are retained following UCSF data retentions policy.

Other testing

Special testing, with various conditions or with special subject populations can also be arranged, at extra charge.

We also offer testing for performance during controlled subject hand motion. Three types of motion are typically used: tapping, rubbing and random motion. Tapping and random motion are done with a computer-controlled motion machine.

Testing during low perfusion conditions is also available at an extra charge.