Accuracy of ScanWatch pulse oximeter with profound hypoxia

Ver.	Date	Changes
1	February 26, 2020	Initial Release
1.1	February 27, 2020	Added investigator, Changed terminology, Corrected math errors, Changed LOA calculation and updated plateau rejection criteria.
1.2	March 5, 2020	Corrected some typos

Principal Investigator

Phillip Bickler MD, PHD UCSF medical center San Francisco, Ca. USA

Additional Investigators

Koa Gudelunas, Clinical Research Coordinator, UCSF medical center San Francisco, Ca. USA, John Feiner MD, PHD UCSF medical center San Francisco, Ca. USA

Support Staff

Michael Bernstein, Physio Monitor San Ramon Ca. USA

Key Study Personnel

KSP name	Responsibilities	Qualifications
Phillip E Bickler MD, PHD	PI, Oversight of lab operations, Inspired gas control	20 + year direct involvement in this study. Attending Anesthesiologist, UCSF
John Feiner MD, PHD	Inspired gas control, Data analysis & report authorship	20 + year direct involvement in this study. Attending Anesthesiologist, UCSF
Mike Bernstein	Equipment accuracy & lab physical plant	25 years' experience in desaturation studies

Objective

This test is performed per ISO 80601-2-61:2017 [2] to determine if the test device oximeter meets the basic safety and essential performance requirements for a pulse oximeter. This protocol is designed as well to meet the additional recommendations of the FDA 2013 guidance [1] on pulse oximetry submissions. The report from this test is intended to support various applications and documentation requirements for FDA ISO and other regulatory bodies.

Institution

To be performed at The Hypoxia Lab, UCSF, San Francisco, California, USA

The Hypoxia Research Laboratory at UCSF laboratory has developed methods that permit the performance testing of pulse oximeters, enabling collection of data for submission to the FDA for device clearance or for engineering development of the devices. The basics of the protocol involve brief stable arterial oxygen desaturation in healthy volunteers and sampling arterial blood when a stable level of hypoxia has been attained. The blood sample is analyzed for oxygen saturation with a gold standard bench CO-oximeter, currently a Radiometer ABL-90. 6 to 8 subjects can be studied in a single day, with 20-25 arterial blood samples from each subject. This protocol is aligned with the latest ISO and FDA guidance documents for pulse oximeter testing [1, 2].

These studies are done with approval of the UCSF Committee on Human Research. Informed consent is obtained from each subject. The UCSF Hypoxia Laboratory conforms to Good Clinical Practice Standards for the involvement of human subjects and handling of test data.

Subjects

The 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.

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 has both wrist circumferences between 14 and 22cm.
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. The subject has piercings that may cause air leaks during the test
10. The subject has any injury, deformity, or abnormality at the sensor sites that in the opinion of the investigators' would interfere with the sensors working correctly.
11. The subject has a history of fainting or vasovagal response.
12. The subject has a history of sensitivity to local anesthesia.
13. The subject has a diagnosis of Raynaud's disease.
14. The subject has unacceptable collateral circulation based on exam by the investigator (Allen's test).
15. The subject is pregnant, lactating or trying to get pregnant.
16. The subject is unable or unwilling to provide informed consent, or is unable or unwilling to comply with study procedures.
17. The subject has a resting heartrate over 120, Systolic BP is over 150, diastolic BP is over 90 or room air SpO2 is less than 94%.
18. The subject has carboxyhemoglobin over 3% as measured by Lab blood gas analysis.
19. The subject has any other condition, which in the opinion of the investigators' would make them unsuitable to participate.

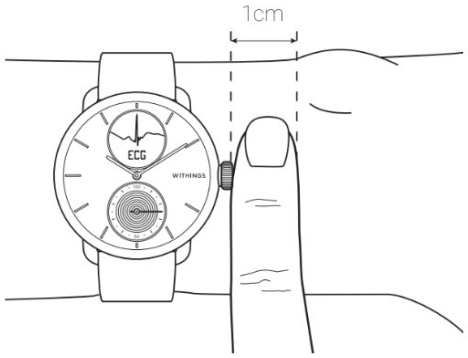
Device under test

The Withings ScanWatch utilizes the form factor of a wrist watch embedding a heart rate sensor and a reflective pulse oximeter sensor on its caseback. Its wristband and case materials are biocompatible. It is worn as a regular watch and

connects to a smartphone through the Withings HealthMate application. It's embedded firmware measures, displays, stores and transmits functional oxygen saturation of arterial haemoglobin (% SpO2) and pulse rate relying on a photoplethysmography (PPG) signal. It is intended for spot-checking of adult patients with wrists between 14 - 22cm circumferences. It can be used in sleep labs, long-term care, hospitals and home use.

Withings ScanWatch: front picture with numeric and analog display (left), and back case picture with PPG and SpO2 sensor (right)

As is typical of wrist watches, the device is applied approximately 1cm from 1 cm from the ulnar bone, although for this study they may be worn closer to the elbow for the arm that will have the arterial line.



Study Design

Study involves up to 14 qualified adult volunteer paid subjects, with 20-25 1-2 ml arterial blood samples from each subject obtained at different steady-state levels of hypoxia from 70-100%.

Blood samples obtained from an arterial line are measured in a CO-oximeter to determine true saturation value. Readings from the test pulse oximeters are recorded and compared to these "gold-standard" blood values. The level of hypoxia is measured and controlled by the investigator. A computer program that displays a prediction, breath by breath, the arterial oxygen saturation, (SaO2) of

the study subject. SaO2 is computed from end-expired Po2 and Pco2 as determined by gas analysis. 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. This computer-estimated saturation is adjusted by the operator to one level of predicted saturation, and is held stable for about 65 seconds at each level.

The key to obtaining stable, safe and controlled hypoxia is 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 hypoxia. An arterial blood sample is obtained from an indwelling catheter at the end of each hypoxic plateau. The operator changes the inspired oxygen concentration at the end of each blood sampling to attain the next desired steady-state conditions hypoxia. A "run" or series of desaturation plateaus takes 10-15 minutes, and each run is terminated by a breath of 100% O2 followed by room air. Two runs together enable obtaining a total of 20-25 blood samples, 2 samples at each different plateau. Saturation of each arterial blood sample is determined by direct oximetry in a Radiometer ABL-90 multi-wavelength CO-oximeter.

Primary Objectives

The aim of this clinical study is to test the accuracy of Withings ScanWatch during mild, moderate and severe hypoxias 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 CO-oximeter), according to ISO 80601-2-61:2017.

Procedure

Before a session, subjects are instructed not to move (especially their extremities), during the whole procedure. They are reminded to do so during the procedure if needed.

Two ScanWatches are positioned on the subject (one on each wrist, so as to maximize the number of points collected). The devices are applied and the band adjusted so that the reflective sensor has good contact with the skin”

Using local anesthesia, a 22 gauge catheter is inserted in one radial artery. Two additional reference finger pulse oximeters are also placed on each hand to identify more easily when there is a plateau or not, and possible discrepancies between the two hands.

Subjects lie semi-supine and breathe through a mouthpiece while the nose is obstructed by a nose clip. The subject rests for 5 minutes before any sample is taken, so the watch sensor can properly settle on the subject wrist.

Subjects are instructed to hyperventilate during all runs, both 2-3 times deeper and faster than normal to speed alveolar gas equilibration and provide frequent end tidal samples for analysis by the CO-oximeter and computer calculation of saturation. 2-4% CO2 is added to inspired air to prevent serious hypocapnia.

The target SpO2 at each run are chosen to be evenly balanced over the 70%-100% SpO2 range: 94%, 90%, 85%, 80%, 75% and 70%.

While the subject is breathing room air a 1.0 - 2.0 ml sample of blood is withdrawn over 5 sec into a 1.5 to 3 ml heparinized syringe. A second blood sample, at the same saturation, is taken 30 seconds later. 10 seconds or more after the sample inspired oxygen is abruptly changed to reduce saturation to the next target level.

When the saturation shown by the test and reference devices has been stable for 35 seconds, and the difference between the values displayed by the reference finger pulse oximeters is less than 1%, a blood sample is taken followed by another 30 seconds later (if the plateau has remained stable). 10 seconds or more after the second sample inspired oxygen is abruptly changed to reduce saturation to the next target level. This 75 seconds is defined as a plateau.

After the room air and 5 target value plateaus are complete the subject is brought up to high saturation with 100% O2. A plateau is completed at this level followed by 5 more per the desaturation targets. The subject is then brought up to high saturation with 100% O2.

All the samples SaO2 is immediately analyzed by direct oximetry in a Radiometer ABL90 multi-wavelength CO-oximeter. At the end of the study, the arterial line is removed and pressure is applied to the site for 10 minutes.

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 Set

Data from subjects who did not complete the protocol will be thrown out.

A plateau is defined as a 30 second period during which the test instrument output varies over a range of 2% saturation, or less. Data points for which no plateau can be found in the data will be excluded per the plateau criteria.

Data Points from Plateaus where the two CO-oximeter readings differed by more than 2 points will be excluded.

Data Analysis

Withings devices will provide two signals sampled at one hertz: SpO2 (labeled *spo2_window*) and a signal quality metric (labeled *spo2_error_window*, which is an estimation of the absolute error). SpO2 measurements will be considered inconclusive if the *spo2_error_window* is strictly higher than 3.5. In the normal use of the product, if the spo2_error_window calculated by the algorithm is higher than 3.5, the watch will indicate that the measurement is inconclusive instead of displaying a SpO2 value. Inconclusive measurements typically occur in the case of motion artefacts or very low perfusion. The data analysis of these signals will be handled by Withings. The data analysis of these signals will be handled by Withings. A copy of the recordings will be provided to the laboratory before Withings receives the reference data.
A time offset between the reference samples and the SpO2 signal provided by the device is expected for physiological reasons. To account for offsets, for each patient-watch pair, we will apply to the reference sample timestamps the time offset that yields the best fit between the device signals and the reference samples. This offset will be limited to +/- 20 seconds, since we expect the physiological offset to be within this range.
RMSE, bias, MAE (mean absolute error) and reject rate (the proportion of samples for which the device measurement was inconclusive) will be provided for the overall validation study, as well as for each patient individually. A correlation plot and a Bland-Altman plot will be provided and additional statistics required by the FDA guidance [2], including calculated limits of agreement (LOA) per the method of Bland Altman 2007.

Subject Safety

The device utilizes conventional reflective pulse oximeter sensor components embedded in the back case of a watch. The LED light energy utilized in the 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.

This study is therefore a “non-significant risk” device study, due to the nature of the devices being tested. The study devices:

- Is not intended as an implant which would thereby present potential for serious risk to the health, safety, or welfare of a subject,
- Is not purported or represented to be for use in supporting or sustaining human life which would thereby present potential for serious risk to the health, safety, or welfare of a subject;
- It is not used for use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health which would thereby present potential for serious risk to the health, safety, or welfare of a subject; and
- Does not otherwise present potential for serious risk to the health, safety, or welfare of a subject.

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. In 24 years of testing we have seen on no more than 3 occasions of twitching or convulsive movements, all lasting no more than 15 sec, and this has occurred only at saturations under 60% which are rarely sought. 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 PCO_2 may make subjects lightheaded or dizzy. Breathing air with added CO_2 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

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.

References

[1] Pulse Oximeters - Premarket Notification Submissions [510(k)s] Guidance for Industry and Food and Drug Administration Staff, March 4, 2013:
4.1. ACCURACY OF PULSE OXIMETERS
4.1.1 IN VIVO TESTING FOR SPO2 ACCURACY UNDER LABORATORY CONDITIONS

[2] ISO 80601-2-61:2017 Medical electrical equipment — Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment Annex EE.2 and clause 201.12.1.101.2
201.12.1.101 SpO2 accuracy of pulse oximeter equipment
201.12.1.101.2 Determination of SpO2 accuracy

[3] Severinghaus JW, Astrup PB. History of blood gas analysis. VI. Oximetry. J Clin Monit 1986;2:270-288

[4] Yelderman M, New W. Evaluation of Pulse Oximetry. Anesthesiology 1983; 59:349-352

[5] Kim SK, Baidan BS, Petty TL. Clinical evaluation of a new finger oximeter. Crit Care Med 1984;12:910-912

[6] ISO14155-1 Clinical investigation of medical devices for human subjects

[7] IEC 60601-1-11:2010 General requirements for basic safety and essential performance Medical electrical equipment

Signature Page

Phillip E Bickler MD PHD

Michael Bernstein