Protocol Title

Measurement of Oxygen Saturation in healthy human volunteers before, during and after hyperemic events using Multi-Modal Techniques: Spatial Frequency Domain Imaging (SFDI), transcutaneous oxygen measurement (TCOM), Pulse Oximeter, and Apple Watch.

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Background & Rationale

Pulse oximeters are commonly utilized medical devices used to measure blood oxygen saturation (SpO_2)[2]. These devices (such as the INNOVO Fingertip Pulse Oximeter) are either stand-alone or integrated into physiologic monitoring systems, using 2 wavelengths of lights to determine SpO_2. With recent advances in technology, Spatial Frequency Domain Imaging (SFDI) using range of light wavelengths from red to near infrared (NIR) such as in Clarifi$^{(R)}$ (Modulated Imaging, Inc., Irvine CA), smartphones such as Apple Watch (Apple Inc., Cupertino, CA), transcutaneous oximetry TCOM (Perimed Inc., Las Vegas, NV) now have pulse oximetry capabilities. Since it is possible that most patients could utilize this technology, we sought to assess the accuracy, reliability and usability of these oximeters and compare outcomes. In this study, a cohort of 20 healthy volunteers above the age of 18 including males and females of different skin colors will be assessed at the same site and data will be compared. We aim to provide a set of data that will support the clinical and scientific community and identify more than one reliable skin oxygen measurement modalities. The Innovo pulse oximeter device will be used for all subjects.

1.0 Objective(s)

1.1 Primary Objective
To investigate multiplatform for tissue oxygen measurement devices

1.2 Secondary Objective
To compare other modalities with FDA approved Pulse Oximetry

1.3 Tertiary/Exploratory/Correlative Objectives
To investigate skin color biasness in the optical Oximeters. Fitzpatrick's skin type chart will be used to evaluate skin type.

2.0 Outcome Measures/Endpoints

2.1 Primary Outcome Measures
Oxygen in tissue and blood measured non-invasively

2.2 Secondary Outcome Measures
Comparison of the devices provides the standard for clinical use

2.3 Tertiary/Exploratory/Correlative Outcome Measures
Melanin or scarred tissue oxygenation compared to normal skin

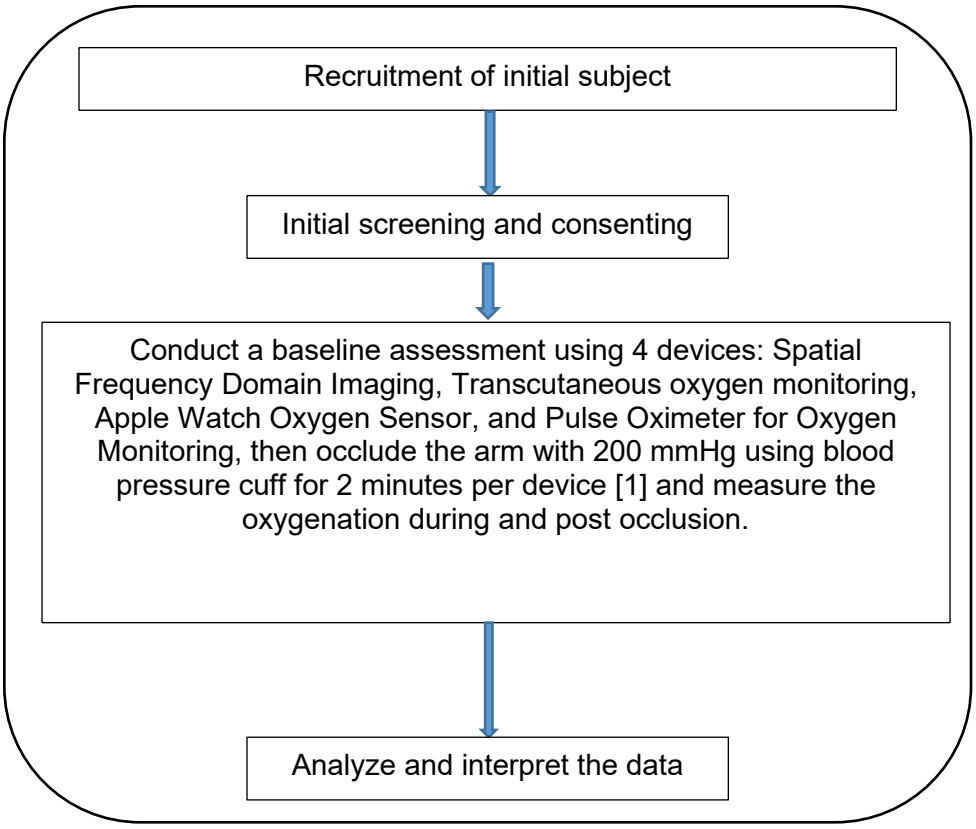
3.0 Eligibility Criteria

3.1 Inclusion Criteria
- Healthy volunteers
- Able to understand and complete the Informed Consent
- Both males and females
- Age between 18-65 years
- All ethnic backgrounds

3.2 Exclusion Criteria
- Patients or limited health conditions
- Under the age of 18 years or above the age of 65 years
- Smoking tobacco product
- Prisoners
- Cannot consent for themselves

- Pregnant individuals

4.0 Study Design



5.0 Enrollment/Randomization

Potential subjects will be identified from IU School of Medicine staff members. Each subject will use all four devices.

6.0 Study Procedures

First the subjects will go through a questionnaire session about their medical history by a designated study team member. The questionnaire data will be placed in RedCap using a subject ID that cannot be linked back to the subject. Then the subject will be consented. Subject will be enrolled. Then the non-invasive data collecting procedure will start on the following equipment:

Spatial Frequency Domain Imaging (SFDI): During consenting period, the Modulim equipment will be calibrated and setup ready for scanning. Subject's volar aspect of the thumb along with the palm surface

will be ready to target the optical camera head. Actual scanning takes less than 60 seconds. The images will be processed offline. During processing 3-5 different regions of interest (ROI) will be taken to measure the oxygen parameters such as tissue oxygen saturation (StO_2), oxy-hemoglobin (HbO_2), deoxy-hemoglobin (HbR), superficial hemoglobin (HbT1, sub-surface hemoglobin (HbT2). The model used is a Clarifi Modulum

Transcutaneous oxygen monitoring (TCOM): Transcutaneous oxygen monitoring (TCOM or $TcpO_2$) is a noninvasive, clinically-approved method to obtain skin oxygen levels. The method is quantitative, and measures oxygen delivery to the skin from underlying tissue. Before positioning the electrode, an adhesive fixation ring will be placed on the dry skin on the volar aspect of the thumb and an electrolyte as a contact liquid will be filled half and the probe is aligned into it by rotating clock-wise to fasten it. Recording will be started and waited for the oxygen level to stabilize and a fixed value will be recorded. The model used is a Perimed PeriFlux 5000. The probe will be heated to about 45^{o}C. Although this device has other options, only the measurement of O_2 will be performed using this device.

Apple Watch Oxygen Sensor: Smart watch blood oxygen sensors also measure blood oxygen level in the tissue. Apple Watch Series 6 introduced this new feature for monitoring blood oxygen level using light emitting diodes (LEDs) at the back of apple watches. A low blood oxygen level can be indicative of a serious health issue that needs immediate attention. The apple watch is equipped with green, red, and infrared LEDs that shine light onto the blood vessels in the wrist, with photodiodes measuring the amount of light reflected back. Apple's algorithms use this information to calculate the color of the blood, which is an indication of how much oxygen is in the blood. Bright red blood is well oxygenated, while darker blood has less oxygen. This can measure blood oxygen levels between 70 and 100 percent. Most healthy people have blood oxygen levels that range from 95 to 100 percent. The apple watch sensor will be positioned on the user's preferred wrist.

Pulse Oximeter for Oxygen Monitoring: The pulse oximeter enables transcutaneous monitoring of the oxygen saturation of hemoglobin in arterial blood (StO_2). Pulse oximetry is so widely prevalent in medical care that it is often regarded as a fifth vital sign[3]. It is important to understand how the technology functions as well as its limitations. To recognize the settings in which pulse oximeter readings of oxygen saturation (SpO_2), an understanding of two basic principles of pulse oximetry is required: (i) how oxyhemoglobin (HbO_2) is distinguished from deoxyhemoglobin (HbR) and (ii) how the SpO_2 is calculated only from the arterial compartment of blood. Pulse oximetry is based on the principle that HbO_2 and HbR differentially absorb red and near-infrared (IR) light. It is fortuitous that HbO_2 and HbR have significant differences in absorption at red and near-IR light because these two wavelengths penetrate tissues well whereas blue, green, yellow, and far-IR light are significantly absorbed by non-vascular tissues and water [3]. HbO_2 absorbs greater amounts of IR light and lower amounts of red light than does HbR; this is consistent with experience – well-oxygenated blood with its higher concentrations of HbO_2 appears bright red to the eye because it scatters more red light than does HbR. On the other hand, HHR absorb more red light and appears less red. Exploiting this difference in light absorption properties between HbO_2 and HbR, pulse oximeters emit two wavelengths of light, red at 660 nm and near-IR at 940 nm from a pair of small light-emitting diodes located in one arm of the finger probe. The light that is transmitted through the finger is then detected by a photodiode on the opposite arm of the probe. In this study, volar aspect of thumb and index finder of the subject will be used to measure SpO_2. The model is Innovo iP 900AP.

Sequence of the events during the study visit:

1) Consenting and enrolling the subjects
2) Medical questionnaire
3) Fitzpatrick's skin type assessment

4) Non-invasive imaging and data collection of the thumb and index fingers with the above devices in the following order:

   a) Baseline imaging and data collection

   b) Occlusion of the blood flow using pressure cuff at 200mmHg for 2 minutes and then collect the data during occlusion. There is a minimal risk of pain on the arm inflation of the pressure cuff up to 200mmHg. Please see literature (1) where they have used 240mmHg.

   c) Releasing the cuff and collecting the data during the hyperemic phase (post-deflation of the cuff).

7.0 Reportable Events

Since all measurement modalities are non-invasive, there are no adverse events anticipated or unanticipated problems involving risk to participants. The risk of the ring adhesive would be minimal as it could chafe the skin when removed.

8.0 Study Withdrawal/Discontinuation

Participant can withdraw/discontinue himself or herself from the study. Since the study involves only one visit the process of withdrawal is not effective. However, participants can withdraw the study in any time during the visit.

9.0 Statistical Considerations

Five sets of data will be collected from each of the devices and statistical mean and standard error of deviation from the mean will calculated.

10.0 Statistical Data Management

Primary data will be collected via direct data measurement and imaging, whichever applies to the devices. TCOM, Pulse oximeter and apple watch date will be recorded with pen & paper and entered on the spread sheet and stored electronically in REDCap. The storage location will be backed up manually for every subject and at the end of the subject visit. The quality control methods will be used single entry with random checks of accuracy.

11.0 Privacy/Confidentiality Issues

Regarding the method for ensuring participant privacy and for protecting privacy and confidentiality, each subject will be given a subject ID and only non-identifiable demographic data will be collected. Data will be stored on REDCap and access will be limited to designated personnel who processes the data.

12.0 Follow-up and Record Retention

The duration of the data collection will be 1-2 hours and the study will be within 6 months. The duration of record retention will be for 5 years and after that destruction or the possibility of indefinite archiving of information.

13.0 References

1. Jones, M.D., J.L. Taylor, and B.K. Barry, *Occlusion of blood flow attenuates exercise-induced hypoalgesia in the occluded limb of healthy adults.* J Appl Physiol (1985), 2017. **122**(5): p. 1284-1291.
2. Nitzan, M., A. Romem, and R. Koppel, *Pulse oximetry: fundamentals and technology update.* Med Devices (Auckl), 2014. **7**: p. 231-9.
3. Chan, E.D., M.M. Chan, and M.M. Chan, *Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations.* Respir Med, 2013. **107**(6): p. 789-99.