Official Title: Alternate Methodology of Pulse Oximeter Validation

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Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

Primary Objectives:

1. Compare the RespirAct-derived end-tidal P_AO_2 values with co-oximeter measured arterial P_aO_2 values.
2. Compare the accuracy (A_{RMS}) of FDA-approved pulse oximeter when calculated with RespirAct-derived end-tidal P_AO_2 values and with co-oximeter measured arterial P_aO_2 values.

Secondary Objectives:

1. Compare the pulse oximeter A_{RMS} when a step-wise desaturation sequence is used against a slope desaturation sequence.
2. Determine if the level of P_aCO_2 (hypocapnia versus normocapnia) has an effect upon the pulse oximeter A_{RMS}.
3. Determine if the OMT signal is altered during controlled oxygen desaturation sequences.

Hypothesis: end-tidal P_AO_2 values are the equivalent of arterial P_aO_2 values when used to calculate pulse oximeter accuracy in healthy volunteers.

Background & Significance

- Should support the scientific aims of the research

The oxygen cascade describes the oxygen concentration (often referred to as partial pressure, P) gradient that exists between ambient air and the cell. The figure depicts important waypoints such as alveolar and arterial oxygen partial pressures as well as factors that contribute to those values.

Fig 1: Components of the Oxygen Cascade

A key junction point within the cascade is the alveolar oxygen tension within the distal airways of the lungs (P_AO_2). In healthy adults the P_AO_2 closely approximates to arterial blood oxygen partial pressure (P_aO_2), usually within 1 – 2 mmHg, such that $P_AO_2 \approx P_aO_2$. Based upon the oxygen dissociation curve (ODC) shown in the figure below, the oxygen partial pressure (*x*-axis) determines the arterial oxygen saturation (S_aO_2). In the example shown below at room air the P_aO_2 of 100 mmHg will produce a S_aO_2 of 98%. If the P_aO_2 is subsequently dropped to 37 mmHg then the resultant P_aO_2 will be 70%. Of particular note, the co-oximeter ('blood gas machine') measures P_aO_2 and then uses the ODC to calculate the S_aO_2, the significance being that S_aO_2 is not measured directly.

Fig 2: Oxygen Dissocation Curve (OCD)

The pulse oximeter oxygen saturation (S_pO_2) is a non-invasive (light-based) estimate of the S_aO_2. The accuracy of the pulse oximeter is determined during a validation study in which the S_pO_2 values are compared to S_aO_2 values. The unit of measure of accuracy is called A_{RMS} and is a composite value of bias and precision.

The University of Florida has provided a **Simplified Alveolar Gas Equation** webpa ge which demonstrates the effect of various factors upon the resultant S_pO_2.

The FDA published the Guidance for Industry and FDA Staff - Pulse Oximeters - Premarket Notification Submissions [510(k)s][1]. This document provides guidance for manufacturers in the preparation of a premarket notification submission. In particular, there is a specific recommendation (Section 4.1.1) on how pulse oximeter and blood gas data from healthy volunteers should be obtained with progressive, controlled desaturation from 100 to 70% – referenced to the publication ISO 80601-2-61:2017 Annex EE.2 *Procedure for invasive laboratory testing on healthy volunteers*[2].

Annex EE.2 describes the conditions required to conduct a controlled desaturation study with reference to the following points:
1. The profile (depicted in figure EE.1) is a series of plateaus at which a variable number of blood gas samples are drawn once steady state conditions attained.
2. The saturation intervals are typically 5 – 10%, creating approximately 5 – 6 plateaus between 70 – 100%.
3. Maximum time at any plateau should not exceed 10 minutes.

Annex EE.3 provides guidance for procedures to conduct non-invasive lab testing in healthy subjects as an alternative to Annex EE.2. In particular, subsection EE.3.d states that other desaturation profiles are possible e.g. gradual desaturation.

Controlled desaturation studies are conducted by changing the S_aO_2. The most basic way to achieve this is through the use of a simple gas blender (**ROBD** [Reduced Oxygen Breathing Device]), which reduces the F_iO_2. The subsequent changes in the oxygen cascade components will eventually result in a lower S_aO_2, frequently taking several minutes to attain a steady state prior to blood gas sampling. There is inter-subject variability i.e. for a given F_iO_2 the S_aO_2 will vary between subjects, related to differences in respiratory ventilation (alveolar ventilation in oxygen cascade figure).

An alternative is the sequential gas delivery system, Thornhill **RespirAct**.This system is based upon control of both end-tidal P_AO_2 and P_ACO_2 values and accounts for the subjects' respiratory ventilation. Under these circumstances the $P_AO_2 \approx P_aO_2$. As noted above, it is the P_aO_2 value that determines the S_aO_2. If the RespirAct-derived P_AO_2 and P_ACO_2 values can be entered into the Alveolar Air Equation to calculate the S_aO_2, then this would eliminate the need for arterial blood gas draws in pulse oximeter validation studies.

Fig 3: Example of RespirAct desaturation sequence showing end-tidal P_AO_2 (green) & P_ACO_2 (blue) values.

Fig 4: Example of RespirAct breath-by-breath end-tidal P_AO_2 values during step changes.

The latest version of the RespirAct, RA-MR, can be programmed to deliver a slope sequence in addition to the standard step (plateau) sequence. The Human Pharmacology & Physiology Lab (HPPL) has successfully completed over 350 controlled desaturation runs in healthy volunteers using earlier versions of RespirAct (IRB#00006285, 00032913, 00031041, 00018006, 00002400, 00005710, 00047658, 00057677). From clinical experience, the PI has noted that subjects tolerate the reduction in $P_AO_2$far better if this is conducted in a series of minor steps than in a single step i.e. from 50 to 40 mmHg via intermediate steps of 47 and 44 mmHg. It is anticipated that subjects would tolerate a slope sequence better than a step sequence. The incline of the slope would still provide sufficient steady state conditions on a minute-by-minute basis to allow blood gas sampling.

Hypoxic ventilatory response (HVR) is the physiological increase in respiratory ventilation during hypoxia. HVR exhibits considerable inter-subject variability. This is manifested by different P_ACO_2 values. The normal range is 35 – 45 mmHg (normocapnia) on room air. During hypoxia P_ACO_2 values will be lowered to 20 – 30 mmHg (hypocapnia) as P_ACO_2 is inversely proportional to respiratory ventilation. The significance of P_ACO_2 is that it is a component of the Alveolar Air Equation. For a given P_AO_2 value (e.g. 50 mmHg) the S_pO_2 value will vary according to P_ACO_2 valu e (S_pO_2 85% at P_ACO_2 40 mmHg versus S_pO_2 93% at P_ACO_2 25 mmHg). ISO 80601-2-61:2011 Annex EE.2 *Procedure for invasive laboratory testing on healthy volunteers* does not provide specific instructions for the control of P_ACO_2 during desaturation sequences, yet the impact of variable P_ACO_2 upon pulse oximeter accuracy is unknown.

Design & Procedures

- Describe the study, providing detail regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue /specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

The study will be a prospective, single-center, non-blinded clinical study. The design of the study will be conducted in accordance with the recommendations of ISO 80601-2-61:2011 Annex EE.2 *Procedure for invasive laboratory testing on*

healthy volunteers. The primary study data will be the analysis of serial blood gas samples taken from a peripheral arterial catheter compared to the FDA-approved pulse oximeter S_pO_2 values.

The study will consist of five controlled desaturation runs with S_aO_2 reduced from 100 to 70% followed by a return to 100%:

- Run #1: RespirAct step [normocapnia]
- Run #2: RespirAct slope [normocapnia]
- Run #3: RespirAct step [hypocapnia]
- Run #4: RespirAct slope [hypocapnia]
- Run #5: ROBD step

Fig 5: Diagrammatic representation of Desaturation Profile from S_pO_2 100 to 70% in decremental steps.

Runs #1 & 2 will be conducted with P_ACO_2 maintained at subject's baseline value (normocapnia); runs #3 & 4 conducted at 10 mmHg below subject's baseline value (hypocapnia). Run #5 will be conducted without formal P_ACO_2 control.

Within each run the S_pO_2 range 100 - 70% will be subdivided into six sections, each ~ 5% coverage, i.e. 70 – 74%, 75 – 79%, 80 – 84%, 85 – 89%, 90 – 94% and 95 – 100%. In each section a total of up to 8 ABG samples will be drawn. A sub-total of 48 ABGs will be drawn per run and a grand total of 240 samples will be drawn per study. The samples will be analyzed by a co-oximeter to measure the P_aO_2 and

S_aO_2. It is anticipated to screen approximately 20 subjects in order to reach an evaluable 10 subjects to yield sufficient data for analysis. This is in accordance with ISO 80601-2-61 Annex EE.2.3.4.f, which provides an example of *"about 20 samples acquired from each of at least 10 subjects, resulting in at least 200 data pairs. Specific numbers of samples and subjects can vary."*

Specific to the safe conduct of the study the following points are noted:

1. The PI is an Attending Anesthesiologist who will be controlling the RespirAct & ROBD gas delivery system. The RespirAct end-tidal P_AO_2 and P_ACO_2 valuesare continuously displayed. The ROBD inspired oxygen value is continuously displayed.
2. The PI maintains continuous verbal contact with the subject throughout the runs 1 – 5.
3. The clinical monitoring of the subject includes ECG, two FDA-approved pulse oximeters and continuous non-invasive blood pressure (Nexfin). The Nexfin provides a plethysmograph waveform that is very similar to the arterial pressure waveform from an indwelling arterial catheter. This provides the systolic & diastolic blood pressure on a beat-to-beat basis (in comparison to an intermittent standard blood pressure cuff set at 1 or 3 min interval). In addition, specific parameters are derived such as cardiac output, stroke volume of each heart beat and systemic vascular resistance. The array of data available during the conduct of this study is in excess of what the standard clinical monitoring would be in an operating room for an elective surgical procedure, such as knee arthroscopy. In order to ensure that all of the available data is to seen, the monitors are integrated such that the parameters are displayed on a large monitor immediately above the study subject that can be viewed by all staff within the room.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Up to a total of thirty (30) individuals will attend a screening visit at which inclusion /exclusion criteria will be established by the completion of medical history, physical exam, lab tests & screening procedures conducted by the Principal Investigator or medically qualified/licensed person if delegated by the PI.

Inclusion Criteria:
1. Aged 18 – 50 years (verified by official document)
2. Subject is willing to provide written informed consent and is able to comply with anticipated study procedures.

Exclusion Criteria:
1. Body Mass Index (BMI) < 18.0 or > 30.0 [calculated from measured height & weight]
2. Known significant respiratory, cardiovascular or medical condition that precludes study participation as judged by PI [self-reported and/or review of health records when available]
3. Anemia [hemoglobin value below lower range of normal for gender]
4. Abnormal hemoglobin electrophoresis result [laboratory result]
5. Exposure to nicotine [positive POC test at screening or study day]

6. Abnormal drug screen [positive POC test at screening or on day of study]
7. Positive pregnancy test for females [serum test at screening; urine POC test on study day]
8. Abnormal Allen's test for collateral circulation [physical exam at screening]
9. Abnormal EKG [screening day; reviewed by PI]
10. Abnormal Pulmonary Function Test (PFT) [screening day; reviewed by PI]
11. Abnormal venous blood gas result [screening day; methemoglobin > 2% or carboxyhemoglobin > 3%; reviewed by PI]
12. Intolerance of facemask [screening day; ROBD mild hypoxia exposure]

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

Potential subjects will be recruited by advertisements placed on DukeHealth.org and DEPRU websites and on noticeboards around the university campus. Within the advertisement the potential subject will obtain a QR code which will take them to a dedicated REDCap study survey website. At the website there is a short introduction describing the capabilities of the HPPL and a quick summary of the planned study. Also available is a PDF link to the informed consent form (ICF) so that they can read the ICF at their leisure. They then answer a screening survey consisting of a series of straight-forward questions based upon most of the inclusion and exclusion criteria, which they submit to the website. A member of the research team will review the submitted screening survey form to determine if the subject is eligible for the screening visit. Subjects who are eligible will be scheduled for a screening visit. All demographic groups represented by race and ethnicities are eligible to participate.

Subjects will receive a total of $400 after completion of the study. If, for any reason, the subject does not complete the study, the subject will be paid $25 for attending the screening visit and a further $75 for the insertion of the arterial catheter, if that has occurred. It is anticipated that 4 hours will be needed to complete the study: screening 1 hr & study day 3 hrs.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

All subjects will be healthy volunteers with capacity to give consent. Subjects will be excluded if they do not possess the capacity to give consent. No legally authorized representatives will be used.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

The study will be conducted in healthy volunteers only. The study consists of 3 phases: Screening, Study Day & Follow Up. The associated activities of each phase will be completed as follows:

Screening: The informed consent form (ICF) will be completed prior to any study investigations. The subjects will have blood & urine tests, EKG & spirometry (in accordance with establishing inclusion/exclusion criteria listed in Design & Produres Section). A medical history and physical exam will be completed. Female subjects will have serum pregnancy test performed. If sexually active, subjects must agree to use appropriate contraceptive measures from the time of the screening visit until after the study visit. Medically acceptable contraceptives include: (1) surgical sterilization (such as tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If a subject may become pregnant during this study or if they have unprotected sex, the subject is instructed to inform study physician immediately. If the subject meets the inclusion criteria, then (s)he will remain eligible for 45 days.

Study Day: The subject will complete enrollment on the day of the scheduled study by confirmation of negative results to urine drug screen and oral ethanol tests. Females will also have a urine pregnancy test performed. Specific interventions are arterial catheter placement and progressive controlled oxygen desaturations.

Follow Up: A follow up phone call will be made by the Clinical Research Coordinator to the subject within 48 hours of completing the study visit.

Blood draws: multiple samples will be taken from study participants at both the Screening Visit & Study Day. The estimated amount of blood drawn over the course of the study is calculated as maximum of 270 mL as follows: 30 mL (CBC, electrophoresis, serum pregnancy & venous blood gas) at screening & 240 mL (0.5 – 1.0 mL per arterial blood gas sample x 240 samples) on study day. In order to reduce waste of additional blood loss during blood gas sampling the kit used to draw the samples will be the **VAMP** [Venous Arterial Management Protection] closed blood sampling system. The Radiometer **ABL90** co-oximeter can process a sample with 0.1 mL of blood. It is intended that a maximum of 1 mL of blood is taken with each sample to permit the analysis in duplicate (each sample is analyzed by two different co-oximeters).

ROBD [Reduced Oxygen Breathing Device] is a commercially available gas delivery system used in simulator training of pilots to in order to experience the effects of hypoxia (24,000 ft). At screening study participants will have a facemask attached and will breathe a gas mixture that will be the equivalent of ascending to an altitude of 8,000 ft. To put this into context the cabin pressure in commercial aircraft is reduced from one atmosphere (sea level) to the ambient pressure experienced at 8,000 ft. The S_pO_2 typically drops to 92%. The purpose of this

activity at screening is to let participants experience breathing gas mixtures through a facemask and to identify which subjects may be intolerant of the breathing mask. On the study day the subjects will breath a gas mixture of oxygen and nitrogen with the F_iO_2 reduced in decremental steps to attain the target S_pO_2. The screen of the ROBD continuously displays the selected F_iO_2. There is an immediate override button that will immediately deliver 100% $O_2$when activated.

The Thornhill **RespirAct** RA-MR gas control system will be used to control the inspired oxygen and carbon dioxide tensions. It provides real-time end-tidal tidal O_2 & CO_2 values (see figs 3 & 4) and has multiple safety features incorporated in order to prevent very low inspired oxygen (see eIRB Section 9 RespirAct Manual).

The OMT device consists of a small, lightweight adhesive strip that is placed on the skin of the upper eyelid and then attached to a single ECG lead placed on the side of the face. The signal is then transferred to a monitor for data collection.

Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

Risks and discomforts will be minimized through careful monitoring of the tests and procedures performed during this study to maximize safety and minimize the risks to the subject[3]. All tests and procedures will be performed bya medically qualified /licensed person if not done by the PI.

Controlled desaturation sequences will be induced by decreasing the inspired oxygen. Published studies, conducted under similar conditions to those defined for this study, demonstrate that healthy subjects tolerate mild hypoxia well and without untoward effects[4]. This study employs methods as recommended by the FDA for testing pulse oximeters in healthy volunteers[1]. Arterial line placement is considered an acceptable technique in healthy volunteers[5].

This study is performed in healthy volunteers and there is no direct medical benefit to the study participants.

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There will be no cost to the subject for participation in the study.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included

for analysis. Include planned sample size justification. Provide estimated time to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

The document, ISO 80601-1-2-61:2017 Annex CC *Determination of Accuracy, CC. 2.6 Accuracy*, provides details of the methods, A_{RMS} and Bland-Altman, to determine accuracy. In Annex EE.2.3.4 *Data Analysis* it specifies that the paired S_pO_2 & S_aO_2 data are to be pooled for all subjects and that the A_{RMS} be calculated. The number of data points should be at least 200 data pairs from at least 10 subjects. Any unpaired data (either S_pO_2 or S_aO_2 data point missing) will be excluded from the pooled data.

For this study the A_{RMS} will be calculated using the traditional paired data (derived from S_pO_2 & S_aO_2 where latter is calculated directly by co-oximeter from P_aO_2) and compared with A_{RMS} calculated using the novel paired data (derived from S_pO_2 & novel S_aO_2 calculated from P_AO_2 using Alveolar Air Equation). The FDA have set a limit of $A_{RMS} < 3\%$ as accepatble threshold for 510k approval.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

For this study, reportable events are limited to adverse device effects, procedure-related adverse events (AE), and unanticipated adverse device effects (UADEs). Standard of care will be implemented whenever an AE occurs to treat and/or resolve the AE and to monitor the subject. Reportable events will be documented on an Adverse Event CRF and will be collected from the time of enrollment through the time of follow-up or through resolution of all procedure- and device-related SAEs and UADEs, whichever is later. Report details will include a description of the event, event classification, treatment, outcome, and relatedness to the device and procedure.

The PI (Dr. MacLeod) will be present for each study. Dr. MacLeod has successfully completed similar desaturation studies in approximately 350 subjects. The PI will perform all cannulations of the radial artery using ultrasound guidance. The insertion of a radial artery catheter is a low-risk procedure when performed by experienced personnel and are widely used for patient monitoring in a variety of clinical settings.

Adverse events related to desaturation are most likely to present on the study day when the subject is present within the research lab. Any further adverse events are most likely to be related to arterial placement and will be reported by the subject when contacted by email and/or telephone within 48 hours of the study day to complete the follow up survey. The subjects will be given contact phone numbers for both the PI and CRC.

A Clinical Summary Report (CSR) will be completed by the PI at the end of the study. Any clinical concerns about the subjects in the study will be referred to Dr. Richard Moon who has dual appointments at Duke as both Professor of

Anesthesiology and Professor of Medicine. He is the Medical Director of the Hyperbaric Center at Duke and has published extensively on his work with high altitude (hypobaric hypoxia) in human volunteers.