Calibration and Validation of High Quality Low-Cost 3D Printed Pulse Oximeter

Investigators

Tarek Loubani, MD. (PI) Department of Emergency Medicine, London Health Sciences Centre, Western University

Student Investigator

Alexander Pavlosky. Schulich School of Medicine and Dentistry, Western University

Background

Pulse oximetry is a vital tool in the rapid and non-invasive assessment of emergency patients, providing a continuous estimate of hemoglobin saturation in arterial blood. Some pulse oximeters are even capable of monitoring carboxyhemoglobin and methemoglobin, though these capabilities dramatically increase costs. Unfortunately, the costs of both the simplified and extended devices are prohibitive and reduce availability in smaller centres and poor countries, putting millions of patients in danger of easily treatable and preventable conditions. The technologies involved in the manufacture of a pulse oximeter are widely known and have no active patents covering them. This includes carboxy- and met-hemoglobin monitoring. Despite this, no high quality device exists whose design and construction are both research-validated and open to the public for study, production and dissemination. With current rapid prototyping technologies such as 3D printing, it is possible to create a very inexpensive pulse oximeter that meets or exceeds the gold standard. Design considerations include: cost, availability of parts, ease of construction, quality, ease of maintenance, ease of use. Preliminary engineering work has been carried out for the pulse oximeter, with design specifications set and a prototype built. The prototype was the result of collaboration between an engineer and an emergency physician with extensive local and international emergency experience. The pulse oximeter device emits light in four wavelengths: 590nm, 610nm, 660nm, 940nm. These allow for the calculation of oxygenated hemoglobin (660nm and 940nm), carboxyhemoglobin (610nm) and methemoglobin (590nm). The current bill of materials for the prototype is included in Appendix A. A printed circuit board of the prototype is included in Appendix B. A photograph of a completed prototype is included in Appendix C. Software must be designed and written to translate the pulse oximeter's sensor signals into usable values, display them, and provide appropriate alarms when necessary. As per widely-understood and validated concepts, an R value is calculated (ratio of emitted to absorbed light). This value is compared to a look-up table created during an empirical calibration phase, which assigns R values to oxygen saturation values. The value is then displayed for the user along with a graphical display of the pulsatile wave to ensure the quality of the signal. An appropriate user interface must accompany this software to allow for the safe setting of limits and alarms. The goal of this two phase study is to develop, validate and certify a pulse oximeter that measures hemoglobin, carboxyhemoglobin and methemoglobin. Phase 1 consists of

calibrating the experimental pulse oximeter and Phase 2 consists of validating it. This pulse oximeter will be certified with Health Canada, and then released under the Open Hardware License (OHL), such that hospitals and ministries of health in rural and impoverished communities in Canada and internationally would have easy access to these devices.

Objectives

The purpose of this 2-Phase study is to calibrate a prototype pulse oximeter and to conduct an equivalence test to determine if the prototype is equivalent to the gold standard pulse oximeter. The primary objectives are

1) to compare arterial blood sample oxygen saturation measurements to the device's R value to create an empirical calibration curve as per the FDA document "Pulse Oximeters - Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff", section 4.1.1 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm341718.htm#s4);

2) to determine if the experimental pulse oximeter measurements correspond with the gold-standard pulse oximeter measurements; and 3) to determine if the prototype pulse oximeter is equivalent to the gold standard pulse oximeter.

Protocol

This clinical ~~randomized controlled~~ trial consists of 2 Phases. Phase 1 will include 50 healthy, non-smoking adults (greater than 18 years of age) to calibrate the experimental, 3D printed pulse oximiter. Participants will be recruited through e-mail advertisements and posters between June 1 ~~May~~ – August 2018. Subjects will participate in both the experimental arm and the control arm as both oximeters will be used to simultaneously generate data during the desaturation study (see Test Protocol). ~~2016.~~ In Phase 2 we will conduct an equivalence study with 350 adult (greater than 18 years of age) emergency department (ED) patients and community volunteers visiting either Victoria or University Hospital at London Health Sciences Centre (LHSC). Investigators will approach patients at the invitation of a member in the circle of care to discuss the study. Recruitment will occur between June 1 and August 30, 2018~~October 2016 and January 2017~~. After going through the LOI and gaining documented written consent, the patient will be enrolled. All study procedures will be conducted in the ED (Victoria and University Hospital) at LHSC by the PI.

Test Protocol

All study procedures will be conducted in the emergency department (VH and UH) at LHSC with an emergency-trained physician (EP) present at all times (PI) between June 1, 2018 and December 31, 2019~~May 2016 and January 2017~~. Phase 1 (Calibration; approximately 50 participants; Sept 1, 2018 – April 30, 2019): Upon obtaining informed consent, participants will be positioned supine in a hospital bed. Participants will be cannulated with an indwelling arterial catheter for frequent sampling of arterial blood. The experimental pulse oximeter will be placed

on the participant's finger and continuously monitored. A gold-standard pulse oximeter (GE Carescape B850 Patient Monitor; license 119340) will be placed on a separate finger on the participant's same hand and continuously monitored as per the institution's procedural sedation protocols. Participant samples will be tested with a CO-oximeter to ensure that background carboxyhemoglobin (COHb) is less than 2%. Two blood samples will be taken with the participant on room air. The participant will then be fitted with 100% oxygen by non-rebreather mask. Under careful monitoring by the EP, oxygen saturation level will be decreased with gas mixtures of progressively decreasing oxygen and increasing nitrogen. Measurements will be recorded until the participant has unstable vitals (e.g., hypotension, tachycardia), is symptomatic or a pulse saturation of 70% is achieved. Oxygen levels will be immediately restored. Arterial blood samples will be drawn and oxygen saturation will be measured when the gas mixture and R value readings have stabilized. 2 cubic centimetres of blood will be drawn for every 5% drop in blood oxygen saturation from 100% to 70% or earlier if the participant experiences unstable vitals or is symptomatic (Table 1). Phase 1 of the study will take approximately 60 minutes to complete.

Step	Target SpO2	PetCO2	Target PetO2	G1 flow
1	95-99	40	90	35
2	95-99	40	59	35
3	90-94	40	50	35
4	85-89	40	44	35
5	80-84	40	40	35
6	75-79	40	37	35
7	95-99	40	100	35
8	100	40	500	35

Table 1: Respiract desaturation protocol

This study design is routine for all pulse oximeters, and is as recommended by the FDA guidance document “Pulse Oximeters - Premarket Notification Submissions [510(k)s]: Guidance for Industry and Food and Drug Administration Staff”, section 4.1.1 (http://www.fda.gov/RegulatoryInformation/Guidances/ucm341718.htm#s4) Phase 2 (validation; approximately 350 community volunteers and ED patients): Study volunteers from the community or patients who have attended the ED for care are eligible to participate. Investigators will approach patients at the invitation of a member in the circle of care to discuss the study. Recruitment will occur between May 1 and December 31, 2019~~October 2016 and January 2017~~. After going through the LOI and gaining documented written consent, the volunteer/patient will be enrolled. The experimental and control pulse oximeters will be placed on two different fingers on the same hand. Participants will not be cannulated in Phase 2. Patients will then have one measurement taken with the experimental pulse oximeter and another measurement taken with a gold standard pulse oximeter. Measurements of oxygen saturation will be recorded to establish equivalence of the two oximeters. Part two of the study takes 5 minutes to complete, is completely non-invasive, and will not interfere with regular clinical care. There will be no interference with a patient's normal care during this phase.

Experimental Oximeter

The experimental oximeter will be manufactured by the research team in London, Ontario under the supervision of Glia Inc. (Corporation #924742-4; HC Company ID #141507). A bill of materials can be found in Table 2. The oximeter has not been granted authorization for use in Canada.

Mfr. #	Manufacturer	Description	Order Qty.
VJ0603V105MXQCW1BC	Vishay	Multilayer Ceramic Capacitors MLCC - SMD/SMT 0603 1uF 10volts Y5V 20%	9
GRM188R60J475KE19D	Murata	Multilayer Ceramic Capacitors MLCC - SMD/SMT 0603 4.7uF 6.3volts X5R 10%	2
06036D106MAT2A	AVX	Multilayer Ceramic Capacitors MLCC - SMD/SMT 6.3V 10uF X5R 0603 20% Tol HIGH CV	2
VJ0603Y104JXJPW1BC	Vishay	Multilayer Ceramic Capacitors MLCC - SMD/SMT 0603 0.1uF 16volts X7R 5%	4
MCP1700T-3002E/TT	Microchip	LDO Voltage Regulators 250mA Adj LDO 2%	1
CRCW06032K00FKEA	Vishay	Thick Film Resistors - SMD 1/10watt 2.0Kohms 1%	1
CRCW0603590KFKEA	Vishay	Thick Film Resistors - SMD 1/10watt 590Kohms 1%	1
CRCW02011M00FKED	Vishay	Thick Film Resistors - SMD 1/20watt 1Mohms 1% 100ppm	3
FSMSM	TE Connectivity	Tactile Switches 3.5X6 SMT TACT TACT SWITCH	2
MCP1640T-I/CHY	Microchip	Voltage Regulators - Switching Regulators 500 kHz 300 mA Syn. PWM/PFM enabled	1
AT-2440-TWT-R	PUI Audio	Speakers & Transducers 3V 80dBA 4000Hz	1
744028004	Wurth Electronics	Fixed Inductors WE-TPC 2811 4.7uH . 85A .265Ohm	1
STM32F030F4P6	STMicroelectronics	ARM Microcontrollers - MCU Value-Line ARM MCU 16kB 48 MHz	1
3-1734592-0	TE Connectivity	FFC & FPC Connectors 0.5mm PITCH B/C 30P	1
XG8S-0231	Omron	Headers & Wire Housings Connector	25
SML-LX0603SRW-TR	Lumex	Standard LEDs - SMD Super Red, 660nm 1.7V, 45mcd	1
SML-LX0603SYW-TR	Lumex	Standard LEDs - SMD Super Yellow,	1

		590nm 2V, 60mcd	
598-8030-107F	Dialight	Standard LEDs - SMD Orange Water Clr 150mcd 610nm	1
APT1608F3C	Kingbright	Infrared Emitters IR 940nm 120 deg Water Clr 1.2 mW/sr	1
TSL13T	ams	Light To Frequency & Light To Voltage Light to Voltage Converter	1

Table 2: Bill of Materials of experimental oximeter.

Subjects

According to FDA recommendations, 15 participants is the minimum number required for calibration studies. In order to ensure the experimental pulse oximeter is adequately calibrated, we have determine a sample of 50 participants is sufficient for Phase 1. In Phase 2, to maintain a power of 0.80 with an alpha of 0.05, the sample size was calculated at 350 participants to establish equivalence.

Phase 1 sample size

The phase 1 (calibration) sample size was determined by considering the FDA and ISO recommendations for calibration studies on healthy volunteers. While 15 is the minimum number required (See FDA document attached), we expect a sample size of 30 patients. To allow for unexpected variability, we have requested a sample size of 50 from the REB, though this number might be reduced after a interim analysis at 25-30 patients.

Phase 3 Sample Size

The phase 3 sample size was calculated in the following way: Consider a clinical trial comparing two groups, a standard therapy (s) and a novel therapy (n). In each group, a proportion of subjects responds to the treatment: Ps and Pn. If the intention of the study is to show that the two groups are equivalent, the usual formulation of the null hypothesis (Ps=Pn) encounters logical difficulty. A statistical test may fail to reject this null hypothesis, but this will not mean that the two treatments are equivalent.

Blackwelder (Controlled Clinical Trials 1982; 3: 345-353) proposes a solution. If a difference between the two treatments, call it D, is specified that *practically* represents equivalence, then the null hypothesis can be restated to include the specified difference. In other words, that: Ps is greater than or equal to Pn + D. Rejection of this hypothesis implies that the difference between the standard and novel treatments is less than or equal to D, indicating equivalence.

The sample size needed to reject this hypothesis at alpha = 0.05 and beta = 0.20 (power of 80%) is:

(Z 0.95 + Z 0.80)2 [Ps(1-Ps) + Pn(1-Pn)] / (Ps-Pn-D)2

We made the following assumptions:

1) "response rate" being the proportion of correct readings, assuming a 4% variance is .96 in both

the "gold standard" and "new pulse ox" groups.

2) A practical difference (accepted clinical difference between the novel and standard device) of also 4%.

With these numbers, we require 296 patients/volunteers in both groups. Equivalence is hard to prove and has the highest sample size needed. We rounded this number up to 350 to account for unexpected variability or difficulties.

If we desired a non-inferiority study, those numbers go down significantly to 13/group. If there is truly no difference between the standard and experimental treatment, then 26 patients are required to be 80% sure that the lower limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will be above the non-inferiority limit of -4. However, because of the very short amount of time required for each participant and no risk, we elected to run an equivalence trial.

Inclusion Criteria

This study has 2 Phases. In Phase 1, healthy, non-smoking adult volunteers greater than 18 years of age are invited to participate. In Phase 2, all adult (>18) non-critical patients and healthy community volunteers visiting the ED at VH and UH are eligible to participate.

Exclusion Criteria

Potential participants will be excluded based on the following criteria: Phase 1: greater than 70 years of age, current smokers, previous history of cardiac disease (e.g., atrial fibrillation, myocardial infarction, congestive heart failure), history of moderate or severe asthma, history of seizures, history of stroke or transient ischemic attack, and pregnant women will be excluded. Patients with any active pulmonary disease such as pneumonia will be excluded. Individuals who are unwilling to participate or are less than 18 years old will be excluded, as will those who are unable to consent. Phase 2, critical patients will be excluded from participating. Individuals who are unwilling to participate or are less than 18 years old will be excluded, as will those who are unable to consent.

Stopping rules

Subject wishes to withdraw from the protocol.

Subject feels untoward in any way.

Data Analysis

Data will be entered directly into a study-specific LibreOffice database (The Document Foundation, Berlin, Germany). No personal identifiers are being collected in this study. Standard descriptive statistics will be summarized using means and standard deviations and differences in proportions will be assessed by the Pearson chi-squared statistic where appropriate. All data analyses will be performed using R (R Foundation, Vienna, Austria). Phase 1: to validate the experimental pulse oximeter, readings from the arterial blood sample will be plotted against the R value from the prototype to establish a best-fit curve. Phase 2: two one sided tests will be employed to determine if the experimental pulse oximeter is equivalent to the gold standard. The confidence interval around the mean difference between the prototype and gold standard will be compared to predetermined acceptance criterion.

Placebo or comparator

Pulse oximetry is a vital tool in the rapid and non-invasive assessment of emergency patients, providing a continuous estimate of hemoglobin saturation in arterial blood. In addition to the prototype pulse oximeter being evaluated, a gold-standard pulse oximeter will be placed on another finger on the same hand of the participant and continuously monitor blood saturation levels as per the institution's procedural sedation protocols. The use of the gold standard as a comparator will allow us to monitor blood saturation levels concurrently with the prototype. Additionally, the use of the gold standard as a comparator poses no risk to the participant.

Risks and harms

During the study protocol in Phase 1, participants will be cannulated with an indwelling arterial catheter for frequent sampling of arterial blood. Participants may feel discomfort during the catheter insertion process. The participant will also be fitted with a non-rebreather mask as part of the Phase 1 study protocol in order to reduce the oxygen saturation level with gas mixtures of progressively decreasing oxygen and increasing nitrogen. Participants may experience low blood pressure, tachycardia or chest pain. Phase 1 is estimated to take 60 minutes to complete. In Phase 2 of the study, participants will wear both the experimental and gold standard pulse oximeter. There are no additional risks associated with wearing two pulse oximeters for the five minute duration of the study. Phase 2 is estimated to take 5 minutes to complete.

The entirety of the study protocol will be conducted within the emergency department at LHSC, on a hospital bed, with an emergency trained physician monitoring at all times. In Phase 1 the arterial catheter will be inserted by an experienced emergency physician. Should an adverse event occur, the participant will be monitored one-on-one by the physician and treated according to best medical practice. Arterial oxygen saturation will be continuously monitored as per the institution's procedural sedation protocols.

Informed consent

Participants will be provided with the LOI and informed consent document. The investigator will verbally describe the study to the participant. The participant will be made aware of the purpose of the study, what their participation in the study entails, assured there is no deception in the protocol, be made aware of the risks of participating, and be assured that they may end their participation in the study at any time without consequence. The investigator will provide ample time to read the LOI and actively solicit any questions or concerns. Documented written consent will be obtained before enrolling the participant. For Phase 2, patients will have first contact within the circle of care for participation.