Protocol for Controlled Desaturation Tests for Non-Invasive Pulse Oximeter Performance Testing

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Abstract

To prove that the investigational pulse oximeter device is accurate also on low oxygen saturation levels, the testing must be done on human beings since there are no reference materials to ensure correct operation. The ISO standard 80601-2-61:2019 Particular requirements for basic safety and essential performance of pulse oximeter equipment offers the option to measure the accuracy of the investigational pulse oximeter by comparing the readings to a secondary standard pulse oximeter equipment. This non-invasive protocol erases the need for arterial cannulation, which is unpleasant for the subject, needs specific medical and laboratory competence and itself involves risks for adverse events. This study protocol enabled a fluent, non-invasive execution of desaturation measurements for pulse oximeter performance testing.

1. Introduction

The milestones in the development of optical measurement of blood oxygen saturation (SpO_2) are many. In 1940, J. R. Squire realized the different behavior in transmission of red and infrared light while using a pressure cuff to block blood flow to hand [1]. Glen Millikan was the first to use the word "oximeter" with his ear oximeter in 1942, that used red and infrared [2]. Earl Wood and his PhD student J. E. Geraci combined these two methods in 1949 to calculate saturation [1]. Takuo Aoyagi improved the accuracy of earpiece oximeters and constructed the first prototype pulse oximeter with photoplethysmography (PPG) in 1973-1974. During the next decade, Minolta and Nellcor made great progress with their pulse oximeters, and by 1990, optical pulse oximeter had become widely recognized as a standard measurement modality in intraoperative patient monitoring. [2,3]

Since then, it has become one of the most important physiological measurements, especially during surgical operations and in intensive care units as well as in polysomnography examination for the detection of sleep apnea. SpO_2 sensors utilize a minimum of two wavelengths of light usually positioned on the opposite sides of a tissue segment such as finger or earlobe, or toes or sole of feet in case of infants. In addition to this transmissive mode PPG, solutions utilizing reflective PPG where the light emitter and the sensor are placed adjacent to each other, have also been introduced for the measurement of SpO_2. These sensors can be placed on the forehead, chest, foot, or even wrist.

SpO_2 is a challenging measurement target. The emitted light is reflected, absorbed and scattered in tissue and blood. The amount of light that passes through all skin structures and is detected by a photodetector varies and can be interrupted by factors such as skin structure, changes in blood volume and arterial diameter on measurement site, hemoglobin concentration, movement, ambient light, body temperature, artificial nails or dark nail polish. Also, in patients with dark skin pigmentation the readings may be overestimated. [4,5]

SpO_2 is a function of the relations of the AC and DC components of the PPG signal in red and infrared wavelengths as shown in Eq. 1. The resulting relation value, also called the perfusion index (R), is often in the range of 2–3%. [6]

$$R = \frac{\frac{AC_{red}}{DC_{red}}}{\frac{AC_{IR}}{DC_{IR}}}$$

2. Aim

The aim was to conduct a clinical investigation protocol for non-invasive pulse oximeter testing according to ISO standard 80601-2-61:2019 Particular requirements for basic safety and essential performance of pulse oximeter equipment [7]. The aim of the clinical investigation was to collect data for development and testing of the SpO_2 estimation algorithm, and to validate the SpO_2 monitoring

accuracy of the investigational device presented in [8]. The pulse oximetry standard states that even though it is desirable for pulse oximeter equipment to achieve high accuracy (<1 %) compared to reference value, it is not routinely achievable with current limitations in technology. The minimum performance requirements are higher for devices in diagnostic use. The accuracy should not be greater than 4 % at 1 standard deviation, since this could lead to mistreatment in clinical practice. [7] To prove that the device is accurate also on low oxygen saturation levels, the pulse oximeter testing must be done on human beings since there are no reference materials to ensure correct operation and replace the complex interaction between human tissue and light [9].

According to the ISO pulse oximetry standard, the accuracy of the investigational pulse oximeter can be measured by comparing the readings to a secondary standard pulse oximeter equipment, that has been calibrated against CO-oximeters [7]. This non-invasive protocol does not include artery blood sample collection. While the FDA suggests using arterial hemoglobin concentration (SaO_2) for primary accuracy method [10], the pulse oximetry standard also allows direct comparison of the investigational device against a secondary standard pulse oximeter. This method has produced identical results compared to invasive testing over many years, proving to be efficient in measuring the accuracy of an investigational pulse oximeter. [7] In this study, the non-invasive protocol was chosen because it is less burdensome for the study subjects, recruitment is therefore simpler, and the study was not executed in hospital environment with proper laboratory equipment available for blood gas analysis.

The safety of the subjects was ensured using standard commercial monitoring (GE Carescape B450 patient monitor) equipped with 5 lead ECG, SpO_2, non-invasive blood pressure and $etCO_2$ measured by capnography. These include all parameters that are listed in the ISO pulse oximeter standard to confirm safety of the study subjects during desaturation period. Masimo RAD-97 was used as a reference pulse oximeter in this non-invasive protocol. Masimo RAD-97 is a leading technology in measuring SpO_2 and has demonstrated high sensitivity and accuracy even during conditions of motion and low perfusion [11,12].

3. Methods

Subjects were recruited among the faculty and students at Tampere University and from the participants of aeroplane pilot training program of Patria company and were able to sign a written informed consent prior to any study procedures.

Inclusion criteria for this voluntary study were ASA category 1 and positive Allen's test, as per suggested inclusion criteria in the pulse oximetry standard, age of 18-40 years, passing the physical examination either in Patria pilot training or by the investigator responsible for the medical safety of the study subjects. Exclusion criteria for the study were age under 18 years or over 40 years, smoking, pregnancy, not passing the physical examination, or presence of any relevant medical illnesses.

Subjects from Patria undergo annual health examinations in their training program and those passing the examination and fulfilling the inclusion/exclusion criteria for the study were directly seen as suitable candidates for the study. Subjects recruited from Tampere University faculty and students underwent a health check by medical doctor of the research group to rule out any health issues that may cause a risk for subject's safety. The health check included height, weight, Hemoglobin, ECG, pulse rate, blood pressure, pulmonary auscultation, spirometry, and question for medical history, particularly of febrile convulsions in own childhood or with close relatives. These ruled out the likeliness of cardiovascular, pulmonary or neurological conditions that would be contraindications for participating in the study. Allen's test was performed for each subject to confirm normal blood circulation in their hands and fingers. The pulse oximetry standard states that the subjects should be under the age of 50 [7], but the local ethics committee suggested that since the risk for asymptomatic coronary artery diseases increases after the age of 40, the age limit should be lowered.

The study protocol was evaluated by the local ethics committee and the national medical agency. Since the measurements were not conducted in hospital environment, the local ethics committee required a Data Monitoring Committee (DMC) presented in the standard ISO 14155:2020 Clinical investigations of medical devices for human subjects – Good clinical practice [13], as optional body, to be formed. The DMC, consisting of anesthesiologists, an emergency physician and a surgeon, was assigned to evaluate the study environment and competence of the research group in case of medical emergencies. The research group was equipped for escalation in hypoxic convulsions, heart arrhythmias and difficulties in breathing. A protocol for medical emergencies was prepared and the roles of the study personnel defined in detail. The medical doctor responsible for the medical safety of the study subjects was appointed as the leader in medical emergencies, investigator A was also a health care professional skilled in intravenous cannulation and acute medical care, and investigator B was responsible for calling help and guiding the ambulatory team in the test lab. In addition, the University suggested a medical doctor experienced in medical emergencies to be present during the measurements and a specialist in anesthesiology was recruited for this position.

In accordance with the pulse oximetry standard, each subject was exposed to hypoxia with the use of Hypoxico Everest II training device designed for high altitude simulation training in sports. A transparent tent was placed

over the subject's upper body to create an environment with decreased levels of inspired oxygen. The investigational device and the reference device were time synchronized at the start of each measurement period by removing pulse oximetry probes from subject's fingers and receiving artifact data. The prevailing level of oxygen inside the tent was measured regularly with a separate oxygen monitor. Inspired oxygen levels were decreased until the subject's blood oxygen saturation reached a level between 79-70 % and the desaturation was terminated if the subject's SpO_2 levels decreased below 70 %.

4. Results

The aforementioned protocol was used in a clinical study during winter and spring 2024. Desaturation measurements were performed on 6 different days. Total of 24 subjects, 8 females (33,3 %) and 16 males (66,7 %), took part in desaturation measurements. Subjects varied in skin pigmentation between levels 2 to 6 on Fitzpatrick's scale estimated by a medical doctor performing the preliminary health checks. According to the particular standard, study population should involve at least 2 subjects with dark skin pigmentation, or 15 % of the whole subject pool depending on which portion is larger [7,10].

Desaturation periods were divided to SpO_2 levels between 100-90 %, 89-80 % and 79-70 % as mentioned in the standard, with several data points in each section. The ISO pulse oximetry standard advices to stay on each SpO_2 level section for no more than 10 minutes. There was some variation between study subjects with individual tolerance for hypoxia, as shown in Table 1.

Table 1. Prevailing level of oxygen at the end of each desaturation period, and measured SpO_2 levels with the reference device.

Nr.	O_2 %	SpO_2 Masimo
1	11,2	72
2	9,7	80
3	9,0	75
4	10,3	73
5	10,8	79
6	10,2	71
7	10,3	73
8	10,4	73
9	10,1	74
10	8,9	97
11	10,5	71
12	11,2	75
13	10,3	73
14	9,8	71
15	10,6	76
16	10,0	74
17	10,2	75
18	9,6	74
19	10,3	76
20	9,0	81
21	10,6	72
22	11,0	67
23	11,1	71
24	10,2	80

The mean O_2 % at the end of desaturation measurements was 10.2 with a standard deviation of 0.6. The mean SpO_2 level with the reference device was 74.9 with SD of 5.7.

In some cases, 70-79 % oxygen saturation levels were not reached in the targeted time frame of 30 minutes stated in the pulse oximeter standard. One subject had such a great tolerance for hypoxia, that even with low oxygen levels their SpO_2 did not decrease under 90 %.

After completing each measurement period, the tent was removed from the subject's upper body, and they were able to breathe ambient room air. None of the participants needed medical oxygen to recover from hypoxia. One subject reported headache after desaturation measurement. No major adverse events were reported.

5. Discussion

The results will be analyzed by using the Accuracy Root Mean Square (A_{rms}) metric, which is considered the primary statistic by regulatory organizations when analyzing pulse oximetry's general performance [9], and Bland-Altman plot to describe bias. Both metrics are recommended by the FDA to describe the performance of a pulse oximeter [10]. Values obtained with the investigational device will be compared to the results from the reference device, as illustrated in the ISO pulse oximeter standard in section EE.3. SpO_2 readings from the reference pulse oximeter replace the SaO_2 values that would be used as a reference in an invasive protocol. In the non-invasive protocol, the A_{rms} value is expressed relative to the secondary standard pulse oximeter, including the error of the reference pulse oximeter. [7]

In the study conducted with the presented protocol, initial analysis showed that there's a lot of variability between the test subjects' tolerance for hypoxia and the attained SpO_2 levels. When some subjects, such as numbers 2, 10 and 20 shown in table 1, did not reach SpO_2 levels under 80 % during the 30-minute desaturation period, others, such as numbers 1, 12 and 23 shown in table 1 reached low SpO_2 levels with over 11 % O_2. Even with

healthy subjects, there are several causes for pulse oximeter to show different values, such as cold periphery, movement, poor probe positioning or venous pulsations caused by a tight pulse oximeter probe [14].

6. Lessons learned

Attention needs to be put into the study design, and a detailed plan is advised for the measurement periods in terms of defining the level of targeted saturations. There were a lot of variations between study subjects, where in some cases the desaturation progressed evenly, and some did not reach oxygen saturation below 80 %. The ISO pulse oximeter standard notices this challenge especially at the lower levels of oxygen saturation and urges to collect at least 200 data points from 10 subjects to have enough data to validate the accuracy of investigational pulse oximeter.

In this study protocol, a transparent tent was used to create an environment where inspired oxygen was decreased gradually. This equipment must be adjusted in great detail, as it is not an airtight system and might hinder the alternation of prevailing oxygen level in the targeted time range of 30 minutes. Another option would be to use a mask.

There also seems to be differences between pulse oximetry devices, even though medical grade pulse oximeters were used in this study. These factors may complicate the description of statistical accuracy. In this sense it would be beneficial to have SaO_2 measurements available. Attention to selecting the pulse oximetry probes is also advised. During the first measurements, a hinged probe was used with the GE Carescape B450 pulse oximetry. The probe was so tight that it showed much lower measurements than the reference device, and was soon replaced with a softer, more flexible probe.

Controlled desaturation measurements raise several concerns in terms of subject safety and are thoroughly discussed in ethics committees and medical agencies during assessment. When conducting this measurement outside hospital environment, it is suggested to have a plan for medical emergencies and medically competent staff present.

6. Conclusion

A protocol for controlled desaturation test using non-invasive approach was presented. The protocol was successfully used in preliminary feasibility testing of the accuracy of the SpO_2 measurement of a wearable patient monitor. Attention should be paid to recruiting volunteers that are in good health and eligible for brief hypoxia. The laboratory setting, monitoring and use of pulse oximetry probes shall be consistent between subjects to avoid falsely estimated SpO_2. In the future, the presented protocol can be used to validate novel monitoring methods and investigative medical devices in an effective and non-invasive way without compromising regulatory conformance or patient safety.

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