

# Validation Experiment of a New Brain Oxygen Saturation Monitoring Instrument

**Kai Chen**

Zhongnan Hospital of Wuhan University

**Zunxu liu**

BLZ Technology (Wuhan) CO.,LTD.

**Meng-Yun Li**

Zhongnan Hospital of Wuhan University

**Lijuan Tang**

Zhongnan Hospital of Wuhan University

**Yufeng Zou**

Zhongnan Hospital of Wuhan University

**Kailin Xiao**

BLZ Technology (Wuhan) CO.,LTD.

**zongze zhang** (✉ [zhangzz\\_0301@126.com](mailto:zhangzz_0301@126.com))

Zhongnan Hospital of Wuhan University

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## Research Article

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# Abstract

## Background

The blood samples of jugular vein and radial artery were obtained from healthy adults by induced oxygen desaturation test under pulse oximetry conditions on each platform. The oxygen saturation of the two blood samples was analyzed and measured by a Co-oximeter. Thus, the oxygen saturation value of jugular vein (SjvO<sub>2</sub>) and radial artery (SaO<sub>2</sub>) were obtained. According to the clinical empirical formula  $Sa/vO_2 = 0.7 \times S_{jvO_2} + 0.3 \times SaO_2$ , the oxygen saturation value of brain tissue for invasive blood gas analysis was calculated. To calculate the difference between brain oxygen saturation (rSO<sub>2</sub>) measured by brain oxygen saturation monitor (hereinafter referred to as brain oxygen analyzer) and brain oxygen saturation (Sa/vO<sub>2</sub>) measured by invasive blood gas analysis, analyze the consistency of brain oxygen saturation measured by brain oxygen saturation analyzer and blood gas analyzer, and calculate the accuracy of brain oxygen saturation monitoring. The blood samples of jugular vein and radial artery were obtained from healthy adults by induced oxygen desaturation test under pulse oximetry conditions on each platform. The oxygen saturation of the two blood samples was analyzed and measured by a Co-oximeter. Thus, the oxygen saturation value of jugular vein (SjvO<sub>2</sub>) and radial artery (SaO<sub>2</sub>) were obtained. According to the clinical empirical formula  $Sa/vO_2 = 0.7 \times S_{jvO_2} + 0.3 \times SaO_2$ , the oxygen saturation value of brain tissue for invasive blood gas analysis was calculated. To calculate the difference between brain oxygen saturation (rSO<sub>2</sub>) measured by brain oxygen saturation monitor (hereinafter referred to as brain oxygen analyzer) and brain oxygen saturation (Sa/vO<sub>2</sub>) measured by invasive blood gas analysis, analyze the consistency of brain oxygen saturation measured by brain oxygen saturation analyzer and blood gas analyzer, and calculate the accuracy of brain oxygen saturation monitoring.

## Methods

In healthy adult volunteers, the induced desaturation test, in which blood gas analysis measures the subjects' internal jugular vein and carotid artery blood samples at each pulse oximetry platform range. Clinical trials were conducted to verify the expected effectiveness and safety of the brain oxygen saturation monitor. Ten subjects were selected into the study according to strict inclusion criteria and exclusion criteria. Subjects should monitor their electrocardiogram, pulse, blood pressure, SPO<sub>2</sub> and other vital signs, perform retrograde puncture catheterization of internal jugular vein and radial artery catheterization, ensure the safety of subjects during the period, and record the values of blood samples before and after collection. The oxygen was lowered according to the set platform (according to Figure 2), and physiological parameters were monitored during the process. There were 9 platforms in total, and each platform lasted about 5 minutes. The oxygen saturation value of jugular vein (SJVO<sub>2</sub>) and the oxygen saturation value of carotid artery (SaO<sub>2</sub>) were obtained, and the tissue oxygen saturation value of sa1vO<sub>2</sub> was calculated according to the clinical empirical formula  $SA1VO_2 = 0.7 \times SJVO_2 + 0.3 \times SaO_2$ . During the blood collection process, the blood oxygen saturation (RSO<sub>2</sub>) of the subjects' brain was continuously monitored by tissue oximeter noninvasively. The consistency of non-invasive

monitoring value  $rSO_2$  and invasive measurement value  $sa_1vO_2$  was compared, and scientific statistical analysis was carried out to confirm whether the accuracy of tissue oxygen meter meets clinical requirements.

## Results

**Absolute accuracy evaluation:** Further linear regression analysis was performed on the non-invasive monitoring value of the test instrument and the blood gas analysis detection value. The fitting linear equation was  $rSO_2 = 4.89 + 0.93 \times Sa/vO_2$ , where the slope was 0.93, close to 1. The regression line was close to the 45° diagonal trend. The correlation coefficient between  $rSO_2$  and  $Sa/vO_2$  was 0.95, indicating that there was a good correlation between the non-invasive monitoring value and the invasive blood gas analysis value.

**Trend accuracy evaluation:** It can be seen that the average difference between the trend change value of the test instrument monitoring value and the blood gas analysis value is very small ( $B_s = \text{Means}(\Delta rSO_2 - \Delta Sa/vO_2) = -0.32\%$ ), indicating that the trend change of the test instrument monitoring value and the blood gas analysis value is basically consistent in statistical significance. The 95% consistency interval of the difference of trend change between the two devices is narrow ( $[B_s - 1.96SD, B_s + 1.96SD] = [-6.13\%, 5.5\%]$ ), indicating that the difference of trend change between the two devices has small variation. The above analysis shows that there is a good consistency between the non-invasive monitoring value of the test equipment and the invasive test results of the blood gas analysis equipment. The linear regression analysis was made on the changes of the test instrument monitoring value and blood gas analysis detection value. The fitting linear equation was  $\Delta rSO_2 = -0.98 + 0.93 \Delta Sa/vO_2$ , and the slope was 0.93, which was close to 1. The regression line was close to the 45° diagonal trend. The correlation coefficient of trend changes of the two equipment is 0.95, indicating that the change trend of the test equipment and blood gas analyzer has a good correlation. Analyze the trend changes value, due to the variation of every subjects is relative to the first platform first blood gas analysis values as the base to calculate, so the data points less than 10 absolute value analysis, the test equipment and the trend of blood gas analysis change the average deviation is 0.32%, the standard deviation is 2.97%, RMS very different trend is 2.97%, The clinical evaluation standard of trend  $Arms \leq 5\%$  was met.

## Conclusion

There is good correlation and consistency between the test instrument monitoring value and the absolute value of blood gas analyzer.

## Trial Registration:

The study has been retrospectively registered in Chinese Clinical Trial Registration with the registration number ChiCTR2100052321, date of registration 24/10/2021.

## Introduction

Blood oxygen saturation is an index to monitor the oxygen supply and oxygenation of human blood or local tissues, and an important physiological parameter of respiratory circulation, as well as a key reference index for the protection of vital organs in perioperative period. Traditional blood oxygen saturation includes arterial (SAO<sub>2</sub>) and venous (SVO<sub>2</sub>) oxygen saturation, in which arterial oxygen saturation has achieved non-invasive continuous monitoring of CSpO<sub>2</sub>, that is, clinical monitoring of finger end pulse oxygen value. However, it can only be monitored when there is pulse in the finger artery, and it only reflects the oxygen saturation of peripheral blood, which cannot truly reflect the oxygenation of an organ (such as brain tissue), and it cannot be measured when there is weak pulse, hypoperfusion, cardiac arrest and other conditions

In recent years, as the noninvasive continuous near-infrared local tissue oxygen saturation monitoring instrument of the clinical application and promotion, clinical practice, has achieved important organs (such as) the brain tissue oxygen supply and oxygen demand comprehensive conditions of real-time, continuous and noninvasive, digital monitoring, the monitoring technology of clinical advantages are more obvious. But the technology has been monopolized by American medical giants, such as Medtronic's INVOS series (INVOS 3100A, INVOS 5100C) and CASMED's FORE SIGHT Elite (now acquired by Edwards). The domestic hospital market is almost monopolized by these two brands, expensive instruments (more than RMB 400,000) and disposable sensors (The cost price is only about 1000 to 2000 YUAN). The import cost has hindered the clinical popularization and application of tissue blood oxygen parameter monitoring technology in domestic hospitals.

Brain oxygen saturation monitor is a non-invasive and continuous monitoring instrument for absolute oxygen saturation of brain tissue based on NIRS tissue oxygen parameter monitoring technology. In tissue optics, Near Infrared Light (NIR) generally refers to Infrared Light with a wavelength of 700-900nm, which has good penetration of human tissues and is called "Spectral Window" [1, 2]. Figure 1 shows the absorption spectra of HHb, HbO<sub>2</sub> and water at 650-1000nm wavelengths [3].

The significant differences among the three can be clearly identified from Figure 1. In particular, the absorption rate of water at this wavelength is much lower than HHb and HbO<sub>2</sub>. Therefore, if near-infrared light with appropriate wavelength is selected, and light with the same light intensity and different wavelength is projected onto human tissue in a certain time sequence, and the outgoing light of each wavelength is received in the same time sequence at the set position (as shown in Figure 2), it is obvious that the light intensity of each wavelength received will be different. These different light intensity signals are converted into electrical signals by special photosensitive chip, and a series of processing such as acquisition, amplification, filtering and calculation of these electrical signals can be obtained.

The concentrations of HHb and HbO<sub>2</sub> in the texture or their changes over time, as well as the oxygen saturation rSO<sub>2</sub> of local tissues (that is, tissues located below the sensor and can be scanned by the light source on the sensor), and other information about tissue oxygenation status. The test instrument, MOC-100, sends different wavelengths of near-infrared light through the scalp and skull to the brain via disposable sensors on the patient's forehead. The reflected light is captured by a detector located on the

sensor for optimal signal acquisition. After analyzing the reflected light, the absolute value of brain tissue oxygen saturation is displayed on the screen and a graphical representation of the historical values is provided.

Due to the late start of research on near-infrared tissue oxygen parameter detection technology in China, and the serious lag in innovative scientific research mode of combining medical and industrial medical devices in China, similar products in China lag behind the United States at least for more than ten years in terms of hardware design, software algorithm and system interaction.

In this field in order to catch up with world-class technical level and developing advanced tissue oxygen monitoring equipment, in recent years, many families (wuhan) co., LTD, wuhan university of science and technology zhongnan hospital in near infrared tissue oxygen saturation monitoring technology launched a series of basic research, technology research, product engineering, clinical trials and other medical professionals combined with scientific research cooperation mode. The purpose of this clinical trial is to verify the expected safety and effectiveness of recent research results of "brain tissue oxygen saturation monitor" through clinical trials.

Brain tissue oxygen saturation monitor (hereinafter referred to as tissue oxygen meter) can monitor the oxygenation of microcirculation vessels (mainly microveins and microveins) in tissues. The method is based on chromophore oxygenated hemoglobin ( $\text{HbO}_2$ ) from human tissues.

With different absorption, scattering and reflection characteristics of deoxyhemoglobin (HHb) in the near infrared spectrum (660~940nm), the self-developed sensor emits non-invasive low-density near infrared light through the patient's cerebral cortex, cranial bone and gray matter, and measures the reflected light received by the near and far phototube(Figure 1). Then the tissue oxygen saturation value and monitoring curve were obtained by analyzing, identifying and calculating the light intensity signal with a unique algorithm.

Tissue oxymeter is a continuous, non-invasive device that monitors tissue oxygen saturation in real time, reflects the balance between tissue oxygen supply and oxygen demand, and alerts medical staff on tissue hypoxia or hyperoxygenation events, so as to remind medical staff to take possible interventions to protect the normal physiological function of patients' vital organs and tissues.

Blood oxygen saturation is an index to monitor the oxygen supply and oxygenation of human blood or local tissues, and an important physiological parameter of respiratory circulation, as well as a key reference index for the protection of vital organs in perioperative period. Traditional blood oxygen saturation includes arterial ( $\text{SAO}_2$ ) and venous ( $\text{SVO}_2$ ) oxygen saturation, in which arterial oxygen saturation has achieved non-invasive continuous monitoring of  $\text{CSpO}_2$ , that is, clinical monitoring of finger end pulse oxygen value. However, it can only be monitored when there is pulse in the finger artery, and it only reflects the oxygen saturation of peripheral blood, which cannot truly reflect the oxygenation of an organ (such as brain tissue), and it cannot be measured when there is weak pulse, hypoperfusion, cardiac arrest and other conditions.

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## Material And Methods

### Ethical approval

After Research Ethics Board approval at Medical Ethics Committee, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, P.R. China. The project has been approved since 28/6/2019 and the approval number is 2019007, and the study has been retrospectively registered in Chinese Clinical Trial Registration with the registration number ChiCTR2100052321, date of registration 24/10/2021. We conducted a prospective randomised, double-blind, controlled clinical trial from September 2019 to November 2019. This was a single-centre study in the Zhongnan hospital in Wuhan, Hubei, P.R. China. That all methods used in the experiment are followed in accordance with the relevant guidelines and regulations.

### Study design and population

Twelve subjects were enrolled in the study, among which 10 subjects successfully completed the clinical trial and 2 subjects withdrew from the study due to personal reasons. All the 10 subjects who completed the experiment cooperated or had poor cooperation record. Subject selection (including control group selection if necessary) 1) Inclusion criteria : Healthy adults aged from 18 to 45 years old had a balanced and reasonable gender distribution. Subjects: Co hemoglobin COHb < 3%, Subjects: methemoglobin MetHb < 2%, subjects: ctHb > 10g/ dL; No smoking history/no smoking history; No history of cardiopulmonary diseases; Those who have passed the physical examination; The subject voluntarily signs a written informed consent to participate in the clinical trial. 2) Exclusion criteria: Smokers or those exposed to high carbon monoxide levels; Those with coagulation dysfunction or artificial blood vessels; People with past heart and lung diseases; There is skin disease, infection or trauma around the measurement site, so that this parameter cannot be measured; Patients with mental illness, epilepsy or other diseases resulting in involuntary movement of the body; Physical condition can lead to high methemoglobin; Subjects should be excluded from clinical trials if they are undergoing procedures that are likely to create undue medical risks for them; Pregnant women; With grey nails; The clinical trial personnel judge that the compliance is not good and the protocol cannot be strictly implemented;

Subjects enrolled in other clinical trials within 30 days; Patients with other diseases not suitable for clinical trials; Unwilling to sign informed consent.

Pulse oxygen clinical range of 70%-100%, pulse oxygen SpO<sub>2</sub> less than 70%, may lead to life-threatening. SpO<sub>2</sub> was divided into nine platforms (Figure 4), and induced hypoxia test was conducted on the subjects. The hypoxia process was induced, and the brain oxygen saturation of the subjects changed from high to low, covering the clinical range of 50%-80%. Two data groups were obtained on each gradient platform, and each data group was recorded as follows: cerebral oxymeter value rSO<sub>2</sub>: rSO<sub>2</sub> left 1 and rSO<sub>2</sub> right 1 at the beginning of blood drawing and rSO<sub>2</sub> left 2 and rSO<sub>2</sub> right 2 at the end of blood drawing, calculated

So let's call the mean rSO<sub>2</sub>; Blood gas analysis value Sa/vO<sub>2</sub>: SjvO<sub>2</sub> was obtained by blood gas analysis of venous blood, and SaO<sub>2</sub> was obtained by blood gas analysis of arterial blood. Sa/vO<sub>2</sub> was calculated according to the formula  $0.7 \times S_{jvO_2} + 0.3 \times S_{aO_2}$  weighted average.

Method and time selection for evaluating, recording and analyzing validity parameters. Pulse oxygen clinical range of 70%-100%, pulse oxygen SpO<sub>2</sub> less than 70%, may lead to life-threatening. SpO<sub>2</sub> was divided into nine platforms (Table 1), and induced hypoxia test was conducted on the subjects. The hypoxia process was induced, and the brain oxygen saturation of the subjects changed from high to low, covering the clinical range of 50%-80%. Two data groups were obtained on each gradient platform, and each data group was recorded as follows: cerebral oxymeter value rSO<sub>2</sub>: rSO<sub>2</sub> left 1 and rSO<sub>2</sub> right 1 at the beginning of blood drawing and rSO<sub>2</sub> left 2 and rSO<sub>2</sub> right 2 at the end of blood drawing, calculated. So let's call the mean rSO<sub>2</sub>; Blood gas analysis value Sa/vO<sub>2</sub>: SjvO<sub>2</sub> was obtained by blood gas analysis of venous blood, and SaO<sub>2</sub> was obtained by blood gas analysis of arterial blood. Sa/vO<sub>2</sub> was calculated according to the formula  $0.7 \times S_{jvO_2} + 0.3 \times S_{aO_2}$  weighted average.

Absolute accuracy of calculation as defined in this clinical protocol, if  $\leq 10\%$ , brain oxymeter can be clinically accepted as an instrument for displaying absolute value of tissue oxygen saturation. Auxiliary Bland-Altman analysis with difference  $(rSO_{2(i)} - Sa/vO_{2(i)})$ . As y axis, bland-Altman plot was drawn with  $(rSO_{2(i)} + Sa/vO_{2(i)}) / 2$  as X axis. The excluded data were explained to calculate the mean deviation Bs, variance S<sup>2</sup> of the total deviation and variance S<sup>2</sup> of different individual deviation, and the consistency limit  $Bs \pm 1.96SD$  was analyzed. If the accuracy of trend calculation is less than 5% as defined in Chapter 15 of this clinical protocol, the brain oxymeter can be clinically accepted as an instrument for displaying trends in tissue oxygen saturation. Bland-altman diagram is plotted with the difference  $[\delta rSO_{2(j)} - \delta Sa/vO_{2(j)}]$  as y axis and  $[\delta rSO_{2(j)} + \delta Sa/vO_{2(j)}] / 2$  as X axis. The excluded data are explained. Average deviation Bs, variance of population deviation and variance of different individual deviation were calculated, and consistency limit  $Bs \pm 1.96SD$  was analyzed. Finally Ten people were selected for the final experiment. We will conduct experiments according to the following procedures(Figure 3), experiments were carried out using a lowering oxygen platform(Figure 4).

## Equipment and procedures

### Preparation

The subject was not sedated or anesthetized the night before the test; The blood gas analyzer must be calibrated before use to ensure its measurement accuracy (SaO<sub>2</sub> accuracy is not less than 1%), and must be used in accordance with the manufacturer's recommendations and auxiliary materials; Preparation of consumable materials: single vena cava puncture catheter, arterial indwelling needle, arterial blood gas sampler, 2ml syringe, 5ml syringe, heparin salt solution, disposable pressure sensor. After testing the normal gas path can produce different partial pressure of oxygen gas mixing instrument, to achieve the mixed output of O<sub>2</sub>, N<sub>2</sub> and CO<sub>2</sub>, the concentration of O<sub>2</sub> in the output gas FiO<sub>2</sub> can be read directly from the equipment; Non-invasive ECG monitoring device and gas monitoring device were used to monitor physiological parameters of subjects. The standard monitor pulse oximeter sensor was placed on the right index finger of the subject. The forehead of the subject is cleaned with alcohol cotton ball. After confirming that the forehead skin of the subject is clean, dry and intact without any powder, oil or lotion, the sensors of the test instrument are placed on the left and right forehead respectively. Put on the respirator mask and perform the oxygen-lowering process according to Figure 1. The oxygen-lowering process (according to figure 4) lasts for 1 minute on each platform and the EtCO<sub>2</sub> is kept at  $\pm 5$  mmHg of the baseline value. FiO<sub>2</sub> on each SpO<sub>2</sub> platform was recorded to make subjects feel adapted to the deoxygenation process, and each FiO<sub>2</sub> value was used as the reference value for subsequent adjustment on each platform. The subjects were placed supine under local anesthesia with 2% lidocaine. The left or right radial artery was punctured with an indent needle, and the catheter was sealed with a pressure sensor connected with prefilled heparinized salt solution. Under local anesthesia with 2% lidocaine, ultrasound guided, the central venous catheter was retrograde penetrated into the right internal jugular vein, and the catheter was placed to the bulb of the internal jugular vein. After the location of the catheter was determined, the pressure sensor of prefilled heparinized salt solution was connected. Medical instrument for the test: Brain tissue oxygen saturation monitor, model: MOC-100; Medical instrument for control: Blood gas analyzer, model: ABL90 FLEX.

### Procedures

According to figure 4 platform 1: The pulse oximeter showed  $98\% \pm 2\%$ , which was the baseline value of the subjects. After two minutes, 0.5-1ml venous blood sample was slowly extracted, and the extraction time should be  $> 30$ s. To reduce the return of non-jugular blood to the jugular bulb. When taking venous blood samples, 0.5-1ml of arterial blood samples were also taken. The cerebral oxygen saturation value rSO<sub>2</sub> was recorded at the beginning and end of venous blood sampling. After the first venous blood sample was taken, the platform was kept stable for 1 minute, and the process of the first group of blood samples was repeated to obtain the second venous blood sample, the second arterial blood sample, and the cerebral oxygen saturation values of the two groups before and after the venous blood sample was taken. Oxygen was lowered and FiO<sub>2</sub> value was adjusted so that the value of the standard monitor pulse oximeter was  $95\% \pm 2\%$ . After two minutes, the blood sample was repeated to obtain two groups of venous

blood samples and arterial blood samples, and the oxygen saturation values of the left and right cerebral brain of the four groups were obtained. Continue to drop oxygen to the pulse oximetry values of each platform, repeat the previous steps to obtain blood and brain oximetry monitoring values, and complete the platform 3-7 test; The subjects were provided with atmosphere, and the baseline value was restored. After two minutes, the blood sampling process of previous steps was repeated. Two groups of venous blood samples and arterial blood samples were obtained in total, and four groups of cerebral oxygen saturation values were obtained.  $FiO_2$  value was adjusted so that the pulse oximeter value of the standard monitor was displayed as 100%. After two minutes, the blood sampling process of the previous steps was repeated. Two groups of venous blood samples and arterial blood samples were obtained, and the oxygen saturation values of the left and right cerebral brain of the four groups were obtained. The subjects breathed directly into the atmosphere, returned to baseline values, and 5 minutes later, the experiment ended. After the completion of the test, the jugular vein, arterial catheter, test instruments, standard monitor, pulse oxygen monitor and physiological monitoring instruments were removed, and the subjects were observed for 2 hours. The medical staff checked that the subjects were safe and allowed to leave. 2 days later, the subjects were followed up by telephone to see if there was any abnormality, or the wound of catheterization was examined in outpatient department, and antibiotics were added. (according to figure 4 and figure 5)

## Statistics

### **Statistical design, methods and analysis procedures**

In this clinical trial, absolute accuracy and trend accuracy were confirmed to be the main indexes to verify the effectiveness of brain oximeter. Refer to the accuracy definition of pulse oximeter and the accuracy definition of brain oximeter in relevant research [11], and the absolute accuracy of brain oximeter

(Arms) was defined as the root mean square difference between the cerebral oximeter monitoring value and the weighted value  $Sa/vO_2$  of blood oxygen saturation measured by the Co-oximeter. The trend accuracy of oximeter was defined as the root mean square of the difference between the change of oximeter value and the change of  $Sa/vO_2$ , a weighted value of blood oxygen saturation, measured by the corresponding Co-oximeter.

- 1) Statistical software: Processing and analysis of data sets by Matlab2016;
- 2) Basic principles: All statistical inferences adopt two-sided test, the test level with statistical significance is set at 0.05, and the confidence interval of parameters is estimated by 95% confidence interval;
- 3) Missing data: Missing data is not estimated in this study;

4) Eliminating data: Eliminate unstable data sets. From the beginning of collection of jugular vein blood samples to the end of collection, data with changes of blood oxygen saturation measured by quality control equipment (pulse oximeter) exceeding 3% [11] should be eliminated. If the blood oxygen platform has been unstable, all data of the subject shall be removed; The blood oxygen platform is unstable, there is air leakage in the blood drawing process, and the data groups with blood gas separation time exceeding 1.5 hours should be eliminated; Data can be excluded if it is confirmed by review that the test conditions for some data are outside the test protocol;

5) Check outliers: calculate the average of the difference value of the data group. If the difference value of the data group exceeds 4 times of the average value, the data group is judged as an outlier;

### Absolute accuracy verification

1) Absolute accuracy of calculation:

The absolute accuracy of the brain tissue oxygen saturation monitor is defined as the root mean square value of the  $rSO_2-SA/vO_2$  difference, and the calculation formula is:

$$A_{rms} = \sqrt{\frac{\sum_{i=1}^n (rSO_{2i} - S_{a/v} O_{2i})^2}{n}} \quad (1)$$

Wherein,  $rSO_2$  is the of  $rSO_{2\text{ left } 1}$  and the of  $rSO_{2\text{ right } 1}$  displayed by the brain oxygen meter at the beginning of blood drawing, and the brain oxygen meter at the end of blood drawing. The mean values of  $rSO_{2\text{ left } 2}$  and  $rSO_{2\text{ right } 2}$ ;  $S_{a/v}O_2$  refers to  $S_{jv}O_2$  obtained by blood gas analysis of venous blood and  $S_{aO_2}$  obtained by blood gas analysis of arterial blood after blood sampling. The weighted average value calculated according to the formula  $0.7 \times S_{jv}O_2 + 0.3 \times S_{aO_2}$ ;  $i$  represents the  $i$ th valid data group. Root mean square calculation was performed on the difference between the effective data sets of the subjects, and the accuracy was obtained, if  $\leq 10\%$ , the acceptable range;

2) Auxiliary Bland-Altman analysis: Take difference  $rSO_2(i) - S_{a/v}O_2(i)$  as Y-axis, and take  $(rSO_2(i) + S_{a/v}O_2(i))/2$  as X-axis, Bland-Altman plot was drawn, excluded data were explained,

average deviation  $B_s$ ,  $\sigma^2$  of total deviation and  $\sigma^2_{\mu}$  of different individual deviation were calculated, and consistency limit  $B_s \pm 1.96sd$  was analyzed.

3) Correlation analysis: linear regression, correlation coefficient calculation, precision  $S_{res}$ .

### Trend accuracy verification

(1) The trend accuracy of the brain tissue oxygen saturation monitor was defined as the root mean square value of  $\Delta rSO_2 - \Delta Sa/vO_2$  difference. The first effective data point  $rSO_{2(1)}$  of the first platform range is taken as the baseline value, and the change between the monitor display value and the baseline  $\Delta rSO_{2(j)}$  when collecting the  $j+1$  effective blood sample is calculated according to Formula (2). Change  $\Delta Sa/vO_{2(j)}$  between the weighted mean of blood gas analysis and baseline within the corresponding platform range was calculated according to Formula (3). Trend accuracy was calculated according to Formula (4). If root mean square  $\leq 5\%$ , it was clinically acceptable.

$$\Delta rSO_{2(j)} = rSO_{2(j+1)} - rSO_{2(1)} \quad (2)$$

$$\Delta S_{a/v}O_{2(j)} = S_{a/v}O_{2(j+1)} - S_{a/v}O_{2(1)} \quad (3)$$

$$A_{rms} = \sqrt{\frac{\sum_{j=1}^m (\Delta rSO_{2(j)} - \Delta S_{a/v}O_{2(j)})^2}{m}} \quad (4)$$

In the type:  $j = 1, 2, \dots, m \times m = n - 1$

2) Auxiliary Bland-Altman analysis: Bland-altman plot with difference  $[\Delta rSO_{2(j)} - \Delta Sa/vO_{2(j)}]$  as y axis and  $[\Delta rSO_{2(j)} + \Delta Sa/vO_{2(j)}]/2$  as X axis. The mean deviation  $B_s$ , the  $\sigma^2$  of the population deviation and the  $\sigma^2_{\text{ind}}$  of different individual deviation were calculated, and consistency limit  $B_s \pm 1.96sd$  was analyzed.

3) Correlation analysis: linear regression, calculated correlation coefficient  $S_{res}$ , calculated precision  $S_{res}$ .

The correlation between the adverse events occurred in the test and the test device was analyzed, and the safety of the test device was described and evaluated.

## Results

### Statistical study population and data set

Demographic indicators include age, sex, race and weight. A total of 10 patients were enrolled in and out of the group, including 7 males and 3 females. Age range: 19-30 years old, average age: 24 soil 7.84 years old (mean soil L.96s D), weight range: 50-85kg, average body weight:  $63.6 \pm 22.5$ kg (mean soil L.96SD). The details are shown in Table 1.

### Absolute accuracy evaluation

Further, linear regression analysis was performed on the non-invasive monitoring value of the test instrument and the blood gas analysis value (as shown in Figure 6). The fitting linear equation was  $rSO_2=4.89+0.93\times S_{a/v}O_2$ , with a slope of 0.93, close to 1, and the regression line was close to the 45° diagonal trend. The correlation coefficient between  $rSO_2$  and  $S_{a/v}O_2$  was 0.95, indicating that there was a good correlation between the non-invasive monitoring value and the invasive blood gas analysis value.

To sum up, the statistical analysis results of the test instrument monitoring values and blood gas analyzer testing values are summarized in Table 2. The mean deviation (Bs), standard deviation (SD), correlation coefficient (R), root mean square difference (Arms) and blood gas analysis were 0.42%, 3.23%, 0.95 and 3.25%, respectively, which met the clinical evaluation standard of  $Arms\leq 10\%$ .

### **Trend accuracy evaluation**

The bland-Altman analysis chart of non-invasive monitoring value of test equipment and invasive detection value of blood gas analysis equipment is shown in Figure 7, indicating that the average difference of trend change value of monitoring value of test equipment and detection value of blood gas analysis is very small ( $Bs=Means(\Delta rSO_2-\Delta S_{a/v}O_2)=-0.32\%$ ). The results showed that, in statistical significance, the trend changes of the test equipment monitoring value and blood gas detection value were basically consistent, and the 95% consistency interval of the trend change difference between the two was narrow ( $[Bs-1.96SD, Bs+1.96SD]=[-6.13\%, 5.5\%]$ ), indicating that the trend change difference variation of the two equipment was small. The above analysis shows that there is a good consistency between the non-invasive monitoring value of the test equipment and the invasive test results of the blood gas analysis equipment.

Linear regression analysis was made on the changes in the monitored values of the test instruments and the measured values of blood gas analysis. The analysis figure was shown in Figure 8. The fitted linear equation was  $\Delta rSO_2=-0.98+0.93\Delta S_{a/v}O_2$ , and the slope was 0.93, which was close to 1. The correlation coefficient of trend changes of the two equipment is 0.95, indicating that the change trend of the test equipment and blood gas analyzer has a good correlation.

Analyze the trend changes value, due to the variation of every subjects is relative to the first platform first blood gas analysis values as the base to calculate, so the data points less than 10 absolute value analysis, statistical analysis of the results summarized as shown in table 3, the test equipment and blood gas analysis the trend of change the average deviation is 0.32%, the standard deviation is 2.97%, The trend root mean square Arms was 2.97%, which met the clinical evaluation standard of trend  $Arms\leq 5\%$ .

## **Discussion**

Brain as the central nervous organ of the human body, its weight is only about 2% of the body weight, but the blood flow and oxygen consumption of brain tissue is very huge, in the quiet state, its blood flow is about 15% of the heart output, oxygen consumption is about the total oxygen consumption of the human

body 20% [4]. However, brain tissue itself has almost no energy supply material reserves, and needs to rely on blood circulation to absorb oxygen to maintain normal physiological functions. Therefore, the human brain is highly sensitive to ischemia and hypoxia, and a short period of ischemia and hypoxia may lead to irreversible brain tissue damage [5]. However, standard monitoring methods of systemic arterial and venous oxygen saturation may not represent the oxygenation state in peripheral tissues such as the brain [6,7]. Therefore, maintenance of adequate cerebral oxygenation may increase patient safety by preventing decreased cerebral perfusion and prolonged cerebral tissue ischemia. According to relevant medical statistics, the limit of tolerance of brain tissue to ischemia and hypoxia is 4-6min, and more than 90% of people dying from brain injury suffer from brain tissue ischemia and hypoxia [6]. Under normal condition, oxygen supply and oxygen consumption keep dynamic balance. However, for critically ill patients with special cerebral resuscitation, pathologically dependent oxygen consumption may occur, that is, the increase or decrease of oxygen consumption varies with the increase or decrease of oxygen supply, reflecting the existence of hypoxia and oxygen debt, which may lead to cerebral ischemia, hypoxia and brain tissue damage [7]. Brain is an organ with poor tolerance to hypoxia, but many central nervous system diseases and complications are caused by abnormal brain oxygen metabolism. Therefore, it is very important to monitor cerebral oxygenation from the perspective of maintaining the balance between cerebral oxygen supply and demand to guide brain protection and brain resuscitation.

The oxygen saturation monitor of brain tissue can monitor oxygen supply and oxygen consumption in time and provide reference index for clinical intervention. The brain oxygen saturation monitor measures ArterioleO<sub>2</sub>, microvenous blood in the brain (SvenuleO<sub>2</sub>) and capillaries (ScapillaryO<sub>2</sub>) blood oxygen saturation weighted average, namely:  $rSO_2 = \alpha \times \text{ArterioleO}_2 + \beta \times \text{SvenuleO}_2 + \gamma \times \text{ScapillaryO}_2$  (equation:  $\alpha + \beta + \gamma = 1$ ), due to the small proportion of capillaries, can be ignored,  $\gamma$  is 0. In the early stage,  $\alpha$  and  $\beta$  were established by algorithm verification. For example, Invos3100A, the first commercially available brain oxymeter product in the world, determined  $\alpha=0.25$  and  $\beta=0.75$  according to the algorithm, and the ratio was verified by clinical trials [8]. Later, positron emission computed tomography (PET) imaging of the head by Ito et al. showed that the arteriovenous ratio was closer to 30:70 [9, 10]. Subsequently marketed brain oxymeter products (FORE-SIGHT, NIRO-200NX, EQUANOX, O3) were designed and clinically validated according to this ratio. The ratio of arteriovenous to arteriovenous was 30:70 for blood gas analysis in this study. This clinical trial protocol was formulated by referring to technical Guidelines for Clinical Evaluation of Pulse Oximeter Equipment issued by China Food and Drug Administration in 2016, special Requirements for the Basic Safety and Main Performance of YY 0784-2010 Medical Pulse Oximeter Equipment for Medical Electrical Equipment, and clinical trials of domestic and foreign commercially available products.

The test instrument, MOC-100, sends different wavelengths of near-infrared light through the scalp and skull to the brain via disposable sensors on the patient's forehead. The reflected light is captured by a detector located on the sensor for optimal signal acquisition. After analyzing the reflected light, the absolute value of brain tissue oxygen saturation is displayed on the screen and a graphical representation of the historical values is provided.

Every clinical innovation monitoring product is required to evaluate its effectiveness and reliability. The basic principle of the brain oxygen saturation monitor is similar to the pulse oximeter, but it directly measures the oxygen saturation of the brain tissue without the need for arterial pulsation Degrees.

According to the Technical Guidelines for Clinical Evaluation of Pulse Oximeter Equipment issued by The State Food and Drug Administration in 2016 and YY 0784-2010, pulse oximeter is used for the induced hypoxia test of healthy adults, and the hypoxia platform covers the range of 70-100% pulse oxygen saturation. The co-oximeter was used to analyze the oxygen saturation of the arterial blood sample as the control or other pulse oximeter was used as the secondary comparison standard but the measured value of the control pulse oximeter could be traced back to the Co-oximeter. The test values of the experimental group were compared with those of blood gas analysis to calculate the accuracy of the test instrument. There is a strong clinical need for accurate tracking of rSo<sub>2</sub> in peripheral tissues, particularly brain tissue during the perioperative phase to avoid ischemia<sup>[11]</sup>. A recent study compared the performance of 5 different commercially available regional oximeters in normal volunteers during hypoxemia. This evaluation demonstrated that currently available regional oximeters often perform with limited absolute accuracy, manifesting in an average ARMS of 9.1% for all 5 devices with a range of 4.28% to 9.68%.<sup>10</sup> We believe these findings demonstrate that enhancements to regional oximetry are desirable and would improve clinical confidence and clinical management with regional oximetry.<sup>[12]</sup>

In this paper, we report the results of a clinical study evaluating the absolute and trending accuracy of a new brain pulse oximeter (MOC-100) for continuous, non-invasive measurements of rSo<sub>2</sub>. The bland-Altman analysis diagram of non-invasive blood oxygen saturation monitoring value and invasive blood gas detection value of the test device obtained in clinical trials is drawn by analyzing the data, as shown in Figure 6. It can be seen that the average difference between the test instrument monitoring value and the blood gas detection value is very small ( $Bs = \text{Means}(rS_0 2 - SA/V_0 2) = 0.42\%$ ), indicating that the test instrument monitoring value and the blood gas detection value are basically consistent in statistical significance. The 95% consistency interval of the difference between the two is narrow ( $[BS - L.96SD, BS + L.96SD] = [-5.9\%, 6.75\%]$ ), indicating that the variation of the measurement difference between the two equipment is small. The above analysis shows that the non-invasive tissue oxygen saturation monitoring of the test equipment is between the invasive test results of the blood gas analysis equipment. These statistics indicate that MOC-100 has an absolute the mean deviation (Bs), standard deviation (SD), correlation coefficient (R), root mean square difference (Arms) and blood gas analysis were 0.42%, 3.23%, 0.95 and 3.25%, respectively, which met the clinical evaluation standard of Arms 30%.

We believe that the correct measurement method is very important for successfully developing a regional oximeter with good absolute measurement accuracy and strike accuracy. In order to be able to accurately calibrate the device, it is important to achieve a stable plateau long enough to achieve stable arterial saturation even in the face of changes in respiratory rate. In addition, care should be taken to avoid injury to the ipsilateral artery when retrograde placement of the jugular catheter and extraction of blood.<sup>[13]</sup>

Reference cerebral tissue oxygen saturation is commonly assumed as a weighted sum of the arterial (A) and venous(V) oxygen saturations, which is kept constant (e.g., our analysis used the A/V ratio of 70/30).

However, A/V ratio is not necessarily constant because both the cerebral blood volume as well as oxy- and de-oxy hemoglobin concentrations change in response to other hemodynamic variations. For example, Bickler et al. [14] reported that patients had different ratios of venous and arterial blood in the sensor field. Such conditions and other factors altering arterial and venous ratio indicate that the reference oxygen saturation has an estimation error, which affects both calibration of the device as well as validation accuracy. Limitations of our study include the population of relatively young, healthy, adult volunteers, which may not reflect the performance in critically ill perioperative patients.

Up to now, there are no relevant standards and guidelines for technical review of registration of cerebral oximeter. In 1996, INVOS 3100A was first approved by the FDA for marketing in the United States to monitor trends in cerebral oxygen saturation [4, 5,23-27] rather than to measure the exact value of cerebral oxygen saturation, mainly because there was no established clinical method to verify the accurate measurement of cerebral oxygen saturation. After more than ten years of clinical application and the marketing of several cerebral oximeter products, a unified clinical validation method has gradually been formed which can be accepted by clinical and regulatory departments. A review of 510K data for certified brain tissue oxygen saturation monitors on the FDA website [5,7-16] shows that the efficacy and safety of brain oxygen monitors can be confirmed by induction deoxygenation tests in healthy individuals, such as INVOS 3100A by Somanetics (acquired by Medtronic) [7,17-22] FORE SIGHT Model 2040[8, 9] MC2000[10]. In addition to the data disclosed by FDA, the research results published by other relevant research institutions in the world [4, 10-16] also show that induction deoxygenation test is a safe and effective feasible method to evaluate brain oxygenation apparatus in healthy subjects.

## Conclusion

Accurate data acquisition is required to study the accuracy of MOC-100 pulse oximeter. Among the methods used in this study, MOC-100 regional oximetry provided mean deviation (Bs) of 0.42%, standard deviation (SD) of 3.23%, correlation coefficient (R) of 0.95, root mean square difference (Arms) of 3.25% compared with blood gas analysis. Healthy volunteers who met the Arms 30% clinical evaluation criteria and received controlled oxygenation experiments. There is good correlation and consistency between the test instrument monitoring value model: MOC-100 and the absolute value of blood gas analyzer. Brain tissue oxygen saturation monitor is used for continuous non-invasive monitoring of local tissue oxygen saturation.

## Declarations

### Ethics approval and consent to participate

This study was approved by Medical Ethics Committee, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, P.R. China 2019007. That all methods used in the experiment are followed in accordance with the relevant guidelines and regulations. The study has been retrospectively registered in Chinese Clinical Trial Registration with the registration number ChiCTR2100052321, date of registration 24/10/2021.

## Consent for Publication

Not applicable

## Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interest.

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## Authors' contributions

Meng-Yun Li Yufeng Zou and Lijuan Tang finished most of the work of the experiments. Kai Chen wrote the manuscript. Zunxu Liu and Kailin Xiao was responsible for data management. Kai Chen and NingbinBu, was responsible for the original design and provided critical revisions. Zongze Zhang Zunxu Liu and Kailin Xiao carried out the statistical analysis and interpretation. All authors read , contributed to and approved the final manuscript.

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None.

## Authors' information

Zongze Zhang is the director, chief physician and associate professor of anesthesiology at Zhongnan Hospital of Wuhan University. Chen Kai is an attending physician in the department of anesthesiology at Zhongnan Hospital of Wuhan University. Meng-Yun Li Yufeng Zou and Lijuan Tang are resident physician in the department of anesthesiology at Zhongnan Hospital of Wuhan University. Zunxu Liu is the Executive President of BLZ Technology (Wuhan) CO.,LTD.

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## Tables

Table 1 Summary table of subject's demographics

Item	Description	Data
Gender	Male	7
	Female	3
Age	Age in years	19-30
	Bias±1.96SD	24±7.84
Weight	Weight in kg	50-85
	Bias±1.96SD	63.6±22.5

**Table2** Statistical results of the absolute value between the subject device and blood gas analyzer

subject	Data	Intercept	slope	Bias	SD	Arms	r	$\sigma^2$	$\sigma_{\mu}^2$	$S_{res}$
10	177	4.89%	0.93	0.42%	3.23%	3.25%	0.95	10.41	5.46	3.17%

**Table3** Statistical results of the trend value between the subject device and blood gas analyzer

subject	Data	Intercept	slope	Bias	SD	Arms	r	$\sigma^2$	$\sigma_{\mu}^2$	$S_{res}$
10	167	-0.98%	0.93	-0.32%	2.97%	2.97%	0.95	8.80	3.76	2.91%

## Figures

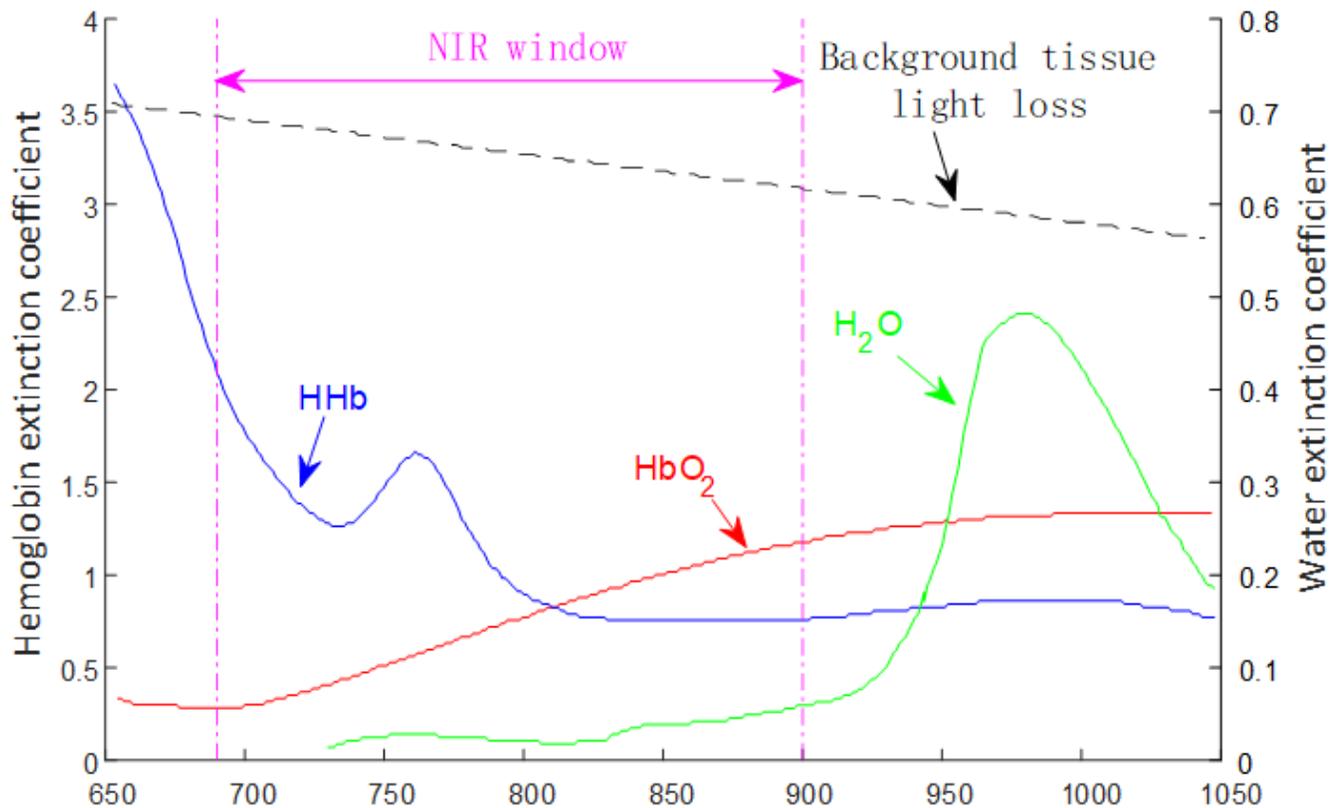


Figure 1

extinction coefficient of HHb, HbO<sub>2</sub> and water between 650~1000nm

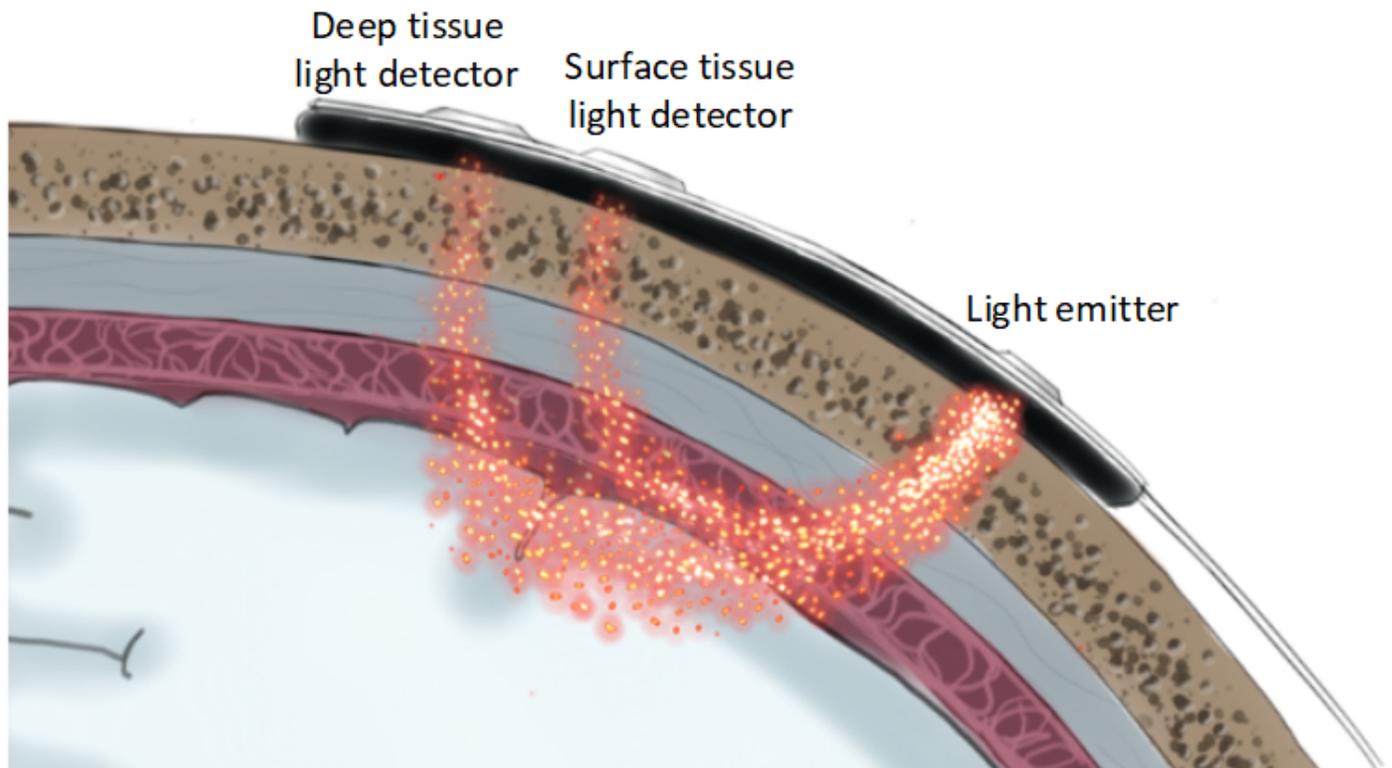


Figure 2

Schematic diagram of light emission and reception of brain oximeter

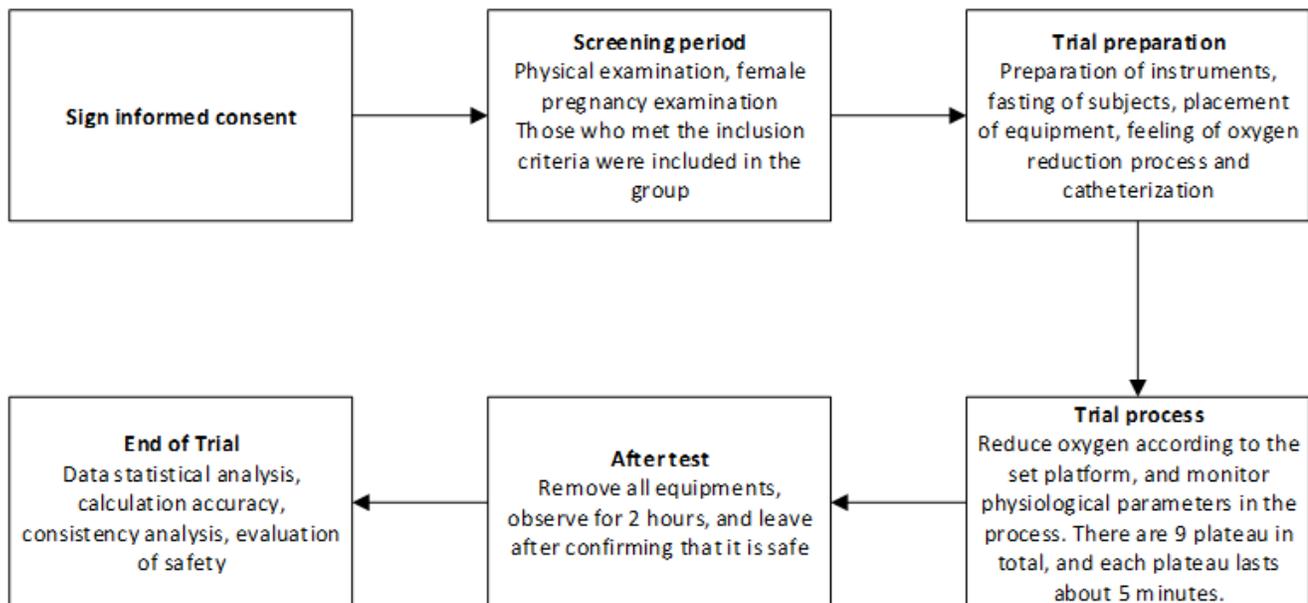
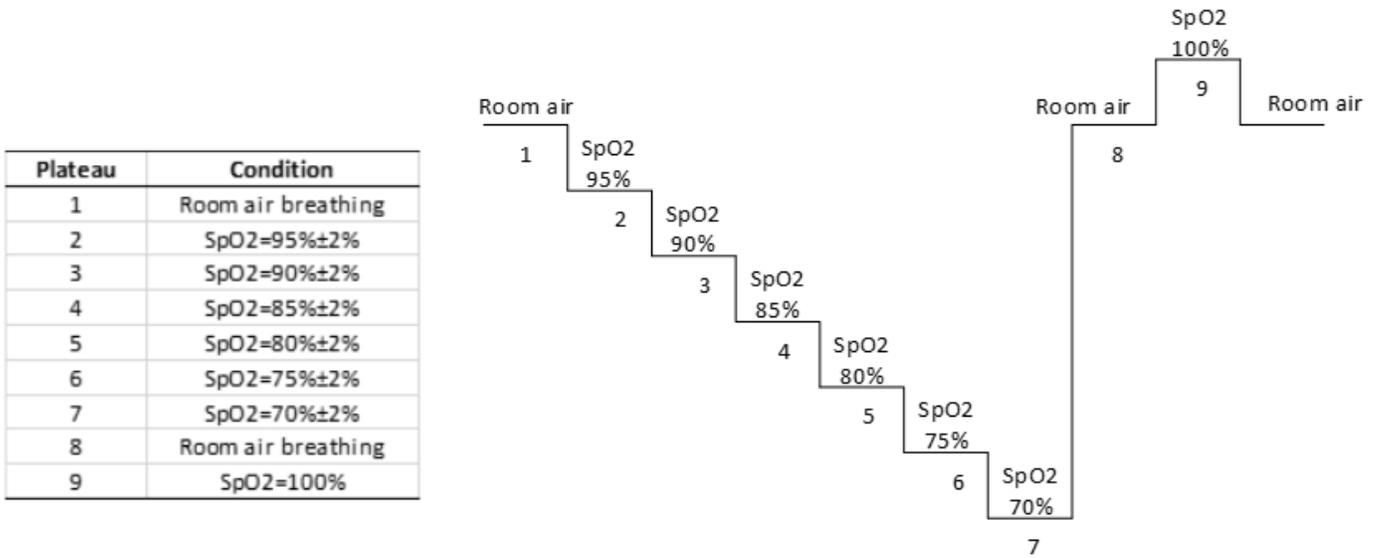


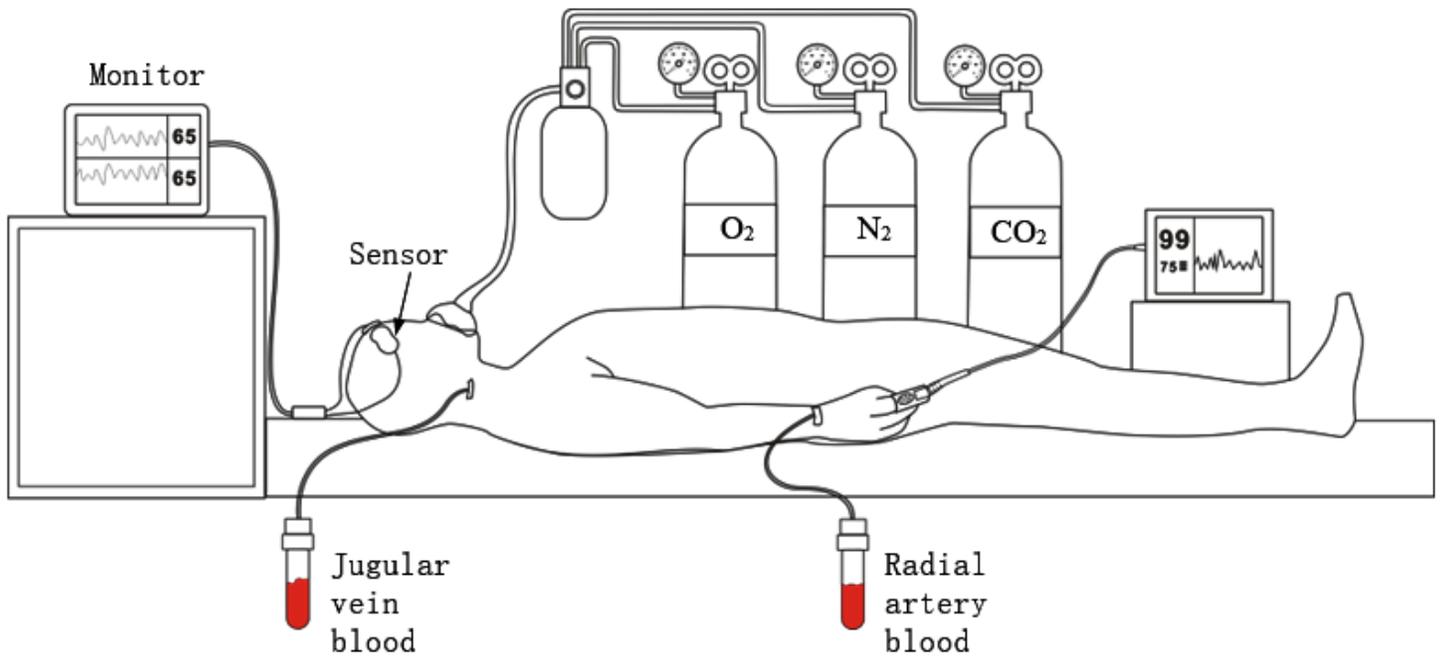
Figure 3

Trial process



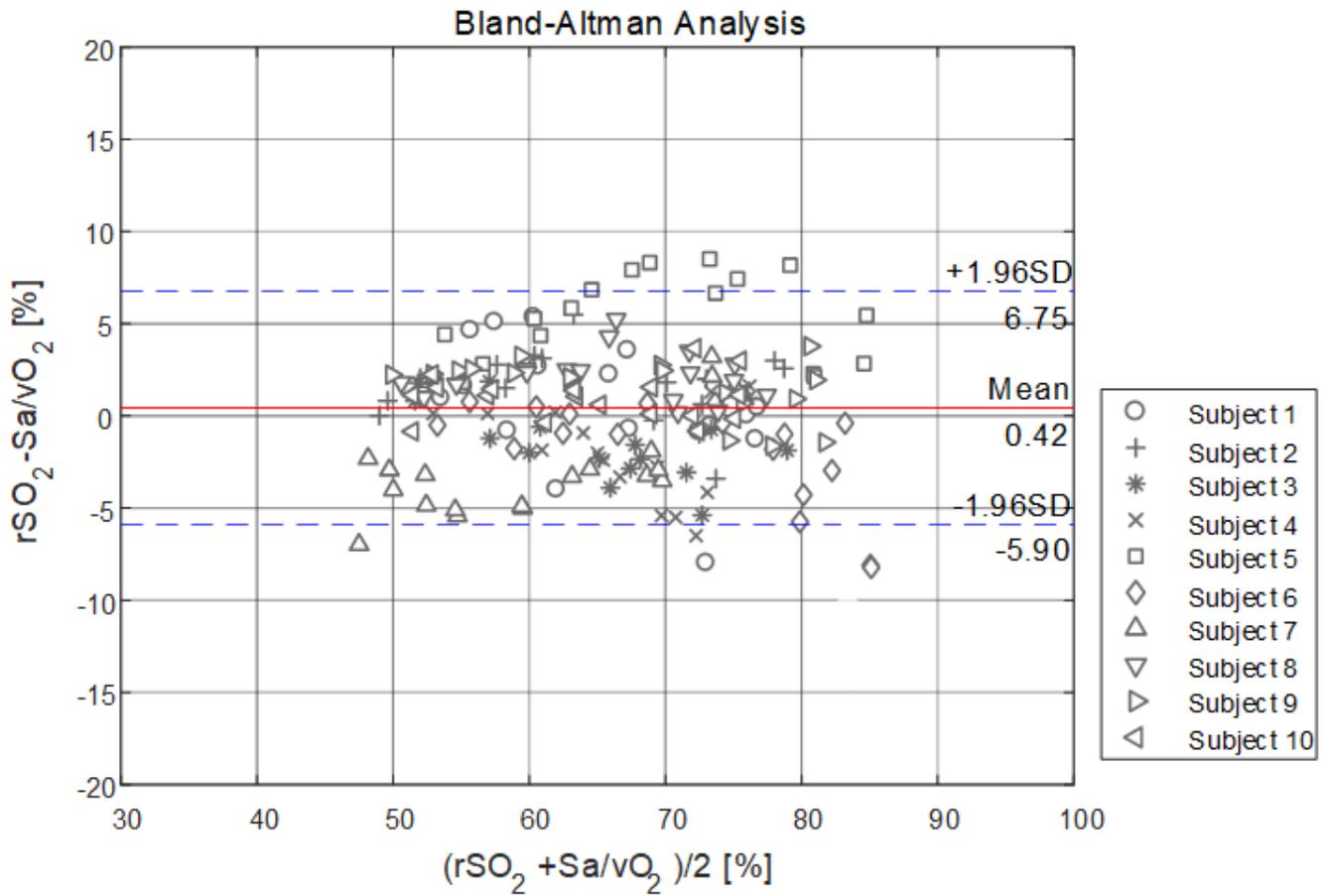
**Figure 4**

Stepped Hypoxia Plateau Sequence Protocol with targeted pulse oximetry SpO<sub>2</sub> values



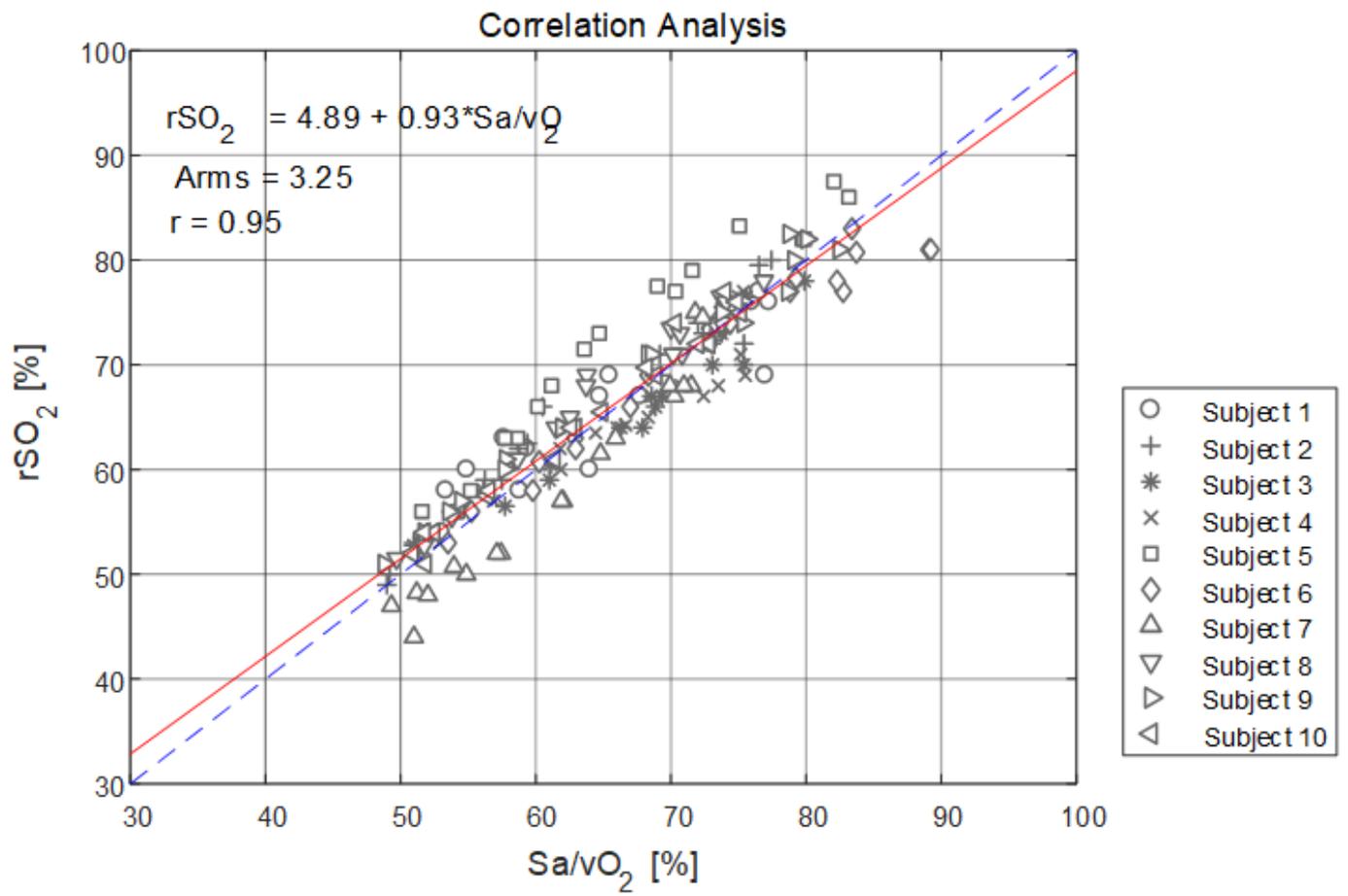
**Figure 5**

Schematic diagram of induced oxygen reduction trial



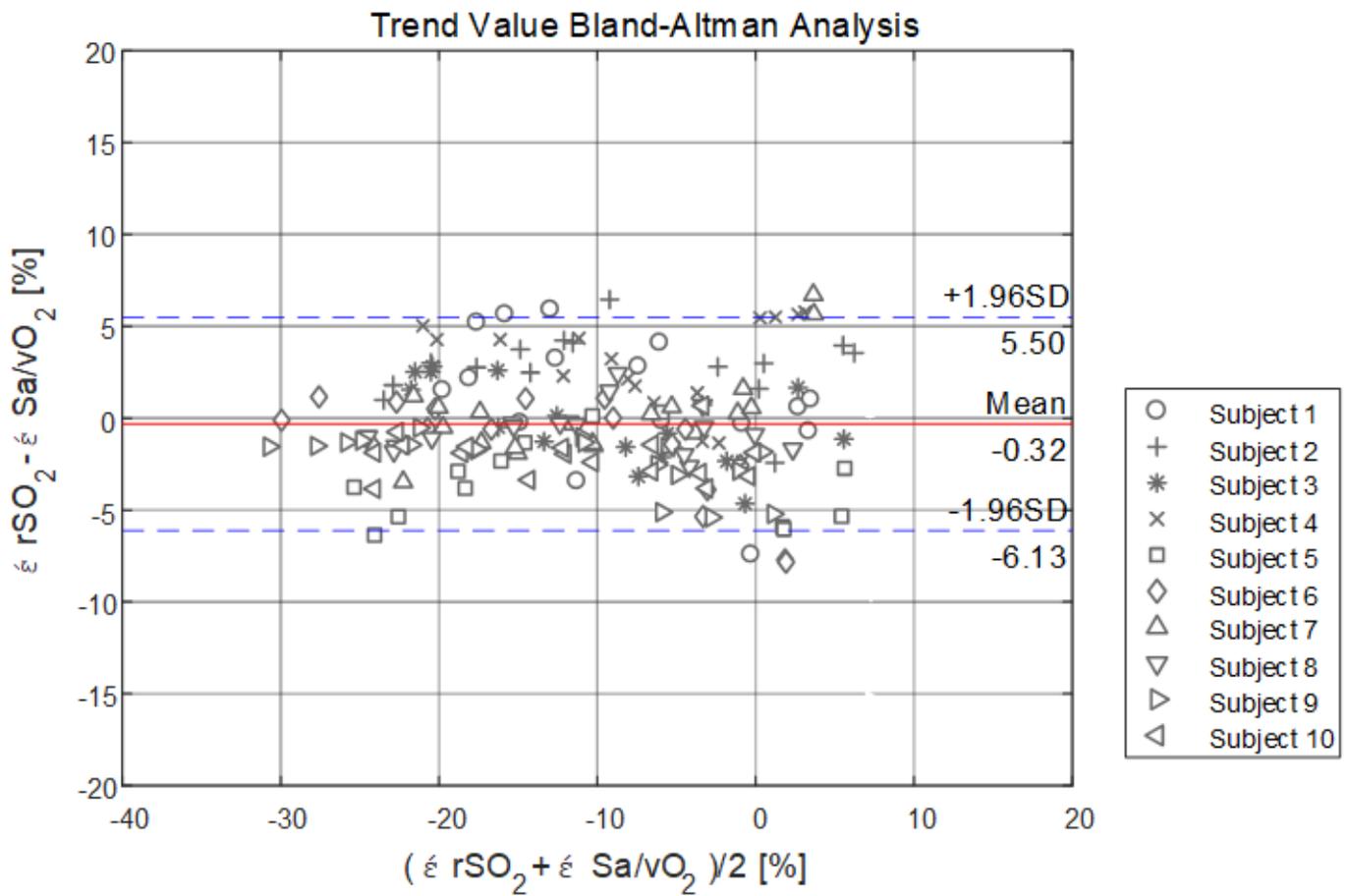
**Figure 6**

Bland-Altman analysis of the absolute value between the subject device and blood gas analyzer



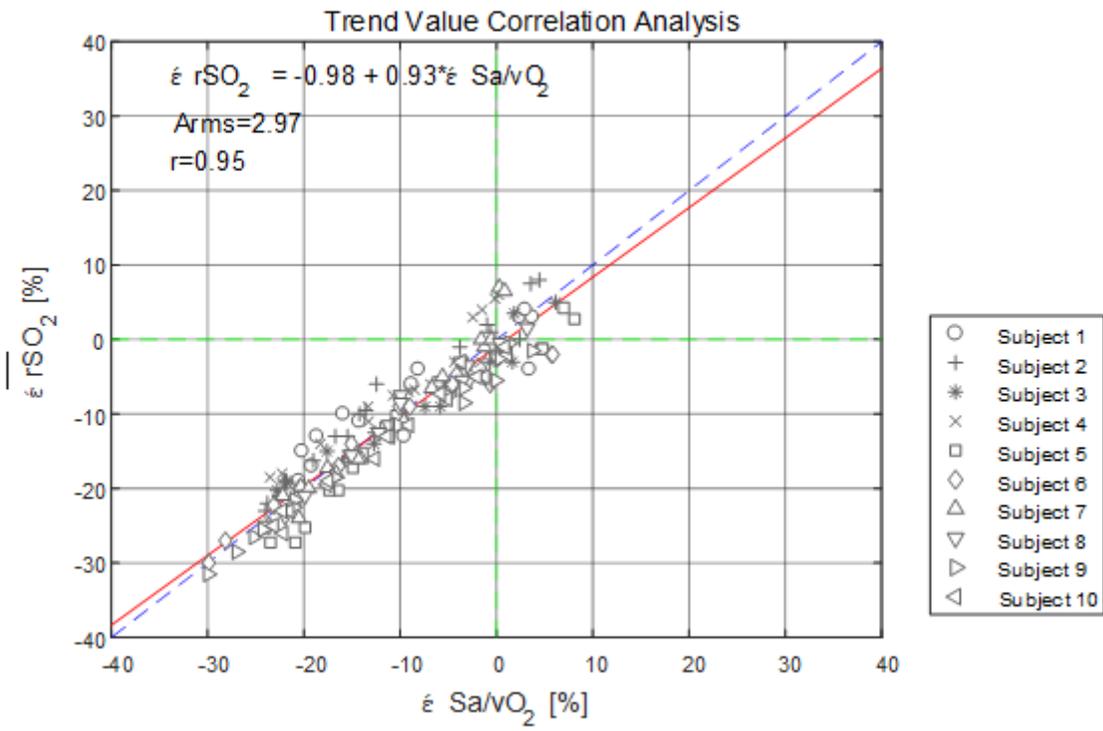
**Figure 7**

Correlation analysis of the absolute value between the subject device and blood gas analyzer



**Figure 8**

Bland-Altman analysis of the trend value between the subject device and blood gas analyzer



**Figure 9**

Correlation analysis of the trend value between the subject device and blood gas analyzer