

Validation of EGOS-600 Near Infrared Spectroscopy to Measure Cerebral Oxygen Saturation by Comparing to NIRO-200nx *In Vitro* and *In Vivo*

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Abstract

Objective: Near-infrared spectroscopy (NIRS) has been increasingly used to monitor regional cerebral oxygen saturation (rScO₂) during cardiac surgery and intensive care. NIRO-200nx (Hamamatsu Phototonics, Japan) is one of widely used NIRS devices. EGOS-600 is a new device developed by Tsinghua University in China. We validated EGOS-600 by comparing to NIRO-200nx in laboratory and clinical settings.

Materials and methods: Laboratory test : A liquid tissue model was made consisting of 40 ml of human whole blood, 25 ml intralipid-20% and 935 ml buffer solution. Oxygen saturation (SO₂) levels ranging 20-100% were made by inflating oxygen or adding sodium hydrosulfite. Eleven pairs of measures were obtained using the two oximeters.

Clinical test: 31 children (aged 0.7-61 months, median 11 months) and 20 adults (aged 18-73 years, median 59 years) were enrolled within one week after cardiac surgery. One probe of each device was sequentially placed at the middle of patient's forehead to measure rScO₂ at 2-3 hour intervals. One hundred pairs of rScO₂ were obtained in each group. Bland-Altman method was used for data analysis.

Results: Laboratory test showed a bias of-2% and limits of agreement 20 to-24% with a trend of overestimating SO₂ by EGOS-600 when average SO₂>50% and underestimating when <50%. This trend disappeared in patients. The bias was-5.9% in children and-4.1% in adults. The limits of agreement were 1.3 to-13.1% in children, and 3.3 to-11.5% in adults.

Conclusions: EGOS-600 introduces a small underestimation of rScO₂ when compared to NIRO-200nx, with acceptable limits of agreement. The new device is applicable in clinical settings in both children and adults.

Keywords: Near-infrared spectroscopy (NIRS); Cerebral oxygen saturation; Cardiac surgery; Children; Adults

Introduction

Near-infrared spectroscopy (NIRS), introduced by Jobsis in 1977 [1], is a non-invasive technology to monitor regional tissue oxygenation. Because of its relative ease to use and providing relevant data, cerebral oximetry using NIRS has been increasingly used in many clinical settings associated with ischemic and hypoxic brain injuries in children and adults [2,3], particularly during cardiac surgery and postoperative period in the ICU [4-6]. There have been various NIRS instruments for clinical use [7]. Currently, two commercially available instruments, the INVOS-4100 (Somanetics, Troy, MI) and the NIRO-200nx (Hamamatsu Photonics, Hamamatsu, Japan) are the most extensively used.

Near infrared light with a wave length between 700 and 900 nm can easily penetrate into human tissue by some centimeters [8]. Because oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb) are the main absorbers in human tissue and their absorption spectra are significantly different in the NIRS band [9], tissue oxygenation can be obtained by NIRS non-invasively. In the past, most NIRS oximeters, such as INVOS-4100, used modified Lambert-Beer law to calculate the concentration changes of HbO₂ and Hb compared with their original values in human tissue [10]. Later, steady-state spatially resolved spectroscopy was brought out in NIRS oximeters, such as NIRO-200nx [11,12] to achieve the optimal coupling with human tissue. EGOS-600 is a new device developed by Tsinghua University in Beijing, China, and like NIRO-200nx, also based on spatially resolved spectroscopy algorithm. It has been correlated with blood gas analysis *in vitro* using liquid tissue model, and the results indicated that its algorithm was little influenced by either background absorption or overlying tissues [13]. However, it has

not been compared with any other NIRS devices either *in vitro* or *in vivo*. The aim of the present study was to compare EGOS-600 with NIRO-200nx in laboratory test to measure oxygen saturation (SO₂) using a liquid tissue phantom consisting of human blood with controlled and graded oxygen saturations, and clinical test to measure regional cerebral oxygen saturation (rScO₂) in children and adults early after cardiac surgery.

Materials and Methods

Instrumentations of NIRO-200nx and EGOS-600 oximeters

Both NIRO-200nx and EGOS-600 use the spatially resolved spectroscopy method based on the solution of the diffusion equation, which describes the interaction of infrared light with the highly-scattering human tissue. By measuring the emitted light intensity as a function of the distance between the light source and the detector and by assuming the wavelength dependence of the reduced scattering coefficient, the ratio of the absorption coefficient under at least two wavelengths can be calculated. Then, the tissue oxygenation saturation can be derived as $HbO_2/(HbO_2+Hb) \times 100\%$.

The sensor of NIRO-200nx oximeter uses a three-wavelength near-infrared laser diode (735, 810, and 850 nm), and two detectors placed at 40 and 50 mm from the source of emitting light for children and adults respectively. The sensor of EGOS-600 oximeter uses a three-wave length near-infrared LED source (760, 810 and 850 nm) and two detectors. The distances between the light source and the two detectors were 30/40 mm for adults, and 20/30 mm for children respectively.

Laboratory test

A liquid tissue phantom was made consisting of 40 ml of human whole blood as the absorber, 25 ml intralipid-20% as the scatter, and 935 ml phosphate buffer solution (pH 7.35-7.45), and the optical absorbing and scattering characteristics were close to human brain cortex in the near-infrared band. The probe of each oximeter was fixed on the liquid surface to avoid the outside light disturbance. Several SO₂ levels were obtained and maintained steady as following. Firstly, pure oxygen was inflated at 300 ml/min for about 5 min so that SO₂ of the phantom reached 100%. Subsequently, the inorganic reducer (sodium hydrosulfite, Na₂S₂O₄) was added into the phantom for 10 mg each time so that the SO₂ was decreased from 100% to 20% by about 10% stepwise and then maintained steady at the level for at least 10 minutes. At each level, the probe of each oximeter was fixed in random fashion at the same position on the surface of the phantom to measure the SO₂. Each set of measurements by the two oximeters was made within 3 minutes.

Clinical test

After the approval by the institutional Research Ethics Board, written assent was obtained from 20 adults (aged 18-73 years median 59 years) and consent from the parents of 31 children (aged 0.7-61 months, median 11 months) in July 2014. Diagnosis in adults included aortic stenosis (n=3), mitral stenosis (n=7), atherosclerosis (n=5), cardiac tumor (n=1), pericarditis (n=1), aortic valve regurgitation (n=1), partial anomalous pulmonary venous drainage (n=1), left ventricular myxoma (n=1); In children, ventricular septal defect (n=14), atrial septal defect (n=3), atrioventricular septal defect (n=1), tetralogy of Fallot (n=4), coarctation of aorta (n=2), pulmonary atresia with ventricular septal defect (n=2), patent ductus arteriosus (n=1), pulmonary stenosis (n=1), total anomalous pulmonary venous connection (n=1), transposition of the great arteries (n=2). Patients were in a steady state, either under sedation and mechanical ventilation or during spontaneously breathing. rScO₂ was measured at 2-3 hour intervals, with one probe of each of the oximeters placed at the middle of patient's forehead in random fashion.

Statistical analysis

The agreement between the values of SO₂ in the laboratory test and rScO₂ in the clinical test measured by EGOS-600 and NIRO-200nx was analyzed using Bland-Altman analysis [14]. Hereby, the difference between the SO₂ or rScO₂ measured by the two oximeters for each pair of measurements is plotted against the corresponding average of the SO₂ or rScO₂ by the two oximeters. The bias is the difference between the SO₂ or rScO₂ measured by EGOS-600 and NIRO-200nx for all the measurements, representing the systematic error. Limits of agreement are the mean of the differences ± 1.96 SD, representing the random error. A bias of near zero indicates close agreement, as would narrow limits of agreement. All the data were analyzed using Matlab 2012. A P value <0.05 indicated statistical significance.

Results

Laboratory test

In the phantom test, a total of 11 pairs of SO₂ values from 100 to 20% were obtained using EGOS-600 and NIRO-200nx. The bias was -2%, and the limits of agreement were 20 to -24%. In addition, there was an overestimation by EGOS-600 when the average of SO₂ by the two oximeters was lower than 50% and an underestimation when higher than 50% (Figure 1). Further analysis was made according to clinical situations in the range of SO₂ from 40 to 80%, the bias was -8% and limits of agreement 4 to -20%.

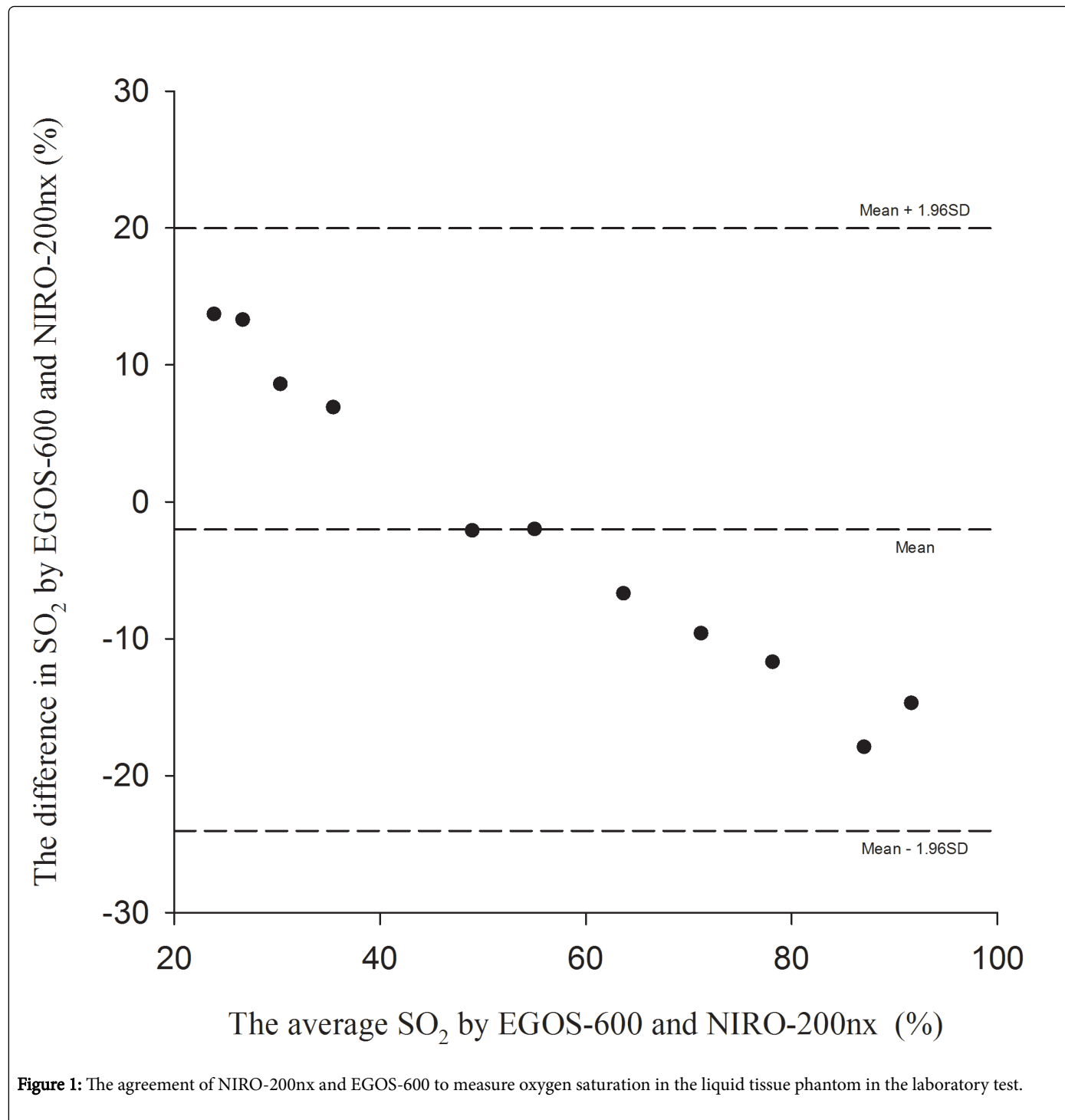


Figure 1: The agreement of NIRO-200nx and EGOS-600 to measure oxygen saturation in the liquid tissue phantom in the laboratory test.

Clinical test

There were 100 pairs of rScO₂ measurements obtained from the two oximeters in the children group and the adult group respectively. In children, the bias was -5.9%, and the limits of agreement were 1.8

to -13.6% (Figure 2). In adults, the bias was -4.2%, and the limits of agreement were 3.5 to -11.8% (Figure 3). The trend of overestimation and underestimation shown in the laboratory test was not observed in either children or adult group.

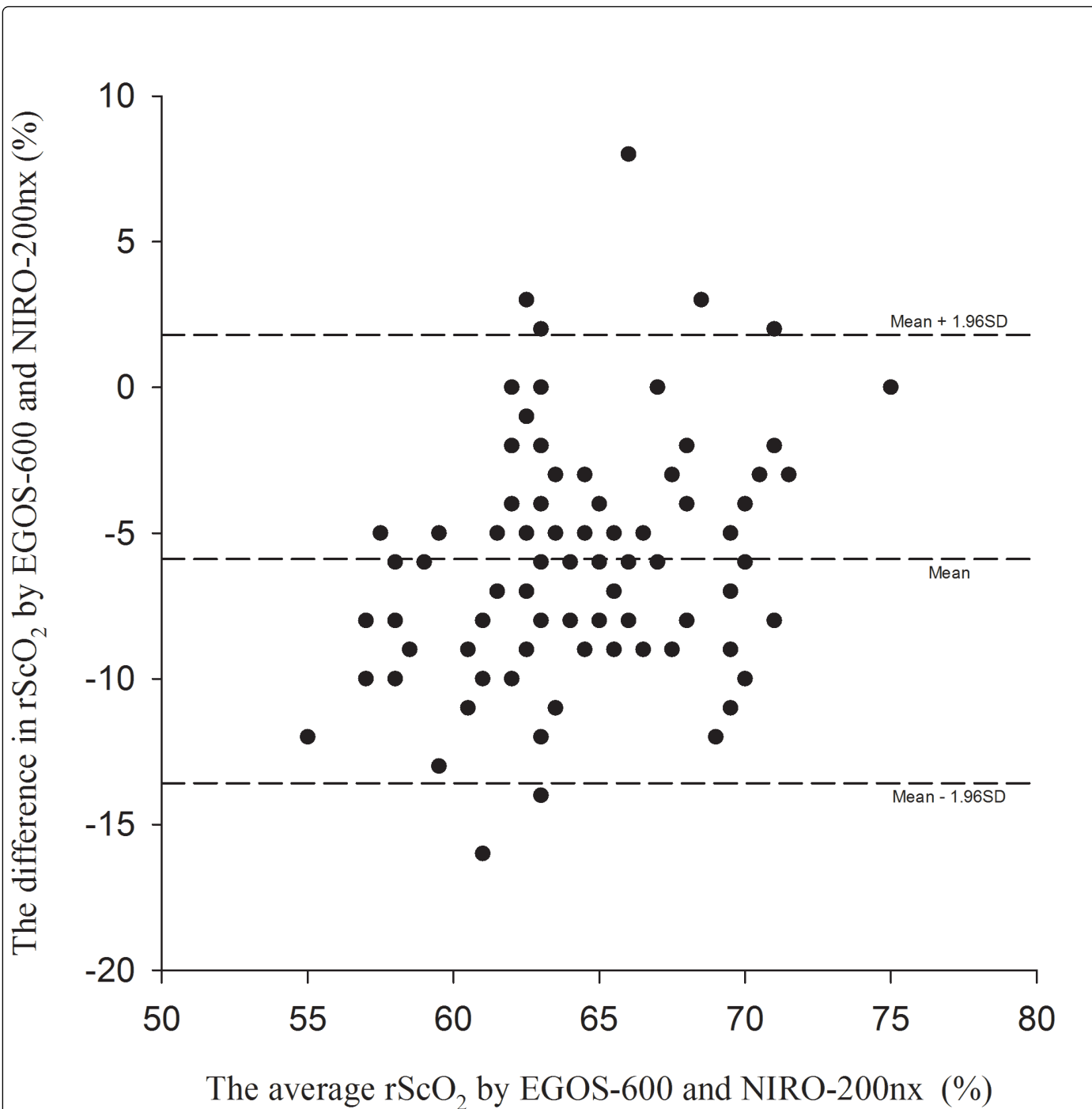


Figure 2: The agreement of NIRO-200nx and EGOS-600 to measure cerebral oxygen saturation in children early after cardiac surgery in the ICU.

Discussion

Our study validated EGOS-600 by comparing to NIRO-200nx in the laboratory and clinical settings. In both settings, EGOS-600 introduced a small underestimation of tissue oxygen saturation as compared to NIRO-200nx. In the laboratory test, the limits of agreement were relatively wide when SO₂ ranged from 100 to 20%, but became close in

the range of SO₂ from 40 to 80% mimicking clinical situations. A trend of overestimating SO₂ by EGOS-600 when average SO₂>50% and underestimating when <50% was observed. This trend disappeared in patients, and the biases were small and limits of agreement close between the values measured by the two devices in adults and children early after cardiac surgery.

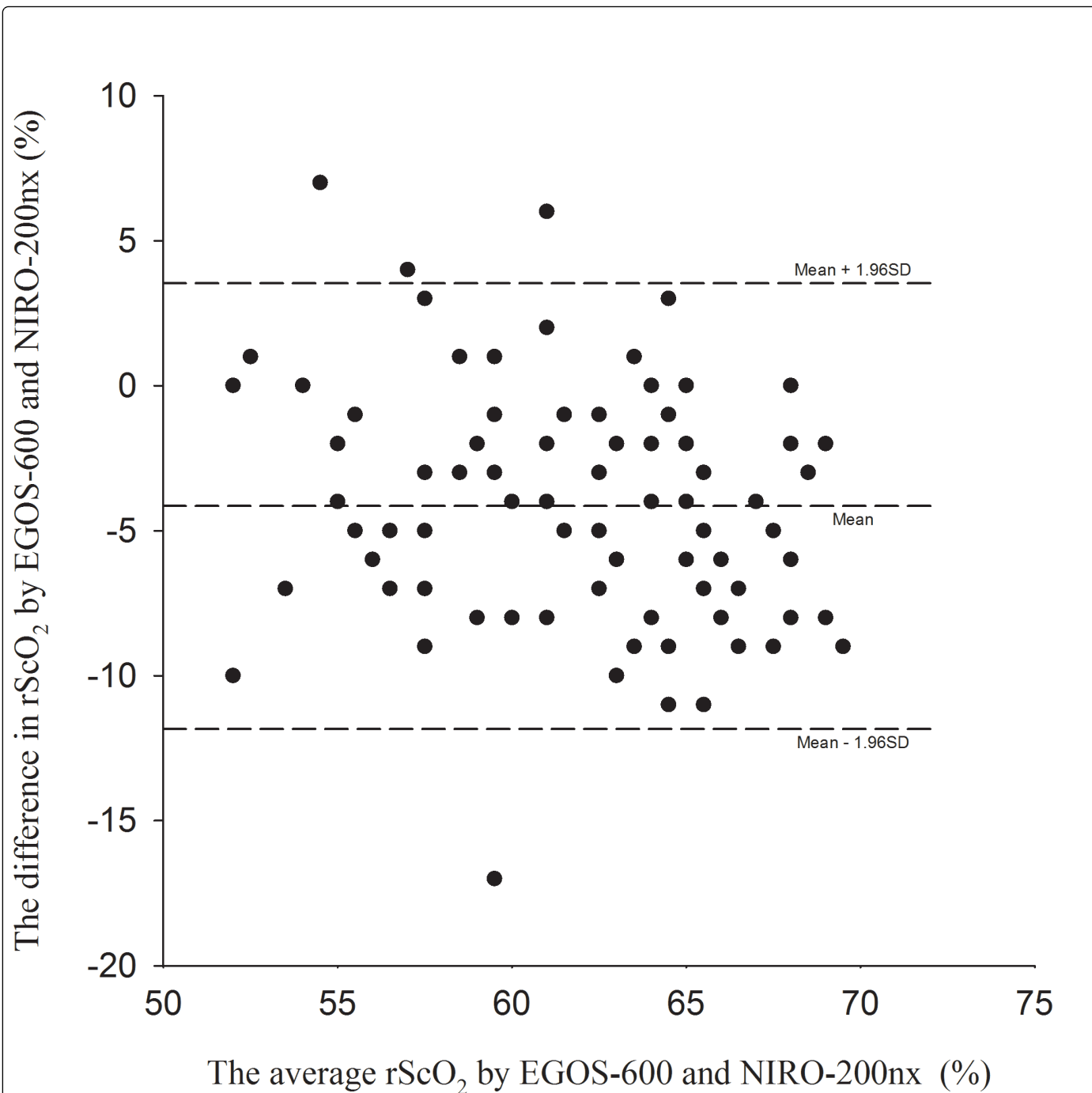


Figure 3: The agreement of NIRO-200nx and EGOS-600 to measure cerebral oxygen saturation in adults early after cardiac surgery in the ICU.

One strength of our study is that the validation consisted of two parts, that is, the laboratory test using a liquid tissue phantom, and the clinical test in children and adults after cardiac surgery. Validation of NIRS oximetry *in vivo* is difficult, as no standard reference exists. This difficulty may be overcome in a laboratory setting. EGOS-600 has been validated using liquid phantom consisting of human blood by comparing to the blood gas analysis as the standard reference [13]. *In vitro* test also has the advantage of controllable optical properties such as sensor positions, and the depth of measurement [15], and without

inter and intra-patients variations. In our laboratory test, liquid tissue phantom was made consisting of 40 ml of human whole blood to achieve optical absorbing characteristics that were close to human brain cortex in the near-infrared band. Stepwise decreases by about 10% in SO₂ were made from 100% to 20%, covering the range seen in human tissues. Each level of SO₂ was maintained steady using certain amount of sodium hydrosulfite. Our data showed that, within the full range of SO₂, there was a small bias of -2% between EGOS-600 and NIRO-200nx but a considerably wide limits of agreement of 20 to -24%.

Additionally, EGOS-600 introduced a trend of an overestimation when the mean measurement from the two oximeters was <50% and an underestimation when >50%. This might be due to some small difference in algorithm between the two oximeters that remains unknown. Nonetheless, when further analyze considered according the clinical range of SO₂, i.e., 40 to 80%, the limits of agreement was improved to be from 4 to-20%, despite a larger bias of-8%. It should be mentioned that there were only 5 pairs of measurements in the clinical range. A limitation when validating NIRS devices in a simple phantom is that the sensor geometry in relation to the multi-layered structure of the human tissue-skin, scalp, and skull are not emulated, although previous study [16] suggest that influence of surface layers is suppressed by spatially resolved spectroscopy. This limitation was at least partly compensated by adding the clinical part in our study.

In our clinical test, the trend of overestimation and underestimation shown in the laboratory test disappeared in both children and adults during the early period after cardiac surgery. The dispersed trend may be resulted from the heterogeneous conditions among patients as mentioned above that may potentially affect the optical properties. This is in contrast to the controlled homogeneous condition in the phantom model. Nonetheless, in consistency with the laboratory finding within the similar range of SO₂, there were close agreements in the clinical patients in both children and adults. In children, the bias was-5.9%, and the limits of agreements were 1.8 to-13.6%. In adults, the bias was-4.2% and the limits of agreements were 3.5 to-11.8%. Therefore, EGOS-600 is applicable in clinical settings in both children and adults.

Limitations

In the laboratory test, there was no blood gas analysis to obtain standard reference values to evaluate the two oximeters, due to the limited resources in the laboratory. Nonetheless, EGOS-600 had been compared with blood gas analysis and a close correlation as found [13]. NIRO series of oximeters have been used extensively [7,17-20]. Therefore, we consider the results of our validation are valid.

Conclusions

EGOS-600 introduces a small underestimation of rScO₂ when compared to NIRO-200nx, with acceptable limits of agreements. The new device is applicable in clinical settings in both children and adults.

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