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Original Article

Advanced Age and Sex Influence Baseline Regional Cerebral Oxygen Saturation as Measured by Near-Infrared Spectroscopy: Subanalysis of a Prospective Study

Cristina Bianca Robu, MD[*,2], Alexandre Koninckx, MD[*,2], Marie-Agnès Docquier, MD, PhD[*], Irina Grosu, MD[†], Laurent De Kerchove, MD, PhD[‡], Stefano Mastrobuoni, MD[‡], Mona Momeni, MD, PhD[*,1]

[*]*Department of Anesthesiology, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium*

[†]*Department of Anesthesiology, Clinique Sainte Elisabeth, Clinique de l'Europe, Brussels, Belgium*

[‡]*Department of Cardiac Surgery, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium*

Objectives: The aging brain shows decreased venous oxygenation predominantly in the frontal cortex, which seems sex- dependent. The authors hypothesized that age and sex would influence baseline regional cerebral oxygen saturation ($rScO_2$) measured by the INVOS 5100.

Design: Subanalysis of published data.

Setting: Tertiary hospital.

Participants: A total of 1,616 adults undergoing cardiac interventions.

Interventions: None.

Measurements and Main Results: Baseline $rScO_2$ was recorded at room air and calculated as mean of the left and right $rScO_2$. Patients were divided into 3 groups: 18- to- 49 years: young; 50- to- 74 years: middle-aged; and ≥75 years: elderly. The $rScO_2$ was significantly different in the middle-aged (63 [56-69]) compared with the young participants (67 [59-74]; $p < 0.001$) and elderly participants (60 [55-66]; $p < 0.001$]. Women were significantly older compared with men (72 [62-79] *v* 66 [56-74]; $p < 0.001$]) and showed lower hemoglobin values ($p < 0.001$) and lower $rScO_2$ (58 [52-63] *v* 65 [58-70]; $p < 0.001$]). Multiple regression analysis revealed age, sex, and hemoglobin as significant determinants of $rScO_2$: $26.665 - (0.030 \times \text{age}) + (2.581 \times \text{hemoglobin}) + (2.799 \times 0 \text{ for female sex})$.

Conclusions: Baseline $rScO_2$, as measured by the INVOS 5100, decreases with advanced age and is lower in women. New definitions of cerebral oxygen desaturation need to be analyzed in future trials that will evaluate neurologic outcome in the aging population or in women.

Key Words: cerebral oximetry; aging; near-infrared spectroscopy

THE CEREBRAL OXIMETER is a noninvasive monitoring device using near-infrared spectroscopy (NIRS) technology. It measures the ratio of oxyhemoglobin to total hemoglobin within the underlying tissue as an indirect estimation of frontal cerebral tissue oxygenation providing regional cerebral oxygen saturation ($rScO_2$). The cerebral oximeters measure mean oxygen saturation in venous, capillary, and arterial blood and

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[1]Address reprint requests to Mona Momeni, MD, PhD, Department of Anesthesiology, Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium, Avenue Hippocrate 10, 1200 Brussels, Belgium.

E-mail address: mona.momeni@uclouvain.be (M. Momeni).

[2]C. B. Robu and A. Koninckx contributed equally to the work.

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often deduce the relative concentrations of arterial versus venous blood in the measured area as being approximately 30:70.[1] Many studies in cardiac and noncardiac surgery have shown the usefulness of cerebral oximetry in the management of patients, as these devices reflect the balance between oxygen consumption and oxygen delivery to the brain. Nevertheless, based on the available meta-analyses and systematic reviews, there is no clear evidence that the use of cerebral oximetry improves the neurologic outcome of patients.[2-6]

With aging, the brain undergoes important structural and physiological changes. Studies in healthy participants have shown that cerebral blood flow significantly declines with age. This decline is most prominent in the prefrontal and frontal cortex.[7-10] Otherwise, it has been demonstrated that advanced age results in a consistent decline in the oxygenation of cerebral venous blood due to an increased oxygen extraction.[7,11,12] On the other hand, the cerebral metabolic rate of oxygen significantly decreases with age in all 4 lobes and on both sides.[13] Magnetic resonance imaging scans acquired in a large population-based study further showed that the changes in volumetric, microstructural, and focal markers are distinct in men and women.[9]

The authors hypothesized that these physiologic changes over the lifespan would manifest themselves in the regional cerebral oximetry reading, as the latter provides mainly venous oxygen saturation and is informative of the frontal regions. The authors therefore sought to analyze whether age, in addition to known factors that influence cerebral oximetry readings, can predict baseline $rScO_2$ values in a cohort of adult patients scheduled to undergo cardiac interventions. The authors further analyzed whether this relationship was influenced by sex.

Methods

This study was approved by Comité d'Ethique Hospitalo-Facultaire Saint-Luc-UCL, Brussels, Belgium (Chairperson Prof J.-M. Maloteaux) on November 25, 2013 (2013/07NOV/508 - B403201318880). The study was registered before patient enrollment by the principal investigator (M.M.) on December 4, 2013. This work was carried out in accordance with the Declaration of Helsinki for experiments involving humans. Written informed consent was obtained for all participants. This was a substudy of a prospective trial predicting postoperative delirium and postoperative cognitive decline, with combined intraoperative electroencephalogram monitoring and cerebral oximetry, in patients undergoing cardiac interventions.[14]

All adult patients undergoing cardiac surgery and cardiacinterventions with or without anesthesia were included in this study. Patients were enrolled consecutively from March 2014 until February 2017. Exclusion criteria for the initial study were preoperative sedation/intubation, clinical signs of delirium, patients who preoperatively could not perform the French version of the Mini Mental State Examination, and those patients in whom 6 months' follow-up was not feasible as requested for the initial protocol.

Intraoperative neuromonitoring consisted of the NeuroSENSE depth-of-anesthesia monitor providing bilateral frontal electroencephalogram and bilateral cerebral oximetry (INVOS 5100; Somanetics Corporation, Troy, MI). The oximetry electrodes were placed above the electroencephalogram electrodes at an approximate distance of 4 cm from the superciliary arch to avoid the frontal sinus.[15] Baseline $rScO_2$ values were recorded at room air before the induction of anesthesia. Whenever there was no possibility of placing the bilateral oximetry electrodes, 1 single electrode was used. Cerebral desaturation was defined as an area under the curve of 25% drop of oximetry values compared with the baseline (area under the curve $<_{25\%}$) for each hemisphere and presented as minutes%.

Patients only received a premedication whenever it was deemed necessary. An arterial line was inserted before the induction of anesthesia, after which a blood gas analysis was performed at room air. In patients in whom the cardiac condition or pathology did not necessitate invasive blood pressure monitoring before the induction of anesthesia, the arterial line was inserted after endotracheal intubation.

Statistical Analysis

The Kolmogorov-Smirnov test was used to check the normality of the data. Categorical data are presented as number and percentage. Continuous variables are presented as median (25th-75th percentile). Patients were divided into 3 different groups in function of their age (18-49 years: young, 50-74 years: middle-aged, ≥75 years: elderly). A Kruskal-Wallis test was used to compare continuous variables among the groups, followed by a Bonferroni post hoc analysis. A Mann-Whitney U test was used to compare a pair group of continuous variables in case of a significant Kruskal-Wallis test. The difference between 2 groups was significant at a level of 0.05 if the endpoint's p value was < 0.017. A Pearson chi-squared test was used to compare categorical variables among the 3 groups. The adjusted standardized residuals were used to compute the p value for individual chi-square test between 2 groups. The Bonferroni post hoc analysis was applied as well, and the difference between 2 groups was significant at level 0.05 if the endpoint's p value was < 0.017.

A multiple linear regression analysis, with the enter method, was used to explore the relationship among age, sex, and baseline $rScO_2$ adjusting for variables that might influence this association. The outcome variable, the baseline $rScO_2$, was calculated as the mean of the left and the right $rScO_2$ values. In the few patients in whom only 1 single oximetry electrode was used, that single $rScO_2$ value was considered as the outcome variable. The preoperative arterial oxygen tension and arterial carbon dioxide tension were included in the initial multiple linear regression analysis but subsequently removed, as the linearity assumption between the outcome variable and these predictors could not be proven. The independent variables included in the final multiple linear regression analysis were age, sex, and baseline hemoglobin concentration. Any pairwise cases were excluded as missing cases. Because this was a substudy of a large prospective trial, no power calculation was performed for the purposes of this subanalysis. Confidence intervals for median differences were calculated using Hodges-Lehmann estimates. The statistical analyses were performed using IBM SPSS Statistics version 25 and SAS version 9.4.

Results

The initial trial included 1,616 adult patients who were selected for the purposes of this subanalysis. Table 1 shows the characteristics of the entire cohort. Blood gas analysis before the induction of anesthesia was not available for 252 patients. Table 2 illustrates the characteristics of the participants as a function of their age. The median baseline $rScO_2$ was significantly higher in young participants compared with the middle-aged patients (67 [59-74] *v* 63 [56-69]; $p < 0.001$), and those of the middle-aged patients showed significantly higher values compared with the elderly participants (63 [56-69] *v* 60 [55-66]; $p < 0.001$). Figure 1 illustrates the boxplot for baseline right $rScO_2$ (only 1 side represented) as a function of the age group. As expected, median baseline hemoglobin levels were significantly higher in young patients (14.5 [13.4-15.6]) compared with middle-aged (14.0 [12.9-15.0]; $p <$ 0.001) and elderly patients (13.0 [11.9-14.1]; $p < 0.001$). This difference was no more statistically significant when the middle-aged and the elderly participants were compared (difference [95% CI]: 0.90 [0.70-1.10]).

The analysis of sex of the whole cohort revealed significant differences. Female patients were significantly older compared with men (72 [62-79] *v* 66 [56-74]; $p < 0.001$]). Median baseline hemoglobin was significantly lower in women (12.9 [11.8-13.8] *v* 14.3 [13.0-15.2]; $p < 0.001$). This difference also was observed for median baseline $rScO_2$, which was significantly lower in women compared with men (58 [52-63] *v* 65 [58-70]; $p < 0.001$), as illustrated in Table 3.

The multiple linear regression analysis was performed on 1,597 data and included the baseline mean $rScO_2$ as an outcome variable and age, sex, and baseline hemoglobin as predictors. There was a significant correlation between age and baseline $rScO_2$ ($r = -0.185$; $p < 0.001$), between baseline hemoglobin and baseline $rScO_2$ ($r = 0.537$; $p < 0.001$), and between sex and baseline $rScO_2$ ($r = 0.285$; $p < 0.001$). The model was statistically significant as follows F (3, 1593) = 234.162; $p < 0.001$. The adjusted R square was 0.305, indicating that 30.5% of the variations in baseline $rScO_2$ were explained by the predictors. The variance inflating factor was 1.112 for sex, 1.073 for age, and 1.165 for baseline hemoglobin, indicating that there was no collinearity among independent variables. The maximum Cook's distance was 0.021, excluding the presence of too many outliers. Figure 2 illustrates that the linearity assumption and the homoscedasticity assumption were valid. The histogram of residuals showed a mean value of 0 and a standard deviation of 0.999 (Fig 2, A). The normal probability−probability plot demonstrated that the values were close to the predicted line (Fig 2, B). The scatterplot of the standardized residuals and the standardized predicted values did not reveal a specific pattern (Fig 2, C). The multiple linear regression analysis revealed age, sex, and baseline hemoglobin as significant predictors of baseline $rScO_2$ (Table 4). The formula obtained to predict baseline $rScO_2$ was as follows: $26.665 - (0.030 \times \text{age in years}) + (2.581 \times \text{hemoglobin as g/dL}) + (2.799 \times 0$ for female sex and 1 in case of male sex).

Discussion

The results of this prospective study indicated that advanced age negatively influences baseline $rScO_2$. Baseline $rScO_2$ is otherwise influenced by sex, with women showing significantly lower values. These findings were observed when adjusted for preoperative hemoglobin value; that was correlated significantly with baseline $rScO_2$. This significant decrease of cerebral oximetry readings over lifespan are consistent with brain imaging results of studies evaluating physiologic changes of normal brain aging. Indeed, previous works in healthy participants have shown that cerebral blood flow declines with age, and this decline is significant in the prefrontal cortex and regions of the frontal lobe in front of the motor cortex.[7,8] Otherwise, venous oxygenation of the brain has been shown to decrease with age due to an increased oxygen

Table 1
Characteristics of the Entire Group (N = 1616)

Variables	
Age (y)	68 (58-76)
Sex male	1,141 (70.6%)
Weight (kg)	78 (67-89)
Arterial hypertension	1,099 (68.0%)
Diabetes mellitus	352 (21.8%)
Insulin-dependent diabetes mellitus	111 (6.9%)
Dyslipidemia	936 (57.9%)
Extracardiac arteriopathy	227 (14.0%)
History of cerebrovascular accident	146 (9.0%)
Right internal carotid artery stenosis (n = 1555)	187 (12.0%)
Left internal carotid artery stenosis (n = 1555)	185 (11.9%)
Interventional cardiology	45 (2.8%)
Redo surgery	197 (12.2%)
Premedication any	1,440 (89.1%)
Arterial oxygen saturation % (n = 1364)	95.5 (94.2-96.5)
Arterial partial pressure of oxygen (mmHg) (n = 1364)	82 (72-95)
Arterial partial pressure of carbon dioxide (mmHg) (n = 1364)	38 (36-41)
Baseline hemoglobin (g/dL)	13.8 (12.6-14.9)
Baseline creatinine (mg/dL)	0.96 (0.83-1.16)
Baseline glomerular filtration rate (mL/min/1.73 m^2)	73 (58-87)
EuroSCORE II (%)	2.3 (1.2-4.0)
Baseline left $rScO_2$	62 (55-68) min-max: 15-95
Baseline right $rScO_2$	63 (56-69) min-max: 17-94
Baseline mean $rScO_2$	63 (56-69) min-max: 16-95

NOTE. All continuous variables are expressed as median (25th-75th) or numbers (percentages).
Abbreviations: EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; max, maximum; min, minimum; $rScO_2$, regional cerebral oxygen saturation.

Table 2
Characteristics of the Participants in Function of the Age Group

Variables	18-49 (Young) n = 218 (%)	50-74 (Middle-Aged) n = 915 (%)	≥75 (Elderly) n = 483 (%)	Overall p	Young Versus Middle-Aged	Young Versus Elderly	Middle-Aged Versus Elderly
Sex male	167 (76.6)	694 (75.8)	280 (58.0)	<0.001	0.036	<0.001	<0.001
Arterial hypertension	58 (26.6)	651 (71.1)	390 (80.7)	<0.001	<0.001	<0.001	0.002
Diabetes mellitus	13 (6.0)	240 (26.2)	99 (20.5)	<0.001	<0.001	<0.001	0.424
Insulin-dependent diabetes mellitus	6 (2.8)	75 (8.2)	30 (6.2)	0.013	0.009	0.016	0.483
Dyslipidemia	49 (22.5)	582 (63.6)	305 (63.1)	<0.001	<0.001	<0.001	0.005
Extracardiac arteriopathy	0	127 (13.9)	100 (20.7)	<0.001	<0.001	<0.001	0.841
History of cerebrovascular accident	5 (2.3)	85 (9.3)	56 (11.6)	<0.001	<0.001	0.016	0.689
Right internal carotid artery stenosis (N = 1555)	0 (n = 201)	108 (N = 895) (12.1)	79 (N = 459) (17.2)	<0.001	< 0.001	<0.001	0.990
Left internal carotid artery stenosis (N = 1555)	1 (n = 201) (0.5)	108 (N = 895) (12.1)	76 (N = 459) (16.6)	<0.001	< 0.001	<0.001	0.764
Interventional cardiology	0	3 (0.3)	42 (8.7)	<0.001	0.007	<0.001	<0.001
Redo surgery	55 (25.2)	95 (10.4)	47 (9.7)	<0.001	0.012	<0.001	0.046
Premedication any	200 (91.7)	852 (93.1)	388 (80.3)	<0.001	0.271	<0.001	<0.001
Baseline mean $rScO_2$ (%)	67 (n = 215) (59-74)	63 (n = 904) (56-69)	60 (n = 478) (55-66)	<0.001	< 0.001 4* (3-6)	<0.001 7* (5-8)	<0.001 2* (2-3)
$rScO_2$ AUC < $_{25\%}$ left Min-Max	0 (n = 199) (0-2) 0-959	0 (n = 863) (0-2) 0-19915	0 (n = 462) (0-0) 0-691	0. 029	0.458 0* (0-0)	0.017 0* (0-0)	0.017 0* (0-0)
$rScO_2$ AUC < $_{25\%}$ right Min-Max	0 (n = 210) (0-2) 0-650	0 (n = 880) (0-3) 0-19105	0 (n = 460) (0, 0) 0-1173	0.002	0.999 0* (0-0)	0.011 0* (0-0)	<0.001 0* (0-0)
Arterial oxygen saturation (%)	96.2 (n = 147) (95.4-97.1)	95.4 (n = 786) (94.2-96.4)	95.5 (n = 431) (94.1-96.5)	<0.001	<0.001 0.30* (0-0.5)	<0.001 0.10* (−0.10 to 0.40)	0.968 −0.10* (−0.30 to 0.10)
Arterial partial pressure of oxygen (mmHg)	92 (n = 147) (80-112)	81 (n = 786) (72-94)	80 (n = 431) (71-92)	<0.001	<0.001 2* (−1 to 5)	<0.001 1* (−2 to 4)	0.245 −1* (−3 to 1)
Arterial partial pressure of carbon dioxide (mmHg)	38 (n = 147) (36-41)	39 (n = 786) (36-42)	38 (n = 431) (35-40)	0.002	0.916 0* (−1 to 1)	0.040 0* (−1 to 1)	<0.001 0* (0-1)
Baseline hemoglobin (g/L)	14.5 (13.4-15.6)	14.0 (12.9-15.0)	13.0 (11.9-14.1)	<0.001	<0.001 0.5* (0.30-0.80)	<0.001 1.5* (1.20−1.70)	<0.001 0.90* (0.70-1.10)
Baseline creatinine (mg/dL)	0.92 (0.80-1.03)	0.96 (0.82-1.14)	1.00 (0.85-1.28)	<0.001	0.001 −0.06* (−0.09 to −0.03)	<0.001 −0.11* (−0.15 to −0.07)	0.002 −0.05* (-0.08 to −0.02)
Baseline glomerular filtration rate (mL/min/1.73 m^2)	90 (78-104)	74 (61-87)	62 (50-77)	<0.001	<0.001 16* (13-19)	<0.001 27* (23-30)	<0.001 11* (8-13)
EuroSCORE II (%)	2.56 (0.94-3.70)	1.79 (0.97-3.37)	2.92 (1.86-5.46)	<0.001	0.053 0.22* (−0.02 to 0.56)	<0.001 −0.75* (−1.04 to −0.48)	<0.001 −0.99* (−1.21 to −0.81)

NOTE. All continuous variables are expressed as median (25th-75th percentile) or numbers (percentages).
Abbreviations: AUC, area under the curve; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; max, maximum; min, minimum; $rScO_2$: regional cerebral oxygen saturation.

* Difference (95% CI).

extraction. Lu et al. found that cerebral venous oxygenation decreased by 1.4% per decade from young adulthood.[7] Recently, the venous oxygen saturation of cerebral blood has been quantified by specific magnetic resonance imaging techniques.[12] These authors also found that the brain venous oxygenation significantly decreased with age. These physiologic changes may result in lower cerebral oximetry readings, as these monitors predominantly provide cerebral venous oxygen saturation of the frontal lobe. In addition to these findings, the Framingham Heart Study[10] and the Rotterdam Study,[9] 2 very large brain imaging studies, showed that with advanced age brain volumes decline. This decline was nevertheless more prominent and first observed in the frontal lobes. This frontal lobe volume decline therefore may affect $rScO_2$ directly. Indeed, the scalp-to-cortex distance, measured on magnetic resonance images as the distance from the surface of the scalp to the frontal cerebral cortex, is correlated negatively with $rScO_2$.[16-18] This distance can increase with frontal lobe atrophy. In case the scalp-to-cortex distance is greater than the depth of penetration of the light that is detected by the NIRS emitter-detector distance, lower $rScO_2$ values can be obtained.

Previous studies in cardiac[17] and noncardiac populations[19] have observed similar lower $rScO_2$ values in elderly patients, as observed in this study. This difference in cerebral oximetry values in function of age even was demonstrated during brain activation. Hock et al. showed that young volunteers (mean age 28 ± 4 years) performing calculation tasks showed a significantly higher increase in the local concentration of oxygenated hemoglobin measured by NIRS compared with elderly volunteers (mean age 52 ± 10 years).[20] Otherwise, in a large retrospective study in cardiac surgery patients that evaluated the influence of skin pigmentation on $rScO_2$, age was found to be associated negatively with baseline $rScO_2$.[21] The results of linear regression analysis in that study were very similar to the present study, with an unstandardized regression coefficient of −0.05 compared with a value of −0.03 in this study. The observations distinguished themselves from others' works in that in this study, the authors specifically analyzed whether age was a predictive factor of decreased $rScO_2$.

Cerebral oximetry, as measured by NIRS technology, is known to be influenced by various factors. Arterial oxygen saturation,[22,23] arterial carbon dioxide tension,[22,23] hemoglobin concentration,[16,17,19] mean arterial pressure,[24,25] cerebral blood volume, cerebral arteriovenous ratio,[22,26] skin- to-cortex distance,[16-18] and even extracranial contamination[27-29] are among the known physiologic and nonphysiologic confounders.[26]

This study was a subanalysis of a large prospective trial. In this regard, the authors were not able to take into account all the important physiologic variables that could have influenced baseline $rScO_2$. However, baseline hemoglobin, arterial oxygen tension, and arterial carbon dioxide tension, known as 3 main independent predictors of baseline $rScO_2$, were available for the purposes of this analysis. When arterial oxygen tension and arterial carbon dioxide tension were put in the linear regression analysis, the model was no more accurate. Therefore, baseline hemoglobin was chosen as an independent predictor of $rScO_2$ in addition to age and sex and shown to be associated significantly with $rScO_2$ value. This positive correlation between arterial hemoglobin concentrations and $rScO_2$ has been observed in other studies.[17,19,21,30] Low arterial hemoglobin concentration has been shown to induce an increase in the differential photon path length through tissue,[31] which by the Beer-Lambert law subsequently results in lower measurement of tissue oxygen saturation.[1,26,32]

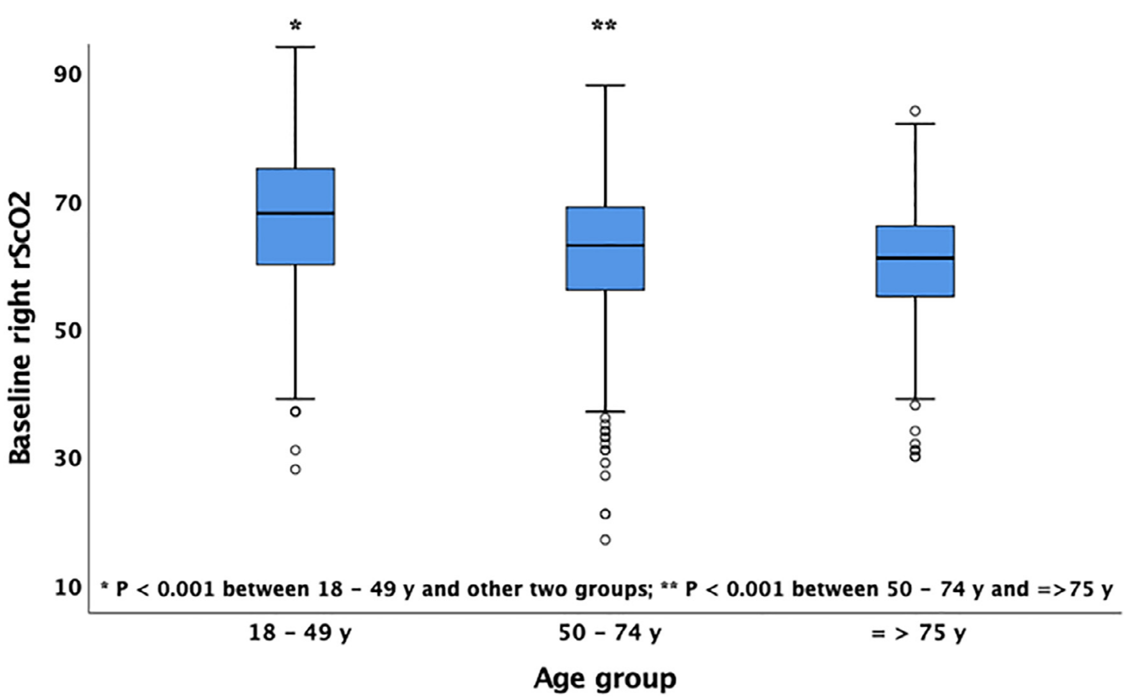

Fig 1. Boxplot representing baseline right regional cerebral oxygen saturation ($rScO_2$) for the 3 different age groups.

Table 3
Age, Baseline Hemoglobin, and $rScO_2$ in Function of Sex

Variables	Female (n = 475)	Male (n = 1141)	p*	Difference (95% CI)
Baseline mean $rScO_2$	58 (52-63)	65 (58-70)	<0.001	−7 (−8 to −6)
Baseline hemoglobin (g/dL)	12.9 (11.8-13.8)	14.3 (13.0-15.2)	<0.001	−1.30 (−1.50 to −1.20)
Age (y)	72 (62-79)	66 (56-74)	<0.001	5 (4-7)

NOTE. All continuous variables are expressed as median (25th-75th percentile).
Abbreviations: $rScO_2$, regional cerebral oxygen saturation.
* Mann -Whitney U test.

Interestingly, in this study there was a significant sex difference that, when adjusted for age and baseline hemoglobin concentration, revealed to be associated significantly with $rScO_2$. The authors observed significantly lower $rScO_2$ values in female patients. These lower values were inconsistent with the observations in a healthy aging population. Lu et al. found significantly higher brain venous oxygen saturation in women compared with men ($p = 0.0205$),[7] whereas Liu et al. could not find any sex differences.[12] However, a study in 111 patients undergoing elective neurosurgery found that after eliminating the confounding effect of hemoglobin, female patients presented significantly lower baseline $rScO_2$. Unfortunately, their results on linear regression analysis were not illustrated fully, making any comparison impossible.[33] The influence of sex on baseline $rScO_2$ also was observed in a large retrospective study in cardiac surgery patients.[21] In the latter study, the unstandardized regression coefficient for male sex was 2.57, which was very close to the 2.799 observed in this study. In another study evaluating the performance of 5 different cerebral oximeters in healthy volunteers, lower $rScO_2$ values were recorded in women across various spectrums of arterial saturations and with all oximeters except the FORE-SIGHT.[34] These findings cannot be explained with magnetic resonance imaging studies in which frontal lobar volumes were smaller in men compared with women.[10] Whether these differences were due to hormonal influences or any other factors need to be evaluated in future trials.

The results of this study may have important clinical implications when designing future trials that will evaluate the usefulness of cerebral oximetry in the prevention of neurologic complications. Indeed, this lower cerebral oxygen reserve, as estimated by cerebral oximetry, may put elderly patients at higher risk of neurologic complications in cases of intraoperative cerebral desaturations. Currently, it is accepted that a 20% decrement of $rScO_2$ compared with baseline values or any values of < 50% need to be treated.[35] The authors' findings provided support for trending values, at least within clearly defined circumstances. New definitions of cerebral oxygen desaturation need to be analyzed in future trials that will evaluate neurologic outcome in the aging population or women.

This study had some limitations. Baseline $rScO_2$ was measured in a population of patients who were scheduled to undergo cardiac interventions. The hemodynamic parameters and, very specifically, the central venous pressure in some of these patients, might have influenced the baseline cerebral oximetry readings. High central venous pressure by venous congestion may indeed result in low $rScO_2$ values. Moreover, many of these elderly patients had cardiovascular disease. Heringlake et al. demonstrated that minimal preoperative oxygen-supplemented $rScO_2$ correlates with short-term and long-term morbidity and mortality and reflects the severity of cardiopulmonary dysfunction.[36] It is therefore plausible that these lower $rScO_2$ values cannot be found in an aging population without any cardiovascular risk factors. However, the authors believe that the participants of this study, in contrast to the healthy aging population, were representative of those patients who require major surgery and who are at highest risk of neurologic complications such as postoperative delirium and postoperative cognitive decline. The authors a priori chose 3 categories of age, and some might argue that 50- to- 74 years is a wide

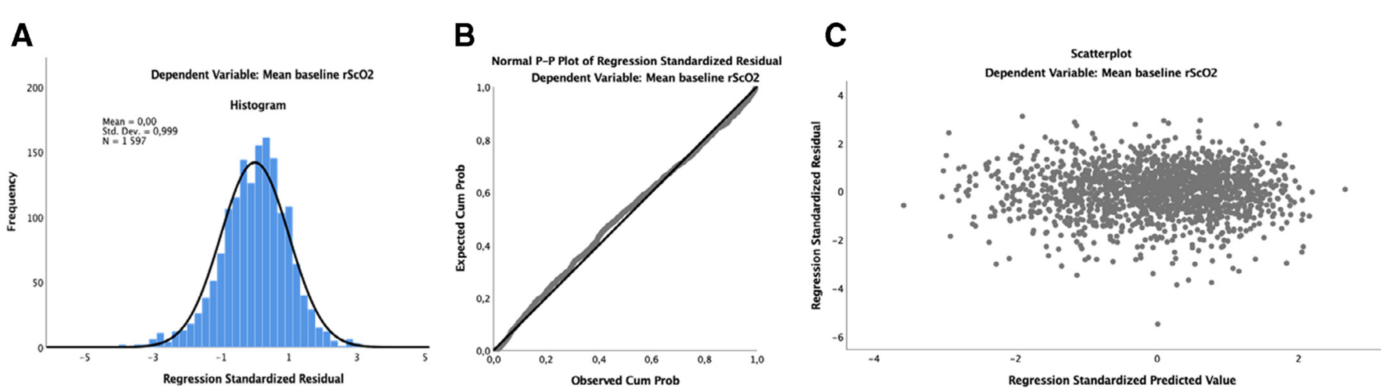

Fig 2. Linearity and homoscedasticity assumption of the multiple linear regression analysis. (A) Histogram of the residuals. (B) The normal probability−probability plot. (C) The scatterplot of the standardized residuals and the standardized predicted values. P-P, probability−probability; $rScO_2$, regional cerebral oxygen saturation.

Table 4
Results of the Multiple Linear Regression Analysis Predicting Baseline $rScO_2$

	Unstandardized Coefficients		95% CI for Beta	Standardized Coefficients Beta	t	p
	Beta	Standard Error				
Constant	26.665	2.041	22.662-30.669		13.063	<0.001
Sex (female = 0, male = 1)	2.799	0.482	1.853-3.744	0.128	5.808	<0.001
Age (y)	−0.030	0.015	−0.059 to −0.001	−0.044	−2.051	0.040
Baseline hemoglobin (g/dL)	2.581	0.120	2.346-2.815	0.486	21.588	<0.001

range as a definition of middle age. However, the authors did not wish to increase the number of categories to not complicate the analyses.

This study was performed with the INVOS 5100 oximeter. It is well established that different cerebral oximeters use various mathematical algorithms, different numbers of wavelengths of light emitted by the probe, and different depths of penetration of light to estimate cerebral oxygenation.[26,37] Baseline values and performance among different cerebral oximeters are not interchangeable.[38] Therefore, the results applied specifically to the INVOS monitor and need to be confirmed with different NIRS technologies. The scalp-to-cortex distance, which is an important variant in the $rScO_2$ reading and is difficult to measure without imaging technology, was not available for the purposes of this study and thus not taken into account in the multiple linear regression analysis. The scalp-to-cortex distance may vary substantially in different individuals and has been shown even to increase from the medial to lateral side of the scalp.[30] Therefore, the hypothesis that the physiologic brain changes solely affect the $rScO_2$ readings may not hold true. Lastly, most of the patients were white but very few patients had some skin pigmentation, which could have influenced the authors' observations slightly.

In summary, the results of this single-center, large prospective trial in cardiac patients illustrated that baseline $rScO_2$ significantly decreased with advanced age and was lower in female patients compared with male patients. Different $rScO_2$ thresholds for intervention need to be evaluated in future trials that aim to show the usefulness of cerebral oximeters in decreasing neurologic complications after cardiac surgery.

Conflict of Interest

Mona Momeni has received in the past speaker's fees from Medtronic. The other authors declare no conflicts of interest.

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