学位論文

「Cerebral oximetry for cardiac surgery: a preoperative comparison of device characteristics and pitfalls in interpretation

(心臓手術における脳局所酸素飽和度測定：機種別測定値の術前比較と虚血評価における留意事項)」

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

Cerebral oximetry for cardiac surgery: a preoperative comparison of device characteristics and pitfalls in interpretation

（心臓手術における脳局所酸素飽和度測定：機種別測定値の術前比較と虚血評価における留意事項）

はじめに：

近赤外線分光法(near-infrared spectroscopy; NIRS)を用いた脳局所酸素飽和度(regional cerebral oxygen saturation; rSO_2)の測定は、心臓外科周術期の脳虚血を検出して神経学的障害の発症を予防するために広く用いられている。今日では複数の測定機器が入手可能だが、測定原理が同じでも測定値の算出法アルゴリズムが異なるために機器間での値の違いを直接比較することはできない。この研究の目的は2種類のNIRS測定機器を用いて術前のrSO_2値を測定し、他の術前因子と合わせて前向きに比較解析することで、検出値の相違や変動に影響を及ぼす因子を明らかにすることであり、これによって症例の特性に合った適切な機器選択が可能になる。

方　法：

2017年1月から2017年8月までの間に行った成人心臓外科手術症例のうち、術前に頭部MRIを施行した80例を対象とした。異なる2つのNIRS測定機器としてINVOS 5100C (Medtronic, Minneapolis, MN, USA)とFORE-SIGHT ELITE (CAS Medical Systems, Branford, CT, USA)を使用した。それぞれの症例の術前rSO_2を各機種で測定してその測定値を”*I* value”、”*F* value”と定義し、各症例での測定値の比を”*F/I*”とした。また頭部MRIの矢状断画像で計測した頭皮大脳皮質間距離(scalp-cortex distance; SCD)、年齢、体表面積、各種検査値とrSO_2との関連を調べた。

結　果：

rSO_2測定値は*F* valueの方が*I* valueよりも有意に高値であった[*I* value: 57.3±8.5(%), *F* value: 68.8±4.5(%); ($p<0.0001$)]。また*F/I*比は1.22±0.23であり、長いSCD ($p<0.038$)、低ヘモグロビン濃度 ($p<0.0001$)、透析症例 ($p<0.0001$)が高い*F/I*比と有意に相関した。*F/I*比が0.85-1.25では同一症例の2機種での測定値が同等性を持つと考えられ、これを担保するカットオフ値はSCD<18.2mm、ヘモグロビン濃度>13.2g/dl、および非透析症例であった。

結　論：

心臓外科手術症例でのNIRS測定機器の臨床使用においては、術前の患者特性に応じた適切な機器を選択するべきであり、脳虚血の正しい評価のためには機器ごとのrSO_2値に影響を及ぼすような因子を考慮して、測定値の解釈を行うことが重要である。

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1. Introduction

Regional cerebral oximetry using near-infrared spectroscopy (NIRS) devices is commonly used for detecting cerebral ischemia during cardiopulmonary bypass (CPB). These easy-to-use, non-invasive, real-time detection devices could serve as early warning systems for intraoperative hemodynamic compromise or as predictors for postoperative cognitive dysfunction [1] and could be used with an aim to avoid poor cerebral perfusion due to inappropriate cannulation, low perfusion pressure, anemia, and other adverse events that may result in perioperative neurological impairment during CPB [2-5].

However, it is common to encounter cases of critically low regional cerebral oxygen saturation (rSO_2) during the induction of anesthesia, or low rSO_2 values unresponsive to any intervention.

A previous retrospective evaluation of 223 cases of adult cardiac surgery with preoperative brain magnetic resonance imaging (MRI) has revealed that brain atrophy, poor left ventricular function, anemia, and hemodialysis were associated with low initial cerebral rSO_2 values [6]

In this study, we prospectively evaluated differences in preoperative rSO_2 values and other preoperative characteristics between two NIRS devices, including the INVOS 5100C (Medtronic, Minneapolis, MN, USA) and the FORE-SIGHT ELITE (CAS Medical Systems, Branford, CT, USA).

2. Materials and methods

From January 2017 to August 2017, a total of 96 consecutive patients underwent elective cardiac surgery at Kitasato University Hospital. Patients without preoperative brain MRI; and

with a past medical history of acute cerebral infarction, previous intracranial hemorrhage or neurosurgery, off-pump coronary artery bypass surgery, and/or left ventricular assist devices were excluded. Finally, 80 patients were enrolled and analyzed in the study. In each patient, preoperative cerebral rSO_2 values were consecutively recorded with two different devices: the INVOS 5100C, defined as "I value", and the FORE-SIGHT ELITE, defined as "F value". This research was conducted with the approval of the ethics committee of our university (approval number: B16 - 96). All patients gave their informed consent prior to their inclusion in the study.

2-1. Cerebral rSO_2 monitoring

Under supine position, the arithmetic mean within 1 min at room air was recorded as cerebral rSO_2. Optodes of each device were placed on the patient's forehead, at 4 cm from the superciliary arch, to avoid the frontal sinus [7] (Figure 1).

2-2. Scalp-cortex distance (SCD)

All patients were evaluated for the presence of cerebrovascular disease by preoperative brain MRI. SCD was measured on a T1-weighted MRI image as the distance from the surface of the scalp on the upper forehead, at 4 cm from the superciliary arch, to the frontal cerebral cortex (Figure 1).

2-3. Data collection

Patient medical records were reviewed for preoperative clinical and demographic characteristics according to the hospital information system.

2-4. Data analysis

Continuous variables were presented as mean ± standard deviation. For each device, data were evaluated by univariate analysis to determine correlationss between rSO_2 values and each clinical variable. Multiple regression analysis by the least-squares method was performed on the data showing significant correlation coefficients in the univariate analysis. The ratio of rSO_2 values measured by each device for each patient was determined as the *F/I* ratio, and univariate and multivariate analyses were conducted in a similar manner to investigate the correlation between differences in the values according to device selection and preoperative characteristics. Furthermore, patient characteristics for which the measured values between the two devices were equivalent were obtained by receiver operating characteristic (ROC) analysis. On the basis of the similar concepts of bioequivalence for drugs [8], variables with an *F/I* value from 0.85 to 1.25 were assumed to be equivalent measured values between the two devices.

Differences with $p < 0.05$ were considered statistically significant. Statistical analyses were performed using JMP ver 12.0 (SAS Institute, Carey, NC, USA).

3. Results

3-1. Patients' characteristics (Table 1)

Patients' characteristics, including age, sex, body surface area, preoperative left ventricular ejection fraction (LVEF), SCD, hemoglobin concentration (Hb), total bilirubin (T-bil), preoperative hemodialysis (HD), and other comorbidities are listed in Table 1.

3-2. rSO_2 values

Mean cerebral rSO_2 was significantly higher in the "F value"; [I value: 57.3 ± 8.5 (%), F

value: 68.8 ± 4.5 (%); ($p < 0.0001$)] than in the "I value". *F/I* ratio was 1.22 ± 0.23 (Table 1).

3-3. Univariate analysis

Univariate analysis was performed with rSO_2 values and all characteristics measured by each device. In the "I value", SCD, LVEF, Hb, HD, hypertension, diabetes mellitus (DM), and dyslipidemia (DL) were correlated with measured values. In the "F value", HD and T-bil were correlated with the measured values. In the *F/I* value, SCD, LVEF, Hb, HD, DM, and DL were correlated with measured values (Table 2).

3-4. Multivariate analysis

Multiple regression analysis was performed using data that showed significant correlation coefficients in the univariate analysis. Results revealed that SCD, LVEF, and Hb remained significant factors in the "I value" and that HD remained a significant factor in the "F value". Further, SCD, Hb, and HD remained significant factors in the *F/I* value (Table 3) (Figure 2). HD cases were associated with 1.4-times higher *F/I* value than non-HD cases (HD: 1.60 ± 0.17, non-HD: 1.18 ± 0.18).

3-5. Evaluation of equality between devices

In multivariate analysis in which rSO_2 values measured by the two devices were equivalent (*F/I* = 0.85 - 1.25), cutoff values of SCD, Hb, and the presence or absence of HD were determined by ROC analysis. The area under the curve was 0.82 ($p < 0.001$). Cutoff values for equivalence were SCD < 18.2 mm, Hb > 13.2 g/dl, and non-HD cases (Figure 3).

4. Discussion

Perioperative central nervous system disorder in cardiac surgery is a prognostic factor [9]. Since Jöbsis et al. have reported their real-time, non-invasive monitoring method of tissue oxygen sufficiency using NIRS devices [10], clinical applications of such devices have expanded and there have been several reports on their use for the early detection of intraoperative cerebral ischemia or preoperative risk stratification [1,11,12]. Furthermore, the application of NIRS devices during cardiac surgery minimizes the risk of stroke and translates to the avoidance of prolonged ventilation, shorter ICU or hospital stay, and reduced medical cost [3,11,13-15]. Thus, the use of such devices can be recommended as an early warning system for ischemic event, which is one of the risks of cardiac surgery.

Most NIRS devices use a fixed reference ratio between the arterial and venous contribution to the signal, as 25/75 (%) or 30/70 (%), and measured values depend on consecutive changes in tissue oxygen consumption [16]. With the INVOS 5100C, the normal cerebral rSO_2 value is 67 ± 9% and values of <50 or >85 in adult patients undergoing cardiac surgery are considered statistically abnormal [17].

Many NIRS devices interpret the difference in near-infrared light absorption between oxyhemoglobin and deoxyhemoglobin using a modified Beer-Lambert method, which has been used for the calculation of NIRS measurements and includes optical path length in its formula as a constant. Therefore, changes in optical path length would cause a discrepancy between actual and measured rSO_2 values [18]. Furthermore, differences in the use of the wavelength of the spectrum and measuring algorithms among the devices result in variations in measured rSO_2 values.

In this research, measured rSO_2 levels were significantly higher for the "F value" than for the "I value". SCD, Hb, and the presence or absence of HD significantly correlated with the

F/I value. Furthermore, SCD, Hb, and LVEF affected rSO_2 levels of the "I value", and the presence or absence of HD affected rSO_2 levels of the "F value".

4-1. Effects of SCD

Near-infrared light passes through tissue, including bones. The skull bone or bone-dura interfaces directly under the optode, and to a lesser extent, the dura and the cerebrospinal fluid (CSF) layer have been reported to function as optical channels [19]. Reportedly, the thickness of the skull bone affects rSO_2 measurement [18,19]. Moreover, less near-infrared light returns to the detector in cases with thicker or large amount of CSF layer [18,20]. Therefore, an SCD that is greater than the distal sensing depth of the device can theoretically cause a low rSO_2 measurement. Also, the thickness of the CSF layer is included in the SCD. Furthermore, the distal sensing depth of each device, which is defined by optical path lengths and other device-oriented parameters, is approximately 20 mm for the INVOS 5100C and approximately 25 mm for the FORE-SIGHT ELITE. Thus, it is possible that the differences in distal sensing depth between the two devices widened their differential measurement due to increase in SCD.

4-2. Effects of hemoglobin concentration

Low Hb concentration increases the spaces between Hb molecules, which allow near-infrared light to travel a greater distance. Therefore, Hb concentration influences mean optical path lengths. A report wherein phase-resolved spectroscopy was used to emit near-infrared light with a modulated intensity and optical path length was measured from a phase shift has confirmed that optical path length increased as blood was diluted and as Hb concentration decreased during CPB [21]. However, as mentioned above, distal sensing depth

affected by optical pathway depth is approximately 20 mm for the INVOS 5100C and 25 mm for the FORE-SIGHT ELITE. These data suggest that in this study, low Hb concentration caused a lower rSO_2 level for the "I value" than for the "F value".

4-3. Effects of hemodialysis

It has been reported that patients on HD have lower cerebral blood flow in the frontal lobe than patients with the end-stage renal disease who are not on HD [22]. Thus, the presence or absence of HD could affect low rSO_2 values. Nevertheless, this study revealed increased cerebral blood flow in patients with the end-stage renal disease, including those not on HD, compared with healthy controls. However, the effect of hemodialysis remains ambiguous and requires further investigation.

4-4. Effects of left ventricular ejection fraction

Patients with reduced LVEF have insufficient oxygen delivery (DO_2) [23]. Therefore, compared to patients with the same preoperative resting oxygen consumption (VO_2), DO_2 in their venous blood is lower, which results in lower rSO_2 values. In this study, rSO_2 values of each device were calculated using the difference between near-infrared light absorptions of oxyhemoglobin and deoxyhemoglobin according to their spectrum range (INVOS 5100C; two wavelengths, FORE-SIGHT ELITE; five wavelengths). However, emitted light can be diffused, absorbed, or scattered, and not all photons return to the detector. Therefore, a fixed mean optical pathway length may indicate that calculated changes in oxyhemoglobin concentrations can result in over- or under-estimation of measured values, depending on the conditions. The advantage of the FORE-SIGHT ELITE that uses additional three wavelengths is that it is possible to compensate for these signal losses and to account for interference from

other factors, such as pigmentation [24]. Thus, we believe that the INVOS 5100C was affected by lower LVEF, which causes changes in oxyhemoglobin consumption under optodes.

4-5. Proposals

In cardiovascular surgeries, the risk of cerebral ischemia related to CPB is a matter of concern. Therefore, the early detection of desaturation is extremely important. Initially, as a first alert, the rSO_2 value indicator will turn yellow at <40% or at a 20% decline from the baseline value for the INVOS 5100C. These threshold values reflect the findings of previous studies [2,3,17]. In contrast, the FORE-SIGHT ELITE sets the first alert of rSO_2 value indicator at absolute value of <60% [25]. However, normal values are not clearly indicated.

From these findings, it is important to consider that rSO_2 can be lower in patients on HD and in patients with anemic, reduced left ventricular function, or brain atrophy. In this study, we demonstrated that an SCD of >18.2 mm and Hb concentration of <13.2 g/dl were associated with a higher *F/I* ratio. Moreover, HD cases were associated with a 1.4-times higher *F/I* ratio than non-HD cases. High *F/I* ratio indicates a measurement discrepancy between the two devices. Notable, there was approximately 10% difference between preoperative values of the two devices that serve as indicators of brain ischemia in patients undergoing cardiovascular surgery. Considering that the measured value of the FORE-SIGHT ELITE is defined as the "absolute value" [24] and that a critical decline from the initial values has not been clearly defined for this device, the alert should be set at a lower fluctuation level of <20% from the baseline value. In particular, inter-patient variations were greater in the INVOS 5100C than in the FORE-SIGHT ELITE, which were caused by variations in SCD, Hb, and LVEF. Thus, the INVOS 5100C can be considered to be more sensitive to changes in

Hb and LVEF, which are prone to occur during cardiovascular surgeries. Moreover, in case of patients with preoperative brain MRI, distal sensing depths should be considered when making appropriate device selections: patients with a short SCD should be subjected to measurements with the INVOS 5100C, whereas patients with a long SCD should be subjected to measurements with the FORE-SIGHT ELITE. Optimal criteria for device selection confirming the avoidance of "patient-device mismatch" may help the precise detection of peripheral cerebral ischemic changes.

4-6. Study limitations

One of the limitations of this study is that its analysis was conducted on data representing a small sample size of ≤ 100 subjects in a single-center design. As for equivalency, it cannot be denied that the findings are unique to this limited number of cases. Moreover, it is possible that the inter-group differences in values measured during cardiac surgery are different from those measured preoperatively due to changes in Hb concentrations and perfusion caused by hemodilution during CPB, thus, warranting further investigation.

5. Conclusion

We prospectively examined differences in preoperative rSO_2 values in adult cardiac surgeries measured using devices from two manufacturers and their correlations with various preoperative factors. rSO_2 values were significantly higher for the "F value" than for the "I value", and SCD, Hb, and the presence or absence of HD showed significant correlations with the *F/I* ratio and rSO_2 values. In clinical practice, an appropriate device should be selected according to preoperative patient characteristics, and factors influencing rSO_2 values should be taken into account to ensure the correct interpretation of measured values.

6. Compliance with ethical standards

Conflict of interest

The authors declare no conflict of interest.

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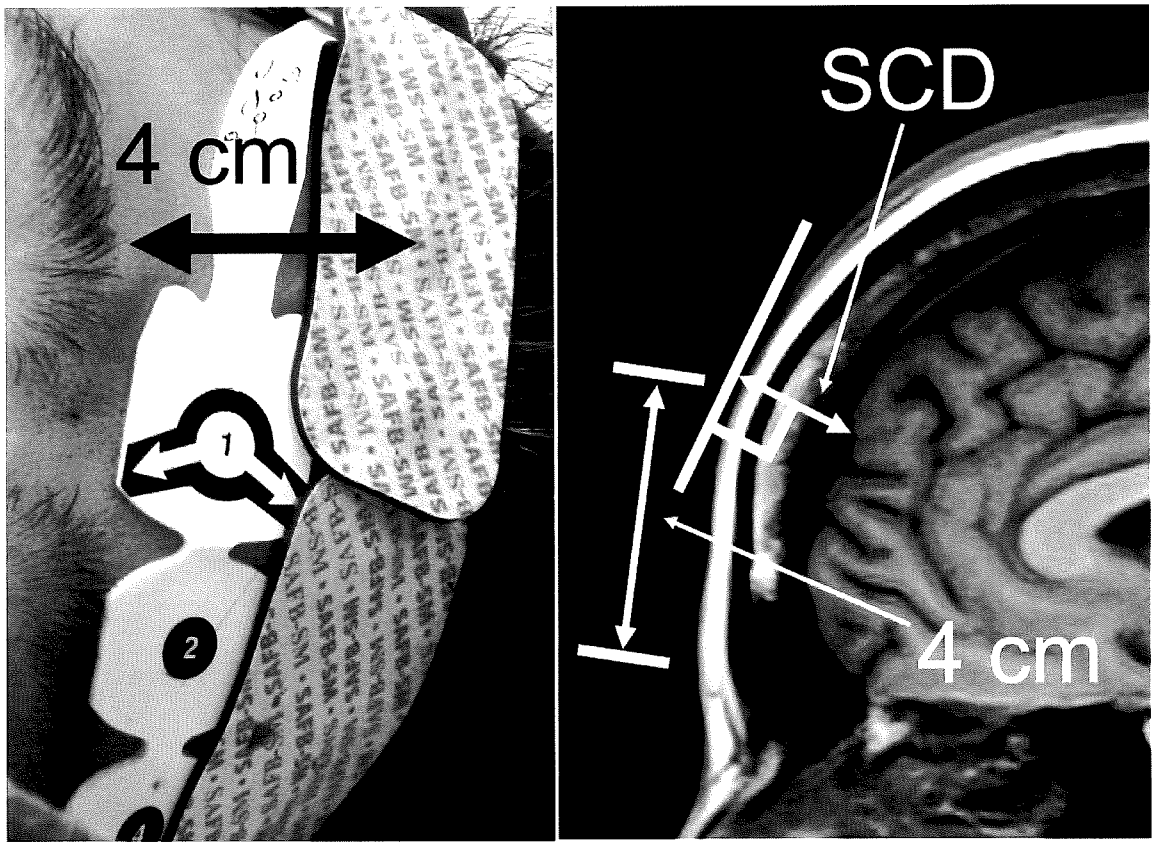
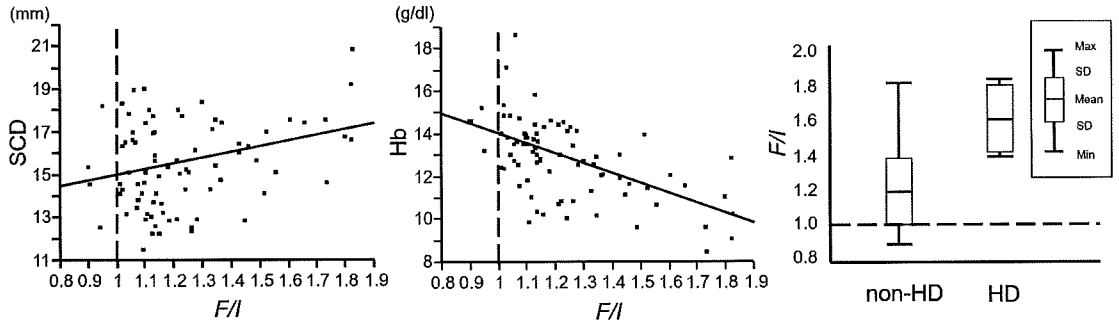
8. Figures

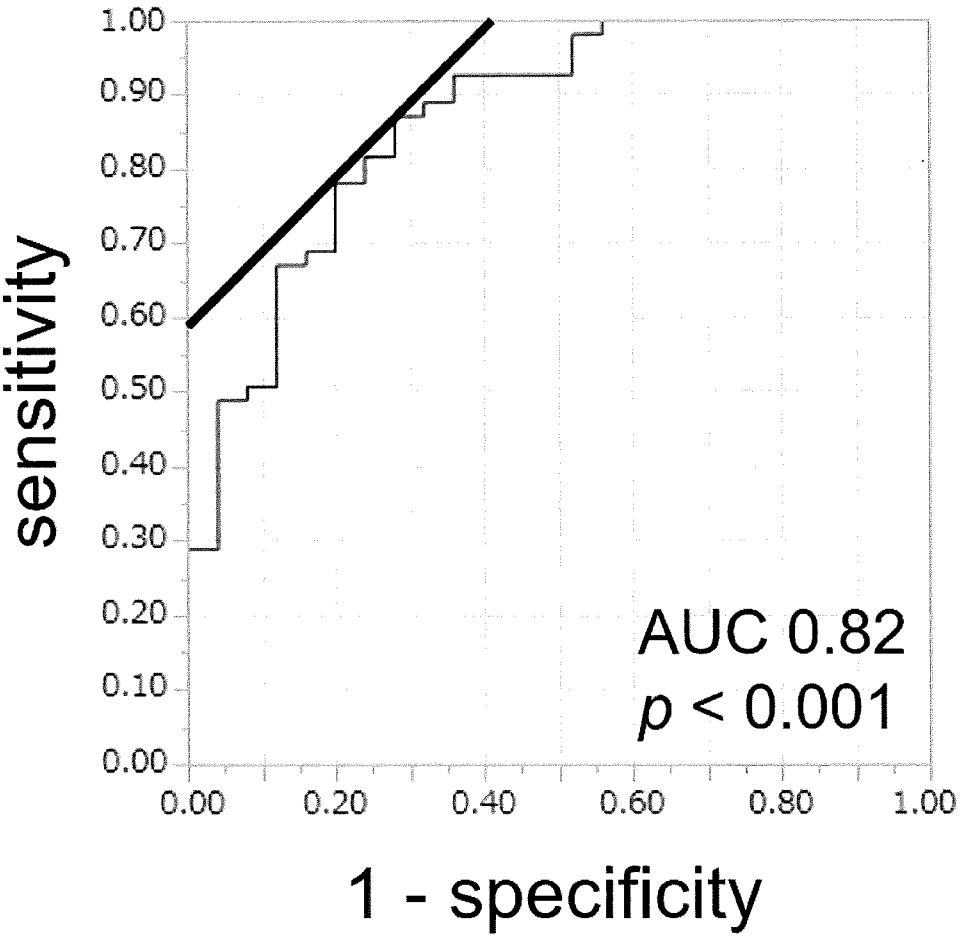
8-1. Figure 1. For optimal optode placement, the frontal sinus was avoided by affixing the optode on the forehead, 4 cm above the superciliary arch (i.e., the eyebrow). Scalp-cortex distance (SCD) was defined as the distance between the scalp surface and the frontal cerebral cortex in reference to a mid-sagittal plane of T1-weighted magnetic resonance image of the head.



8-2. Figure 2. In the *F/I* ratio, scalp-cortex distance (SCD), hemoglobin concentration (Hb), and the presence or absence of hemodialysis (HD) remained significant factors in multiple regression analysis. A higher *F/I* ratio indicates a measurement discrepancy between the two devices. The *F/I* ratio for the non-HD cases was 1.18 ± 0.18 and that for HD cases was 1.60 ± 0.17.



8-3. Figure 3. Results of receiver operating characteristic analysis for the evaluation of equality between devices are shown. Measured rSO_2 values of the two different devices were equivalent with the *F/I* value of 0.85 to 1.25. Area under the curve (AUC) was 0.82 ($p < 0.001$). Cutoff values for equivalence were a scalp-cortex distance of <18.2 mm, a hemoglobin concentration of >13.2 g/dl, and absence of hemodialysis.



9. Tables

9-1. Table 1. Patient characteristics and measured rSO_2 values.

Age (years)	67.7±13.8	
Sex (male)	49/80 (61.3%)	
Body surface area (m^2)	1.60±0.21	
LVEF (%)	60.1±13.5	
SCD (mm)	15.6±2.0	
Hb (g/dl)	13.0±1.8	
T-bil (mg/dl)	0.71±0.40	
Hemodialysis	10/80 (12.5%)	
Cerebral infarction	10/80 (12.5%)	
Hypertension	51/80 (63.8%)	
Diabetes mellitus	16/80 (20.0%)	
Dyslipidemia	33/80 (41.2%)	
Procedure		
CABG	15/80 (18.8%)	
Valve	38/80 (47.5%)	
Aortic	9/80 (11.3%)	
CABG+Valve	11/80 (13.8%)	
CABG+Aortic	2/80 (2.5%)	
Valve+Aortic	1/80 (1.3%)	
Miscellaneous	4/80 (5.0%)	
rSO_2 value (%)		
INVOS 5100C (*I* value)	57.3±8.5	$p<0.0001$ **
FORE-SIGHT ELITE (*F* value)	68.8±4.5	
F / I	1.22±0.23	

LVEF, left ventricular ejection fraction; SCD, scalp-cortex distance; Hb, hemoglobin concentration; T-bil, total bilirubin; CABG, coronary artery bypass grafting

**$p < 0.01$

9-2. Table 2. Association between each device's rSO_2 values and clinical factors.

	INVOS 5100C (*I* value)				FORE-SIGHT ELITE (*F* value)				*F / I*			
	r	*p*	95% CI		*r*	*p*	95% CI		*r*	*p*	95% CI	
Age	-0.191	0.091	-0.394	0.031	0.149	0.188	-0.073	0.357	0.181	0.069	-0.042	0.429
BSA	0.111	0.325	-0.111	0.323	-0.070	0.535	-0.286	0.152	-0.094	0.406	-0.308	0.128
LVEF	0.300	0.007 **	0.086	0.488	-0.138	0.222	-0.347	0.084	-0.288	0.010 **	-0.477	-0.073
SCD	-0.274	0.014 *	-0.466	-0.058	0.054	0.636	-0.168	0.270	0.301	0.007 **	0.088	0.489
Hb	0.574	<0.0001 **	0.405	0.705	-0.210	0.061	-0.411	0.010	-0.580	<0.0001 **	-0.709	-0.413
T-bil	-0.006	0.960	-0.225	0.214	-0.224	0.046 *	-0.423	-0.004	-0.066	0.564	-0.281	0.157
HD	-0.434	<0.0001 **	-0.597	-0.236	0.460	<0.0001 **	0.267	0.617	0.585	<0.0001 **	0.420	0.713
CI	-0.086	0.447	-0.300	0.136	-0.098	0.388	-0.311	0.125	0.057	0.617	-0.165	0.273
HT	-0.228	0.042 *	-0.427	-0.009	0.021	0.856	-0.200	0.239	0.208	0.064	-0.012	0.409
DM	-0.258	0.021 *	-0.452	-0.041	0.139	0.218	-0.083	0.348	0.306	0.006 **	0.092	0.492
DL	-0.291	0.009 **	-0.480	-0.077	0.069	0.543	-0.153	0.284	0.297	0.008 **	0.082	0.485

BSA, body surface area; LVEF, left ventricular ejection fraction; SCD, scalp-cortex distance; Hb, hemoglobin concentration; T-bil, total bilirubin; HD, hemodialysis; CI, cerebral infarction; HT, hypertension; DM, diabetes millitus; DL, dyslipidemia

$*p < 0.05$, $**p < 0.01$

9-3. Table 3. Multivariate analysis of relation between each device's rSO_2 values and clinical factors.

	INVOS 5100C (*I* value)					FORE-SIGHT ELITE (*F* value)					*F* / *I*				
	CO	95%CI		*p*		CO	95%CI		*p*		CO	95%CI		*p*	
SCD	-0.898	-1.685	-0.111	0.028	*	-	-	-	-		0.020	0.001	0.039	0.038	*
LVEF	0.120	0.012	0.229	0.033	*	-	-	-	-		-0.002	-0.005	0.000	0.087	
Hb	2.297	1.449	3.144	<0.0001	**	-	-	-	-		-0.054	-0.075	-0.034	<0.0001	**
HD	-4.727	-9.859	0.405	0.075		6.139	3.189	9.089	0.0001	**	0.259	0.136	0.382	<0.0001	**
HT	-0.172	-3.426	3.082	0.918		-	-	-	-		-	-	-	-	
DM	2.452	-1.782	6.686	0.260		-	-	-	-		-0.053	-0.155	0.049	0.311	
DL	-2.848	-6.404	0.708	0.121		-	-	-	-		0.078	-0.002	0.158	0.061	
T-bil	-	-	-	-		-1.002	-3.339	1.334	0.403		-	-	-	-	

SCD, scalp-cortex distance; LVEF, left ventricular ejection fraction; Hb, hemoglobin concentration; HD, hemodialysis; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; T-bil, total bilirubin

$*p < 0.05$, $**p < 0.01$