Relationship between Anesthetic Depth and Venous Oxygen Saturation during Cardiopulmonary Bypass

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ABSTRACT

Background: During cardiopulmonary bypass, mixed venous oxygen saturation (SvO_2) is frequently measured to assess circulatory adequacy. Fluctuations in SvO_2 not related to patient movement or inadequate oxygen delivery have been attributed clinically to increased cerebral oxygen consumption due to "light" anesthesia. To evaluate the relationship between anesthetic depth and SvO_2, we prospectively measured bispectral index (BIS) and SvO_2 values in patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods: Adults scheduled for cardiac surgery with cardiopulmonary bypass were recruited for this prospective observational study. During bypass, BIS and SvO_2 values were recorded every 5 min. To control for confounding effects of changes in other variables known to affect SvO_2, temperature, hematocrit, bypass pump flow, muscle relaxant use, and intravenous and inhaled anesthetic doses were also recorded. Only periods with limited variation in other variables affecting SvO_2 were analyzed. The relationship between BIS and SvO_2 was evaluated using mixed linear regression.

Results: One thousand thirty-four data points were obtained in 41 patients. No overall association between BIS and SvO_2 was observed, either in unadjusted analysis or adjusted for covariates. In data points with temperatures less than the median ($T < 34.1°C$), a significant association between BIS and SvO_2 was observed both in unadjusted ($\beta = -0.32$, $P = 0.01$) and adjusted ($\beta = -0.27$, $P = 0.04$) analyses.

Conclusions: In patients undergoing cardiopulmonary bypass, we found no overall association between BIS and SvO_2. A weak but statistically significant association between BIS and SvO_2 was observed in patients with temperatures less than $34.1°C$. These data suggest that low SvO_2 values on bypass are unlikely to be due to light or inadequate anesthesia. The relationship among temperature, BIS and SvO_2 deserves further study.

What We Already Know about This Topic

❖ Cardiac surgery caries a higher than normal risk for awareness
❖ During cardiopulmonary bypass, some clinicians consider lower than expected mixed venous oxygen saturation (SvO_2) to indicate possible awareness

What This Article Tells Us That Is New

❖ In more than 1,000 data points in 41 patients, there was no relationship between the bispectral index as a measure of anesthetic depth and SvO_2 during cardiopulmonary bypass, suggesting that SvO_2 is not a good measure of anesthetic depth

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DURING cardiopulmonary bypass, mixed venous oxygen saturation (SvO_2) is helpful for measuring circulatory adequacy. A decreased SvO_2 indicates inadequate oxygen delivery relative to oxygen consumption and suggests either that oxygen consumption has increased or that oxygen delivery has decreased.[1] In principle, during periods of cardiopulmonary bypass when oxygen delivery is constant and the anesthetized patient is at a constant temperature, SvO_2 should not change. However, SvO_2 values can vary in the absence of changes in temperature or oxygen delivery.

One explanation cited in cardiac anesthesia textbooks for changes in SvO_2 is a change in anesthetic depth.[2,3] Existing data demonstrate that decreased anesthetic depth increases cerebral metabolic rate and cerebral oxygen consumption.[4–6] Conversely, deeper levels of anesthesia decrease oxygen consumption.[7] Against a background of constant temperature, unchanged systemic oxygen delivery, and no patient movement, changes in SvO_2 may thus be potentially

explained by changes in anesthetic depth and cerebral oxygen consumption. Clinically, lower than expected SvO_2 values during bypass increase the possibility that the patients are aware under anesthesia and may lead clinicians to deepen anesthetic levels.[2,3]

Case reports of intraoperative awareness[8] demonstrate that anesthetic depth can be difficult to assess. Because patients with circulatory instability often do not tolerate normal anesthetic doses, the incidence of intraoperative awareness in patients having cardiac surgery $(1.1–1.5\%)$[9] may be almost 10-fold higher than that in patients undergoing noncardiac surgery.[10] One approach in reducing the risk of inadequate anesthetic depth is the use of brain function monitors such as the Bispectral Index (BIS®) monitor (Aspect Medical Systems, Needham, MA). Using a three-lead electroencephalograph/electromyograph electrode and a proprietary algorithm, the BIS® monitor processes the raw electroencephalogram to produce BIS values ranging from 0 to 100. Readings less than 40 designate a deep hypnotic state, values between 40 and 60 indicate adequate anesthetic depth, and the risk of awareness increases with values more than 65.[11]

To determine whether changes in anesthetic depth affect SvO_2 during cardiopulmonary bypass, we examined the relationship between anesthetic depth, as measured by the BIS® monitor, and SvO_2 in adult patients undergoing cardiopulmonary bypass. We hypothesized that if decreased anesthetic depth alters SvO_2, we would find a negative association between BIS and SvO_2 values.

Materials and Methods

Patients
This study was approved by the University of Chicago Institutional Review Board, Chicago, Illinois. Informed consent was obtained from all subjects. Enrollment was limited to patients aged 18 yr or older who were to undergo cardiopulmonary bypass as part of their procedure. Patients scheduled for deep hypothermic circulatory arrest and those unable to provide informed consent were excluded from the study.

Study Design
This was a single-center, prospective study conducted in patients undergoing cardiac surgery at the University of Chicago between July 2008 and April 2009. Preoperative data collection included patient age, gender, procedure, and presence of left ventricular dysfunction. Left ventricular dysfunction was assessed using the preoperative transthoracic echocardiogram (if available), or intraoperative transesophageal echocardiography, and defined as an ejection fraction less than 40% or less than 50% for patients with moderate or severe mitral regurgitation. Cumulative doses of intravenous anesthetic agents and muscle relaxants were recorded for each case. During cardiopulmonary bypass, SvO_2, inhaled anesthetic concentration, temperature, glucose, hematocrit, FIO_2, and bypass pump flow rate were recorded. BIS values, electroencephalomyographic activity, and signal

quality index (SQI) data were obtained from the BIS® monitor (Aspect Medical Systems). Postoperatively, in-hospital mortality data were obtained. Anesthesia providers, perfusionists, and surgeons were all aware of patients enrolled in the study. No support was provided by the manufacturers of the BIS® monitor, and they had no role in the study design, data collection, data analysis, or manuscript preparation.

Procedures
Before anesthetic induction, a BIS® Quatro Sensor (Aspect Medical Systems) was applied to the forehead of each patient. BIS, electromyographic, and SQI data were collected at 1-s intervals using the BIS® Vista monitor (Aspect Medical Systems) from induction of general anesthesia through the end of the procedure. All information obtained from the BIS® monitor was continuously downloaded to a computer for offline analysis.

During cardiopulmonary bypass, mixed venous oxygen saturation, hematocrit, and the partial pressure of oxygen in arterial blood were measured at 5-min intervals using the CDI blood parameter monitoring system (Terumo Cardiovascular Systems, Ann Arbor, MI). This device continuously sampled blood from both the venous and arterial lines of the cardiopulmonary bypass machine. During the same 5-min intervals, patient body temperature was recorded using an esophageal temperature probe, and mean arterial pressure was recorded using an invasive arterial blood pressure monitor. Vaporized agent concentrations were obtained from the inspired concentration on the vaporizer dial and were confirmed by measuring anesthetic concentrations in gas evacuated from the cardiopulmonary bypass pump scavenging system. Isoflurane was the inhaled anesthetic for all cases.

Statistics
To minimize the confounding effect on SvO_2 of factors unrelated to anesthetic depth, BIS and SvO_2 data were only evaluated during periods of stability. These periods were defined postcollection as sequential measurement times during which temperature varied by no more than 1°C; hematocrit by no more than 2% of the average value; and oxygen concentration, vaporized anesthetic concentration, cardiopulmonary bypass flow rate, and hematocrit remained constant. Patients typically experienced multiple periods of stability, which differed from each other with respect to one or more of these variables. Measurements from time points that did not meet the criteria for stability were excluded from analysis.

The association between the BIS values (scale 0–100) and SvO_2 (mmHg) during periods of stability was evaluated using mixed linear regression modeling, with BIS as the dependent variable and SvO_2 as the primary independent variable. All models incorporated correlation due to repeated measures during stability periods nested within patients by including patient as a random effect and specifying an autoregressive correlation structure for the repeated measures within stabil-

ity periods. First, the unadjusted association between BIS and SvO_2 was estimated. Then, multivariable models were fit to adjust for the variables used to define stability (temperature, oxygen concentration, anesthetic concentration, pump flow, and hematocrit) and other clinical and anesthetic variables (left ventricular function, intravenous anesthetic doses) that might confound the association between BIS and SvO_2. The potential impact of muscle activity and signal quality was also evaluated by adjusting for muscle relaxant dose, electromyogram activity, and SQI data. The variability in length of stable periods was incorporated into the analysis by including period duration as a covariate. Finally, sensitivity analyses were conducted to confirm that results within subgroups defined by period duration and by signal quality were consistent with results for the entire sample. BIS, SvO_2, and all other covariates were analyzed as continuous variables, with the exception of left ventricular function, which was dichotomized as normal or decreased. Indicator variables identified individual patients and stable periods within patients. Pooled means with 95% confidence intervals were estimated by fitting intercept-only mixed linear regression models with the covariance structure described in this paragraph and with the variable of interest as the dependent variable. Associations were considered significant if the Wald *P* value for the regression coefficient was ≤0.05. The main analysis was conducted using the Mixed procedure in SAS, version 9.1.3 (SAS Institute Inc., Cary, NC); graphics were produced and analyses for input to graphics were performed in Stata 11.0 (StataCorp, College Station, TX).

Results

Demographics

Forty-five patients were enrolled during a 10-month period from July 2008 to April 2009. Four of these patients could not be included in the analysis because of incomplete data. Of the remaining 41 patients, 27 were men, and the average age (±SD) was 63.9 ± 14.5 yr. In all cases, the anesthetic consisted of isoflurane supplemented with midazolam, fentanyl, and pancuronium. Propofol was used for induction in 10 patients, and etomidate was used in three patients. The average bypass time was 145 ± 49 min. Fifty-six percent of the patients had pre-bypass left ventricular dysfunction. The median temperature during bypass was 34.1°C (range, 31.8°–37.6°C). The mean difference between lowest and highest glucose levels was 55.2 ± 31 mg/dl, and the lowest recorded glucose level was 76 mg/dl. Twenty-two patients underwent valve replacement or repair or aortic repair procedures, eight patients had coronary artery bypass grafting, seven underwent combined valve repair or replacement and coronary artery bypass grafting, three had ventricular assist device placement, and one patient underwent inferior vena cava thrombectomy. Of the 41 patients, three died while in the hospital, yielding a 30-day mortality rate of 7.3%.
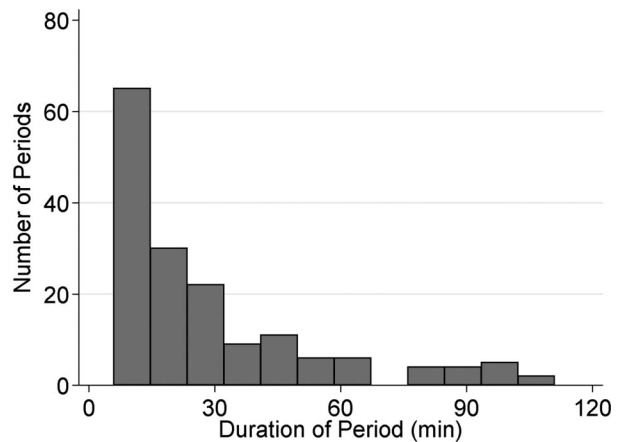

Fig. 1. Distribution of stable periods by duration in minutes.

Time Course of Measurements

For all patients, the mean (±SD) duration of measurement was 132.1 ± 42.8 min, with a range of 46 to 245 min. Initially, 1,088 time points were obtained. After removing 54 time points that occurred outside stable periods, 1,034 time points and 164 stable periods were included in the analysis. Unstable periods typically occurred at the beginning of the total sequence of measurements or during a shift between stability periods. The total number of measurements per patient ranged from 8 to 50 with a median of 24. Overall, patients experienced between two and eight periods of stability (mean 4, SD 1.6), with 28 (68%) experiencing two to four stable periods. Stable periods lasted from 6 to 111 min (mean = 28, median = 21) and included from 2 to 23 measurements (mean = 6.3, median = 4.5; fig. 1).

BIS® Monitor Data

BIS values were recorded for all patients in the study population. Associated SQI and electromyogram information were available in 882 (85%) of the 1,034 total data points. SQI was more than 75% in 828 (94%) data points, and electromyogram activity was less than 38 (1 bar on the BIS display) in 848 (96%) data points (overall mean electromyogram = 29 ± 5.2).

Association of BIS and Mixed Venous during Periods of Stability

As described earlier, the relationship between BIS and SvO_2 was examined only during periods of stability. Table 1 shows the mean, confidence interval, and range for BIS, SvO_2, and each of the variables used to define stability.

When the association between BIS and SvO_2 was modeled before or after adjustment for factors defining stable periods, no association between BIS and SvO_2 was observed (table 2, fig. 2). In the 83% of patients (n = 34) with SQI and electromyogram data, additional adjustment for SQI and electromyogram data yielded a regression coefficient of −0.004 (95% CI −0.12 to 0.11) for BIS and SvO_2. Similarly, incorporating pancuronium, fentanyl, and midazolam doses, and/or variability in stable period length also resulted in no association between BIS and SvO_2.

Table 1. Characteristics of Stable Periods: BIS, Mixed Venous, and Criteria for Stability

Variable	N	Mean*	95% CI*	Range (Min–Max)
BIS	1034	44.8	41.6–47.9	0–86
Svo_2, mmHg	1034	81.8	80.3–83.3	50–96
Temperature, °C	1034	34.8	34.5–35.1	28.7–37.6
Fio_2, %	1034	0.75	0.73–0.77	0.4–1.0
Vaporized anesthetic concentration, %	1034	0.58	0.45–0.70	0.0–3.0
CPB flow, L/min	1034	2.38	2.33–2.44	1.4–3.0
Hematocrit, %	1034	27.7	26.9–28.4	21–39

* Patient entered as a random effect, and autocorrelated (AR1) error structure specified for repeated measures during stability periods within patients. Models are based on 1,034 observations in 164 stable periods in 41 subjects.

BIS = bispectral index; CI = confidence interval; CPB = cardiopulmonary bypass; Fio_2 = fraction of inspired oxygen; Svo_2 = mixed venous oxygen saturation.

When the association between BIS and Svo_2 was adjusted for each covariate individually, we found that aside from anesthetic concentration, temperature varied significantly with BIS and markedly attenuated the regression coefficient relating BIS and Svo_2 (table 2). To better identify the effect of temperature on the relationship between BIS and Svo_2, we stratified our data into stable periods occurring above and below the median temperature in our dataset (34.1°C). When the 29 stable periods spanning the average temperature were removed, 135 periods remained, including 41 patients and containing 775 data points. In the subset of periods in which the temperature was less than 34.1°C (26 patients, 45 stable periods, and 371 data points), we found a weak but statistically significant association between BIS and Svo_2 ($\beta = -0.32$ with $P = 0.005$, CI −0.55 to −0.09),
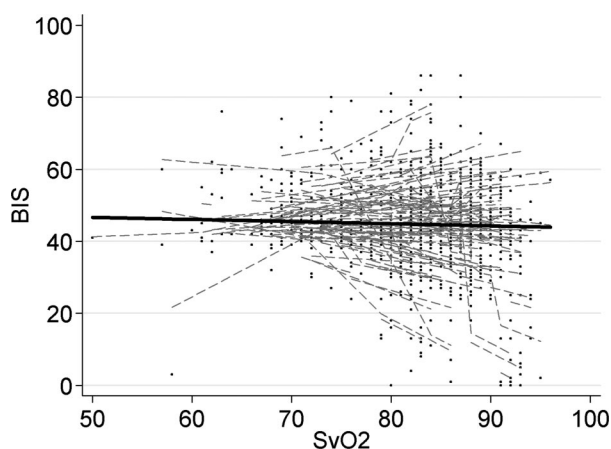
Fig. 2. Linear association between bispectral index (BIS) and mixed venous oxygen saturation (Svo_2). *Solid line* is fitted regression line (slope = −0.06, P = 0.24) from mixed linear regression of BIS on Svo_2, with patient as a random effect and autoregressive correlation structure among repeated measures during stability periods within patients. *Dashed lines* are fitted regression lines for individual stability periods, obtained as best linear unbiased predictors from a mixed linear regression model with random intercept and slope, which was used to illustrate between-period variability and yielded a similar estimate of the overall slope (−0.09, P = 0.25).

which remained after adjustment for all other covariates. The mean temperature in this group was 32.5°C. Clinically, this association would correspond to a 3.2 unit increase in BIS for every 10 unit decrease in Svo_2. No association between BIS and Svo_2 was observed during periods with temperatures more than 34.1°C.

As a covariate, left ventricular function was not significantly associated with BIS and did not modify the association between BIS and Svo_2. When our data were strat-

Table 2. Association between BIS* and Mixed Venous as Estimated Using Mixed Linear Regression Modeling*

Dependent Variable: BIS†	Regression Coefficient	95% CI	P Value	SD (Range) of Covariate
Models				
Unadjusted model				
Svo_2, mmHg	−0.06‡	(−0.16 to 0.04)	0.24	7.11 (50–96)
Multivariable model§				
Svo_2, mmHg	0.01‡	(−0.09 to 0.12)	0.79	7.11 (50–96)
Temperature, °C	1.25‡	(0.66 to 1.85)	<0.0001	1.79 (28.7–37.6)
Fio_2, %	1.22‖	(−0.04 to 2.48)	0.06	0.10 (0.4–1.0)
Vaporized anesthetic concentration, %	−5.92‡	(−8.33 to −3.51)	<0.0001	0.39 (0–3.0)
CPB flow, l/min	5.61‡	(−3.65 to 14.86)	0.24	0.19 (1.4–3.0)
Hematocrit, %	−0.16‡	(−0.51 to 0.19)	0.38	2.86 (21–39)
Muscle relaxant, mg · kg^{-1} · h^{-1}	0.18#	(−2.77 to 3.14)	0.90	0.01 (0.01–0.05)
Midazolam, mg · kg^{-1} · h^{-1}	2.99‖	(−22.0 to 28.0)	0.81	0.01 (0.005–0.06)
Time points in stable period, min	0.24‡	(0.05 to 0.43)	0.01	5 (2–23)

* Patient entered as a random effect, and autocorrelated (AR1) error structure specified for repeated measures during stability periods within patients. Models are based on 1,034 observations in 164 stable periods in 41 subjects.   † Bispectral index (BIS): range 0–86, standard deviation 12.72.   ‡ Change in BIS corresponding to a 1 unit change in covariate.   § In the 34 (83%) patients with signal quality index (SQI) and electromyograph measurements, additional adjustment for SQI and electromyograph yielded −0.004 (95% confidence interval [CI] −0.12 to 0.11) as the regression coefficient for mixed venous.   ‖ Change in BIS corresponding to a 0.1 unit change in covariate.   # Change in BIS corresponding to a 0.01 unit change in covariate.

CPB = cardiopulmonary bypass; Fio_2 = Fraction of inspired oxygen; Svo_2 = mixed venous oxygen saturation.

ified by normal or decreased left ventricular function (18 patients with normal left ventricular function and 25 with decreased left ventricular function), relationships between BIS and SvO_2 in both groups were similar to those in the entire sample.

Discussion

This study has two main findings. In our prospective study of adults undergoing cardiopulmonary bypass, we found no overall association between BIS and SvO_2 after adjusting for factors potentially affecting SvO_2 or oxygen delivery (hematocrit, temperature, inhaled and intravenous anesthetic concentrations, fentanyl dose, pancuronium dose, SQI, electromyogram activity, FiO_2, and cardiopulmonary bypass flow rate). In *post hoc* analysis, we found that during hypothermic periods (temperature $<$ 34.8°C), BIS and SvO_2 correlated significantly. This association remained significant after adjusting for all other stability factors either singly or in combination. However, the magnitude of this association was small, with an average 2 to 3 unit decrease in BIS corresponding to a 10 mmHg increase in SvO_2. The implication of our findings is that during stable cardiopulmonary bypass, low SvO_2 readings are unlikely to be due to light anesthesia.

In light of the multiple factors potentially affecting SvO_2 during cardiopulmonary bypass, the overall lack of association between BIS and SvO_2 is reasonable. Clinical texts suggest that low SvO_2 levels during cardiopulmonary bypass may be due to light or inadequate anesthesia and consequent increased cerebral oxygen consumption.[2,3] However, increases in skeletal muscle tone or visceral organ activity may also play significant roles in global oxygen consumption and affect SvO_2 values. Because brain metabolism accounts for only 20% of total body oxygen consumption, its effect on SvO_2 may be limited.[2] Although existing data show correlation between cerebral tissue oxygenation and central venous oxygen saturation in children,[12] it is unclear whether changes in cerebral oxygen consumption drive changes in SvO_2, or *vice versa*.[13]

The relationship between anesthetic depth and cerebral oxygen consumption may also be complicated by anesthetic effects on cerebral blood flow and oxygen extraction. In one of the studies in 1998, increasing doses of propofol decreased both cerebral blood flow velocity and cerebral oxygen extraction rate.[14] However, in another study of neurosurgical patients under both hypothermic and normothermic conditions, increasing propofol concentrations did not alter jugular venous bulb saturation.[15] Assessment of cerebral oxygen consumption itself may depend on the specific technique used.[16] Taken together, these data suggest that many factors may affect the ability to identify a relationship between anesthetic depth and cerebral oxygen consumption.

Cardiopulmonary bypass may also have altered the ability of the BIS® monitor to assess anesthetic depth accurately. Existing research does not clearly identify an effect of bypass on BIS readings, with some data suggesting increased variability in BIS readings during bypass[17] and others finding no effect.[18] In one small study,[19] patients undergoing hypothermic bypass had significantly lower BIS readings than those undergoing normothermic bypass. In light of these data, an effect of cardiopulmonary bypass on the association between BIS and SvO_2 cannot be ruled out.

Our second finding, that stratifying our data by temperature exposed a weak but statistically significant negative correlation between BIS and SvO_2 under hypothermic conditions, deserves mention. One explanation for finding a significant association in hypothermic patients is that lower temperatures may reduce the contribution of other tissues to total oxygen consumption, increasing the impact of changes in brain metabolism due to changes in anesthetic depth. The implication of this finding is the same. Under normothermic conditions, high SvO_2 levels are not associated with light anesthesia. Even under hypothermic conditions in which an association between SvO_2 and BIS does exist, the regression coefficient of -0.32 suggests that a 10 mmHg change in SvO_2 would result, on average, in only a 3 unit change in BIS. This association is unlikely to be clinically relevant.

Our study had clear limitations. None of the anesthesia providers, perfusionists, and surgeons were blinded. However, we believe it unlikely that bias due to blinding would have contributed to incorrect data analysis as treatment decisions were based on absolute SvO_2 values and BIS monitoring was not used for clinical decision-making while on bypass. In addition, although we used a standard anesthetic regimen for all cases (isoflurane, midazolam, fentanyl, and pancuronuim), we did not protocolize the use of inhaled or intravenous agents. In particular, variation in pancuronium use may have contaminated BIS readings with high-frequency electromyogram activity or confounded our results with differences in muscle oxygen consumption. Nevertheless, incorporating midazolam, pancuronium, electromyogram, and SQI data as covariates in our model did not alter our findings. Although creation of "stable" periods within individuals allows evaluation of the relationship between BIS and SvO_2 holding other influential factors constant, this preprocessing of the data represents a potential source of bias that has unknown implications for the estimation of the coefficients. Because our study was conducted at a single center, subtleties in our management of cardiopulmonary bypass may prevent the generalizability of our results. Finally, we did not do a formal power analysis before performing our study because no prior data existed to allow us to estimate the likely correlation between BIS and SvO_2. As such, because we studied only 41 patients, our study should be considered hypothesis generating only. Nevertheless, the size of our regression coefficient (-0.06) and narrowness of the confidence intervals ($-0.16-0.04$) in our model strongly suggest that a clinically significant association between BIS and SvO_2 is unlikely (table 2).

In summary, we found that in adult patients undergoing cardiopulmonary bypass, SvO_2 did not correlate with BIS readings in unadjusted analysis or after adjusting for changes

in temperature, hematocrit, inspired oxygen fraction, inhaled and intravenous anesthetic concentrations, SQI, electromyogram, and cardiopulmonary bypass flow. Our findings indicate that overall, a low Sv_{O_2} during bypass is unlikely to be due to light or inadequate anesthesia. We did observe a statistically significant association in a hypothermic subset of patients. However, the small size of the regression coefficient in that subset implies that even under hypothermic conditions, clinical manipulation of anesthetic depth is unlikely to exert a large impact on Sv_{O_2}. Further work may shed more light on the effect of temperature on the relationship between BIS and Sv_{O_2}.

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