Advances in diagnosis and treatment of cerebral arterial gas embolism
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Detection of cerebral arterial gas embolism using regional cerebral oxygen saturation, quantitative electroencephalography, and brain oxygen tension in the swine

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submitted for publication
**Abstract**

**Introduction**: Cerebral air emboli are a contributing factor in the development of neurological injury during cardiac surgery. Although peroperative cerebral monitoring is increasingly used to detect insults to the brain during high-risk procedures, the ability of these methods to detect cerebral air emboli is not known. This study investigates the utility of processed electroencephalography (EEG) and near-infrared spectroscopy derived regional cerebral oxygen saturation (rSO$_2$) in the detection of various volumes of intracerebrovascular air. Results were compared to invasively measured brain oxygen tension (PbtO$_2$) and brain lactate and glycerol.

**Methods**: In 12 pigs a catheter was placed in one of the main arteries feeding the brain. Probes were placed to perform microdialysis and to measure rSO$_2$ and PbtO$_2$. An eight channel EEG was recorded and the quantitative parameter temporal brain symmetry index (tBSI) was calculated. Doses of 0.2, 0.4, 0.8, and 1.6 ml of air were injected into the cerebral arterial vasculature.

**Results**: rSO$_2$ and tBSI were both able to detect the effects of air emboli on the brain almost instantaneously, but were less sensitive than PbtO$_2$. There was reasonable correlation between rSO$_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol.

**Conclusions**: Our results show that regionally measured rSO$_2$ and processed EEG can detect the local effects of air emboli on cerebral oxygenation, but with reduced sensitivity as compared to intraparenchymal PbtO$_2$. Prospective human studies using multimodal monitoring incorporating EEG and rSO$_2$ should be performed.
Introduction

Cerebral injury is one of the most devastating complications of cardiac surgery. Approximately 3% of patients undergoing cardiac surgery suffers stroke, while 20-40% develops long-lasting postoperative neurocognitive deficits (1, 2). Cerebral damage due to cardiac surgery is a multifactorial process, in which embolization of solid and gaseous material is a relevant contributing factor (3). Air emboli can arise during cardiac surgery from various sources, for instance due to inadequate de-airing of the cardiac chambers or during cardiopulmonary bypass. Furthermore, cerebral air emboli can occur in other types of surgery, usually after introduction of air in systemic veins and subsequent arterialization through a patent foramen ovale (paradoxical embolism).

In an effort to decrease the number of surgical cerebral complications, there is an increasing tendency to monitor brain function during high-risk procedures, especially in cardiac surgery (4). Two commonly used non-invasive methods for brain monitoring are electroencephalography (EEG) and regional cerebral oximetry (rSO$_2$) using near-infrared spectroscopy (NIRS). However, the sensitivity of these methods to detect air embolism has never been investigated, and therefore, these techniques are currently not used to detect embolic insults to the brain (5).

In the present study, we use an established porcine model of cerebral arterial gas embolism (6, 7) to test the hypothesis that rSO$_2$ and EEG can detect air embolization. As secondary aim we compared these non-invasive cerebral monitoring methods with invasive intracerebral measurements. We injected increasing amounts of air into the cerebral arterial vasculature and continuously measured rSO$_2$, EEG, intraparenchymal brain oxygen tension (PbtO$_2$), as well as lactate and glycerol concentrations derived from intracerebral microdialysis catheters.
Methods

General handling and surgical preparation
After approval of the animal ethics committee of the Academic Medical Center, Amsterdam, The Netherlands and in accordance with European Community guidelines, 12 female Landrace pigs weighing on average 49 kg (SD 2.1 kg) were used for this study. Animals were premedicated with intramuscular ketamine 15 mg/kg (Eurovet Animal Health, Bladel, The Netherlands), midazolam 2 mg/kg (Actavis, Hafnarfjordur, Iceland) and atropine sulfate 0.01 mg/kg (Pharmachemie, Haarlem, The Netherlands), followed by tracheal intubation and volume controlled ventilation with an inspiratory oxygen fraction of 0.4, positive end-expiratory pressure of 4 mm Hg, frequency of 18/min, and tidal volume adjusted to maintain end-tidal carbon dioxide of 38-42 mm Hg. Anaesthesia was continued with ketamine 10-15 mg/kg/h, sufentanil 5-10 µg/kg/h (Hameln Pharmaceuticals, Hameln, Germany), midazolam 1.5 mg/kg/h, and pancuronium bromide 0.15 mg/kg/h (Organon, Oss, The Netherlands). A single bolus of 2 g ceftiraxone (Fresenius Kabi, Zeist, The Netherlands) was given as antibiotic prophylaxis. Glucose was continuously administered through a catheter in the right cephalic vein at a rate of 170-300 mg/min, targeted to maintain normoglycaemia (4-8 mmol/l) as measured in arterial blood every 30 min. Further preparation was as described earlier (7) and included invasive blood pressure measurement, a urinary catheter, temperature management to maintain normothermia, and placement of an Ascent Occlusion Balloon catheter (Johnson & Johnson, New Brunswick, NJ) in the right ascending pharyngeal artery. The ascending pharyngeal arteries are the primary feeding arteries of the porcine brain, feeding the bilateral internal carotid arteries through the rete mirabile (8). The balloon catheter allows for selective introduction of air into the ascending pharyngeal artery, while preventing backflow of air into the external carotid vasculature.

Cerebral probes and electrodes
In the prone position, a midsagittal incision was made over the cranium,
after which two burr holes were created in the skull (figure 1). Both burr holes were positioned 1 cm in front of the crossing of the coronal and sagittal sutures, with one burr hole 1 cm to the left and the other 1 cm to the right of the sagittal suture. After piercing of the dura, in each burr hole a Licox PbO₂ probe (Integra, Plainsboro, NJ) and a microdialysis catheter (Carnegie Medicine AB, Solna, Sweden) were advanced approximately 1 cm into the brain parenchyma. An intracranial pressure (ICP) sensor (Codman, Raynham, MA) was advanced 2 cm into the brain through the left burr hole and a brain temperature probe (Integra) was advanced 2 cm into the brain through the right burr hole.
The temperature probe was needed to correct PbtO$_2$ for the actual brain temperature. The microdialysis probes were continuously flushed with artificial cerebrospinal fluid (Carnegie Medicine AB) at a rate of 1 µl/min. After careful hemostasis the probes were fixed in the burr holes using bone wax. Investigations by other researchers (9) as well as preliminary experiments performed in our own laboratory showed that in pigs of the size used in our experiments, rSO$_2$ obtained with transeutaneous measurement (as done in humans) is largely influenced by skin instead of cerebral oxygenation. Although this phenomenon has also been described in humans (10), the effect is larger in pigs, probably due to the thicker skin and skull. We avoided this problem by placing the sensors subcutaneously. At the posterior end of the midsagittal skin incision a transversal incision was created, after which two Adult SomaSensor rSO$_2$ probes (Covidien plc, Dublin, Ireland) were subcutaneously. Before tunneling, part of the adhesive portion of the sensors was cut away to fit the probes into the tunnel, taking care not to damage the electrical structure of the sensors. The orientation of the rSO$_2$ sensors was dorsal-ventral and the center of the sensors was positioned over the burr holes (figure 1). After careful hemostasis, the skin incisions were closed to prevent ambient light contamination. Nine needle electrodes (Ives EEG Solutions, Newburyport, MA) were placed in the skin as described earlier (7), to measure EEG.

**Data acquisition**

General parameters (heart rate, blood pressure, end-tidal carbon dioxide, body temperature, ICP, blood glucose) were recorded at 30 min intervals. Blood gas analysis for pH, arterial oxygen tension, and arterial carbon dioxide tension was performed hourly. rSO$_2$ was continuously displayed on and stored in an INVOS 5100C monitor (Covidien) for offline analysis. PbtO$_2$ was extracted from the Licox monitors (Integra) through a NI USB-609 data acquisition device (National Instruments Corporation, Austin, TX) and stored for offline analysis. The eight-channel EEG signal was continuously stored for offline analysis. Temporal brain symmetry index (tBSI) was calculated over each 10 s of EEG data
as described earlier (7). In brief, the tBSI calculates spectral changes in EEG by comparing the current EEG with a defined normal baseline. It is a normalized parameter within the range [0-1]. A higher tBSI value represents a larger deviation from the baseline EEG (11). For final data presentation one value of rSO$_2$, PbtO$_2$, and tBSI was calculated for every 30 s of data. The vials containing the effluent of the microdialysis probes were changed every 15 min. Microdialysate was analyzed for glucose, lactate, and glycerol using a CMA 600 analyzer (Carnegie Medicine AB). Values were corrected for their in vitro recovery rates as determined in previous experiments (8). Before start of the embolizations, a 10 min increase in inspiratory oxygen fraction to 1.0 was performed to check correct placement of the sensors. If bilateral PbtO$_2$ did not increase at least 10 mm Hg or bilateral absolute rSO$_2$ did not increase at least 5%, the sensors were carefully repositioned until the required conditions were met.

**Experimental protocol**

Preliminary experiments (not published) showed that injection of 0.5 ml air generally results in detectable changes in EEG and PbtO$_2$. We were interested in the smallest amount of air that would still generate detectable injury, and therefore we chose 0.2 ml as the lowest dose. In order to investigate the effect of larger doses as well as the effect of cumulative doses of air, we designed the following experimental setup using three groups. Group A received only the two largest doses (0.8 ml and 1.6 ml), group B started with a lower dose (0.4 ml, then 0.8 ml, then 1.6 ml), and group C started with the lowest dose (0.2 ml, then 0.4 ml, then 0.8 ml, then 1.6 ml). 1.6 ml was chosen as the positive control in all groups, since we hypothesized that this amount of air would induce severe injury in all animals. Before start of the series of experiments, animals were randomly assigned to one of the three groups.

After the preparations described above, at least 1 h of stabilization was allowed before start of embolization. The balloon of the catheter in the ascending pharyngeal artery was inflated and correct position of the tip
of the catheter was confirmed using contrast angiography. Air boluses were introduced by first injecting them into the catheter using a syringe, followed by flushing of the catheter with saline. The saline used to push the emboli into the vasculature was injected manually at a rate of approximately 0.1 ml/s. After each embolization, the next embolization was delayed until \( rSO_2 \), tBSI, and PbtO\(_2\) had returned to their baseline values, or, if this did not occur, until these values had stabilized for at least 10 min. At the end of the experiment, the animals were sacrificed using an overdose of pentobarbital.

<table>
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<td>av br glycerol (µmol/l)</td>
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Table 1. General parameters at start and end of the experiment in the three groups, displayed as average (SD). Group A received 0.8 and 1.6 ml of air, group B received 0.4, 0.8, and 1.6 ml of air, group C received 0.2, 0.4, 0.8, and 1.6 ml of air. Values for brain glucose, brain lactate and brain glycerol are the averages of values obtained in left and right hemisphere. There were no significant differences between the three groups at start or end of the experiment. Asterisks denote significant change between start and end of the experiment for the given parameter in the given group. etCO\(_2\) = end-tidal CO\(_2\); MAP = mean arterial pressure; ICP = intracranial pressure; av = average; br = brain.
Statistical analysis
Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). The outcome parameters of the study were $rSO_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol. Differences between groups A, B, and C at the start and end of the experiments were analyzed using one way ANOVA. In exception, the Kruskal-Wallis test was used when ANOVA could not be performed because the requirement for homogeneity of variance was not met. Differences between start and end of the experiment in each group were tested using t-tests for paired samples.

Absolute values of PbtO$_2$ and $rSO_2$ at the beginning of each embolization varied between animals, but did not change significantly between embolizations within each animal (tested using one way ANOVA). Therefore, in order to define a standardized baseline for each embolization, the values of PbtO$_2$ and $rSO_2$ at the beginning of each embolization were defined as 100% for that embolization.

In consultations with a statistician, the influence of side (left or right hemisphere), bolus volume (0.2, 0.4, 0.8, or 1.6 ml), and group (A, B, or C) on $rSO_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol was tested using linear mixed models. Since the behavior of the dependent variables over time was not linear and could not be linearized by transformation, time would have to be treated as a factor in the models, which would have resulted in a large number of parameters because of the short sampling interval of our measurements. Therefore, it was decided to reduce the number of parameters of the models by summarizing the reactions to the embolization as one value per embolization per side. For brain lactate and brain glycerol this value was the maximum value reached after the embolization. For $rSO_2$, tBSI, and PbtO$_2$ this value was the area under the curve (AUC) for the first 30 min after each embolization. $rSO_2$ AUC was calculated for the duration of desaturation under baseline value, thereby omitting any rebound increase above baseline. This is the procedure for data analysis recommended by the manufacturer of the INVOS device. For comparability, PbtO$_2$ AUC was calculated using the
Figure 2 (continued on opposite page). Time course of rSO$_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol. Side (left or right hemisphere) and group (A, B, or C) were not taken into account in these graphs. X-axes show time after embolization in min. Panels show the different bolus volumes. All error bars indicate 1 standard deviation. (A) rSO$_2$. (B) tBSI. (C) PbtO$_2$. (D) brain lactate. (E) brain glycerol.
same method. Factors used in the linear mixed models were group, side (not for tBSI), and bolus volume. Group, side, bolus volume, and group by bolus volume were included as fixed effects. A random intercept for each animal was included. Since the linear mixed model for PbtO$_2$ did not meet the normality requirements, PbtO$_2$ AUC values had to be log-transformed. All other linear mixed models met the normality requirements without transformations.

Correlations between outcome parameters are expressed as Spearman’s rho correlation coefficients. All tests were two-sided and statistical significance was accepted at $p < 0.05$. 
Figure 3 (continued from opposite page). Boxplots of $rSO_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol, quantified using area-under-the-curve for $rSO_2$, tBSI, and PbtO$_2$, and using maximum value after each embolization for brain lactate and brain glycerol. Graphs are split out by bolus volume (x-axis), group (dark grey = group A, light grey = group B, white = group C), and side (not for tBSI). (A) $rSO_2$. (B) tBSI. (C) PbtO$_2$. (D) brain lactate. (E) brain glycerol.
Results

General and microdialysis values of the three groups are shown in table 1. There were no statistically significant differences between groups A, B, and C at start and end of the experiments. There were small but significant decreases in mean arterial pressure during the experiments in groups B and C. There were significant increases in ICP in groups A and B, and in brain lactate in groups A, B, and C.

Graphs displaying the time course of rSO$_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol are shown in figure 2. The values displayed in these graphs are averaged over group and side. The general reaction of rSO$_2$ and PbtO$_2$ to the embolizations consisted of a sharp decrease followed by a slower return to baseline, sometimes including a rebound increase above 100% before the return to baseline. The reaction of tBSI was generally a sharp increase followed by slower return to baseline. In all boluses that resulted in changes of rSO$_2$, tBSI, and PbtO$_2$, these changes started almost immediately after the embolization.

A clinically detectable decrease (defined as <90% of baseline) of PbtO$_2$ was seen in conjunction with all boluses (of either 0.2 ml, 0.4 ml, 0.8 ml, or 1.6 ml) and clinically detectable decreases (defined <90% of baseline) of rSO$_2$ were seen in conjunction with 0% of 0.2 ml boluses, 38% of 0.4 ml boluses, 83% of 0.8 ml boluses, and 100% of 1.6 ml boluses. Clinically detectable increases of tBSI (defined as >0.1) were seen after 25% of 0.2 ml boluses, 63% of 0.4 ml boluses, 92% of 0.8 ml boluses, and 92% of 1.6 ml boluses.

Figure 3 displays the responses of all outcome parameters to the embolizations (quantified as described in the methods section), split out according to bolus volume, group, and side (left or right hemisphere). These values were used as the dependent variables of the linear mixed models, to determine the significance of the effect of bolus volume, group, and side. For all outcome parameters there was a significant
effect of bolus volume (for all outcome parameters p<0.001). Only for PbtO₂ a significant group by bolus size effect was found (p=0.024), which indicates that only for PbtO₂ the reaction to a specific bolus volume was influenced by the preceding boluses. rSO₂ was significantly lower in the left hemisphere (p=0.005), there were no significant differences between left and right hemisphere with regard to PbtO₂, tBSI, brain lactate, and brain glycerol.

Correlations between rSO₂, tBSI, and PbtO₂ as calculated across all time points until 30 min after each embolization was weak to intermediate (correlation coefficient of rSO₂ vs PbtO₂ 0.137, rSO₂ vs tBSI 0.232, PbtO₂ vs tBSI 0.506). In order to compare our different outcome parameters with each other, all parameters were condensed to one value per embolization per side as described in the methods section. The resulting correlations were intermediate to good, as displayed in table 2.

### Discussion

This study is the first to test the utility of NIRS and EEG in the setting of cerebral arterial gas embolism. We have shown that rSO₂ and tBSI can detect air emboli as early as more invasive measurements, but with a reduced sensitivity as compared to PbtO₂, especially when using low air
volumes. We observed reasonable correlations between rSO$_2$, tBSI, PbtO$_2$, brain lactate, and brain glycerol.

The incidence of cerebral injury during surgery, especially cardiac surgery, has been a concern to clinicians and researchers for decades. The etiology of perioperative stroke, encephalopathy, and cognitive decline has been the subject of extensive reviews (1, 2, 12). Current opinion suggests that these cerebral insults arise from a multifactorial process, involving hypoperfusion, alterations in neuronal metabolism, inflammation, and embolization (3, 13). One study stated that 62% of strokes related to coronary artery bypass surgery are due to solid or gaseous emboli (14). Air emboli can arise during cardiac surgery in various ways, for instance through inadequate de-airing of cardiac chambers (15) or due to cardiopulmonary bypass, although the latter is subject to ongoing debate (16-19).

Several strategies for cerebral monitoring during high-risk procedures are clinically employed. In this study two of the three most commonly used methods were tested, namely measurement of rSO$_2$ using NIRS, and EEG (20). The other frequently used method is transcranial Doppler (TCD). Although this technique is known to be very sensitive to even small amounts of emboli, TCD embolic counts correlate poorly with postoperative neurocognitive function (21). A possible explanation might be that this highly sensitive method detects even the smallest emboli, which are unlikely to cause neurological injury. A second disadvantage of TCD is that it does not provide functional information on the brain. In our model, the use of TCD was not possible because the large thickness of the skulls of our pigs precluded obtaining a reliable temporal window.

Cerebral oximetry using NIRS relies on the different absorption of near-infrared light by oxygenated versus deoxygenated hemoglobin (22). Since tissue is relatively transparent to near-infrared light, applying the sensor to the human skin allows transcranial measurement of cerebral mixed arterial and venous oxygen saturation. Maintaining adequate rSO$_2$ has been shown to decrease morbidity after coronary artery bypass surgery (23).
Interestingly, however, a published algorithm developed to determine the correct course of action when cerebral desaturation occurs, does not include the possibility of cerebral embolism as a cause of these desaturations (5). The fact that rSO$_2$ values represent only a small area of brain tissue may have generated the idea that measuring rSO$_2$ is not capable of detecting localized events as occur in cerebral embolism. In our study we used a commercially available apparatus and used the sensors, monitor, and data analysis methods as advised by the manufacturer. The only difference was the subcutaneous placement of the sensors, which was done to reduce the influence of the porcine extracranial tissues to the signal. We took great care in positioning the tip of the PbtO$_2$ and microdialysis probes in the region covered by the rSO$_2$ sensors.

EEG has been used to monitor the brain since the first years of open heart surgery (24). Theoretically, measuring cerebral activity can detect changes in cerebral function due to embolic processes, but in practice, a reliable indicator of cerebral injury has been difficult to find (20). Problems include the influence of anesthesia and hypothermia on the EEG, the fact that many electrodes are needed to cover the whole brain, and the large amount of data generated in classic EEG measurement. In the current study we used an eight channel EEG to obtain a global overview of cerebral function and used tBSI to quantify the signal. The main advantage of this parameter is that it requires definition of a normal baseline (11). This baseline can be determined after induction of anesthesia and hypothermia, which reduces the influence of these factors on the results obtained. A second advantage of tBSI is that it is a normalized parameter, which allows for easy comparison between patients. Thirdly, the utility of tBSI in cerebral arterial gas embolism has been demonstrated in a previous study (7). It must be noted, however, that tBSI has thus far not been used in clinical studies.

Our study has produced a number of interesting results. It seems that of the techniques used in this study, PbtO$_2$ is the most sensitive method to detect air embolism. This is somewhat surprising, since the localized na-
ture of the PbtO$_2$ measurements had led us to hypothesize that ischemic events occurring elsewhere in the brain would be easily missed. We believe it is unlikely that the smallest amount of air injected in our animals was large enough to disperse through the whole brain, causing widespread ischemia. More probably the position of the PbtO$_2$ probes – localized in the central gyri, in the middle cerebral artery territory – was in an area that is vulnerable to the ischemia as induced in our model. Given the sensitivity of the PbtO$_2$ probes, it is interesting to note the lower sensitivity of our rSO$_2$ and EEG measurements. As for EEG, the global nature of this measurement may cause small ischemic events to remain unrecognized in the middle of the normal electrical activity of the rest of the brain. In regard to rSO$_2$, we hypothesized that these more regional measurements, which covered areas that included the areas in which the PbtO$_2$ probes were located, would be able to pick up the same ischemic effects that were recorded by the PbtO$_2$ probes. Our results may in part be explained by the influence of extracerebral tissues on the rSO$_2$ measurements, despite our efforts to reduce these effects by subcutaneous sensor placement (25). Nevertheless, these disadvantages are offset by the most important benefit of this technique, which is its non-invasive nature.

Correlations between rSO$_2$, tBSI, and PbtO$_2$ during the entire 30 min after each embolization were weak and less than reported in previous studies (26). Clustering of the dependent variables to one value per embolization per side increased correlation up to a level comparable with previous research (26), indicating that PbtO$_2$ and rSO$_2$ followed the same trend and thus contain essentially the same information, as demonstrated by others before (27).

In earlier studies using this model, we observed no significant differences between left and right hemisphere (7). This is explained by the fact that the air is injected proximal to the rete mirabile, a network of arterioles anastomosing across the midline at the base of the brain (8). While PbtO$_2$, brain lactate, and brain glycerol indeed showed no significant interhemispheric differences in the current study, rSO$_2$ was significantly lower in
the left hemisphere. This is an interesting and unexplained result, since the catheter was placed in the right ascending pharyngeal artery, and we had therefore hypothesized that if any difference between embolization of left and right hemisphere would occur, the right hemisphere would receive a larger amount of air.

The relationships between air dose and effects found in our study cannot be translated to the human situation one-to-one. Firstly, the subcutaneous placement of our sensors circumvented part of the contamination by extracranial tissues that occurred when sensors were placed on the skin. It remains to be seen if the NIRS sensors are as sensitive in humans, where extracranial contamination is also a matter of concern (10). Secondly, the pig brain is much smaller than the human brain, so a given amount of air will disperse to a relatively larger portion of the brain in pigs and may therefore be more easily detected by local measurements. One might argue that the chance that a small amount of air will end up in exactly the two regions covered by the rSO\textsubscript{2} sensors is small and that any use of NIRS in detecting air emboli is therefore futile. However, NIRS sensors are generally placed on the forehead, overlying the watershed areas between anterior and middle cerebral territories. Exactly these regions of the brain are known to be specifically vulnerable to ischemia in the setting of cerebral air embolism (28). rSO\textsubscript{2} measurement may therefore detect a relatively large proportion of air emboli, and for this reason we believe the use of rSO\textsubscript{2} for detecting cerebral air emboli should be considered. Specific therapies for peroperative air embolism are available, such as more extensive de-airing, retrograde cerebral perfusion, and ultimately, hyperbaric oxygen therapy (29). Since detection is the first step towards outcome modification we believe it to be crucially important to increase clinical awareness of air embolization by optimizing detection methods for gaseous emboli (20).

In conclusion, our study shows that transcranially measured rSO\textsubscript{2} and EEG quantified using tBSI can detect small volumes of cerebral air emboli almost instantaneously, albeit with less sensitivity than PbtO\textsubscript{2} measurement.
Future clinical research should focus on prospective trials employing multimodal monitoring with TCD, NIRS, and EEG (30), in order to extend our knowledge of the influence of air emboli on cerebral outcome in surgery.
References

Detection of CAGE using EEG and NIRS


