Advances in diagnosis and treatment of cerebral arterial gas embolism

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Quantitative electroencephalography in a swine model of cerebral arterial gas embolism

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Abstract

Introduction: Cerebral arterial gas embolism (CAGE) is a serious hazard in cardiovascular surgery and other invasive procedures. We used a swine model of CAGE to determine if quantitative electroencephalography (qEEG) is a useful tool in diagnosis and prognostication of CAGE.

Methods: 0.05 ml/kg of air was injected into the ascending pharyngeal artery in 16 pigs. Intracranial pressure, lactate in brain microdialysate, and brain oxygen tension were measured during 4 h after embolization. The qEEG parameters mean amplitude (MAMP), alpha-delta ratio (ADR), spectral edge frequency (SEF$_{90}$), spatial brain symmetry index (sBSI), and temporal brain symmetry index (tBSI) were calculated.

Results: MAMP and tBSI, but not ADR, SEF$_{90}$, and sBSI correlate with intracranial pressure, brain lactate, and brain oxygen tension after 4 h. Early levels of MAMP and tBSI can predict intracranial pressure, brain lactate and brain oxygen tension after 4 h.

Conclusions: MAMP and tBSI can diagnose and predict outcome in a swine model of CAGE. This study provides evidence for the utility of qEEG for diagnosis and prognosis in CAGE. Further studies are necessary to investigate the use of this method in patients.
Introduction

Cerebral arterial gas embolism (CAGE) is a risk in cardiovascular surgery and other invasive procedures (1, 2). CAGE may be regarded as a type of transient multifocal ischemia resulting in grossly inhomogeneous cerebral blood flow, profound changes in cerebral metabolism and electrophysiological status, and immediate disruption of the blood-brain barrier (3). CAGE is a serious disorder often leading to permanent neurological deficits. In a recent study half of CAGE patients had a Glasgow Coma Score <8 on admission (4). In these patients only limited clinical examination is possible. Early monitoring of CAGE patients is therefore a prerequisite. Application of invasive measurements such as intracranial pressure (ICP) is not indicated or technically feasible in all patients. It would therefore be interesting to use a non-invasive method to assess neuronal function in comatose CAGE patients.

Electroencephalography (EEG) is a commonly used method to study cerebral function. Analysis of EEG data is usually performed qualitatively, which requires much training and limits comparison between patients. Quantitative analysis of EEG data (qEEG) reduces the amount of data and produces results that are easy to interpret without much knowledge on the background of EEG. Since qEEG is a very sensitive tool for detecting acute cerebral ischemia (5), it might be of special interest in CAGE.

As the collection of large series of patients with arterial gas embolism is limited by the prevalence of only 0.57 per 100,000 hospital admissions (4), an adequate animal model is needed in CAGE research. Our group has established a swine model of CAGE, using relevant measurements such as ICP, brain oxygen tension (PbtO$_2$), and cerebral microdialysis to assess neuronal function (6, 7). The current paper reports on the use of qEEG in this model. We determined correlations between ICP, PbtO$_2$, brain lactate, and several qEEG features to determine which parameters are of most interest in assessing the neuronal effects of CAGE. Furthermore, we were interested if qEEG values obtained early after induction of CAGE can predict outcome.
Methods

Experimental setup
This study was approved by the Animal Ethics Committee of the Academic Medical Center Amsterdam, The Netherlands. Care and handling of the animals was in accordance with the latest European Community guidelines. Our group recently published a detailed description of the surgical and analytical procedures of the model (7). Briefly, 16 Landrace pigs (35-40 kg) were anesthetized with intramuscular ketamine 15 mg/kg (Eurovet Animal Health, Bladel, The Netherlands), midazolam 2 mg/kg (Actavis, Hafnarfjördur, Iceland), and atropine sulfate 0.01 mg/kg (Pharmachemie, Haarlem, The Netherlands). Animals were intubated and ventilated to maintain normocapnia. Anesthesia was continued with intravenous 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). Blood pressure was measured invasively through a catheter placed in the brachial artery, rectally measured body temperature was regulated by means of an aluminum blanket, and a bladder catheter was placed in all animals. A 4F angiography catheter (Radiofocus Glidecath, Terumo, Tokyo, Japan) was placed under fluoroscopic guidance in one of the ascending pharyngeal arteries, which are the most important arteries supplying the pig brain. Three burr holes were made in the skull, and a calibrated ICP sensor (Codman, Raynham, MA, USA), a temperature sensor (Integra, Plainsboro, NJ, USA), a left and right PbtO₂ sensor (Integra), and a left and right microdialysis probe (Carnegie Medicine AB, Solna, Sweden) were inserted into the brain. Microdialysis probes were continuously flushed with artificial cerebrospinal fluid (Carnegie Medicine AB). Subdermal wire electrodes (Ives EEG Solutions Inc., Manotick, Canada) were placed in the skin in the positions shown in figure 1.

Experimental protocol
A 1 h stabilization period was provided after all surgical procedures, after
Quantitative electroencephalography in CAGE

which 0.05 ml/kg of room air was injected through the catheter placed in the ascending pharyngeal artery over a period of 60 s. Heart rate, blood pressure, body temperature, ICP, brain temperature, and left and right hemispheric Pbto2 were recorded at t=15 min, t=30 min, and every 30 min thereafter. Blood gas analysis was performed every 60 min. EEG was recorded continuously. Vials containing the effluent of the microdialysis probes were changed at t=15 min, t=30 min, and every 30 min thereafter. The microdialysate was analysed for glucose and lactate with a CMA 600 analyzer (Carnegie Medicine AB), and values were corrected for the recovery rate as determined in an earlier in vitro experiment (76% for glucose and 89% for lactate). Position of the arterial catheter was reassessed using angiography if no change in any of the measurements was observed after air embolization. The animal was excluded from analysis if the catheter had dislocated from the ascending pharyngeal artery. Animals were terminated using potassium chloride at t=240 min, or earlier if they developed an iso-electric EEG in combination with a cerebral perfusion pressure (CPP, equals mean arterial pressure minus ICP) <30 mmHg for 30 min.

Figure 1. Position of the EEG electrodes is related to the crossing of coronal and sagittal sutures (bregma point). Nomenclature of electrodes corresponds with the international 10-20 system, distances are adapted to fit the pig skull.
Quantitative EEG analysis

A personal computer system was used for the recording of the EEG signal from a Schwarzer PTMS1-EEG headbox (OSG, Rumst, Belgium), with a sample frequency of 500 Hz, an analog bandpass filter of 0.53 to 70 Hz (-3 dB), and a sensitivity of 70 μV/cm. All signals were recorded with the average of all electrodes as the common reference. Offline quantitative EEG analysis was performed using Matlab 2010a (The Mathworks Inc., Boston, MA, USA). EEG signals were bandpass filtered using a zero-phase 6th order Butterworth filter with cut-off frequencies 0.5 and 30 Hz. A Hamming window was applied before fast Fourier transform of each EEG epoch (10 s of EEG, using Welch’s method). The following qEEG parameters were calculated: mean amplitude (MAMP), alpha-delta ratio (ADR), spectral edge frequency (SEF$_{90}$), spatial brain symmetry index (sBSI), and temporal brain symmetry index (tBSI). MAMP was calculated for each epoch by averaging the mean of the absolute value of the EEG from the eight channels. The estimate of the power spectral density was calculated using Welch’s method with an epoch length of 2 s and 25% overlap resulting in a spectral resolution of 0.5 Hz. From the power spectral density the ADR was calculated (8), which was defined as the power in the alpha band (8-13 Hz) divided by the power in the delta band (0.5-4 Hz). SEF$_{90}$ was calculated as the frequency below which 90% of the power between 0.5 and 20 Hz was contained (9). sBSI and tBSI were calculated as proposed by Van Putten (10). The sBSI calculates the difference between the spectral characteristics of the left and right hemispheres and is defined as:

$$sBSI(t) = \frac{1}{K} \sum_{n=1}^{K} \left| \frac{R_n(t) - L_n(t)}{R_n(t) + L_n(t)} \right|$$

with

$$R_n(t) = \frac{1}{M} \sum_{ch=1}^{M} a_{n, ch}^2(t)$$

for the right hemisphere and a similar expression $L_n(t)$ for the left hemisphere. M stands for the number of channel pairs, while $a_{n, ch}(t)$ is the
Fourier coefficient with index n of channel ch, evaluated at time t, corresponding to a particular epoch with a duration of 10 s. sBSI was calculated in the frequency range 0.5–25 Hz with a spectral bandwidth of 0.5 Hz. The tBSI defines the BSI as the normalized difference between the actual spectral characteristics and a baseline EEG epoch, in our experiments a segment prior to embolization. The tBSI is defined as:

$$tBSI(t) = \sqrt{\left| (\Delta R(t) - \gamma) \cdot (\Delta L(t) - \gamma) \right|}$$

with

$$\Delta R(t) = \frac{1}{K} \sum_{n=1}^{K} \left| \frac{R_n(t) - R_n(t_0)}{R_n(t) + R_n(t_0)} \right|$$

and with a similar expression for $\Delta L(t)$. t0 is the baseline time point, in our experiments an EEG segment prior to embolization. The expressions for both hemispheres quantify the relative hemispheric changes in the mean spectral characteristics of that hemisphere. Only if both of these expressions significantly differ from zero, the tBSI will change, indicating a diffuse change in the spectral characteristics. The offset correction factor $\gamma$ was introduced to account for the systematic error in the estimation of the spectral difference due to the finite epoch size that is used to estimate the spectrum. In our experiments $\gamma=0.2$. For each 10 s and a frequency range from 0.5 to 25 Hz the power spectral density is used for calculation. For all features a moving average smoothing filter was applied over the current and the five previous epochs of 10 s.

**Statistical analysis**

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and R (R Development Core Team, Vienna, Austria) were used for data analysis. If the endpoint of iso-electricity and CPP<30 mmHg was reached before $t=240$ min, the last recorded values were used as the $t=240$ min values. The Shapiro-Wilk test was used to test for normality, and parametric or non-parametric tests were used appropriately. PbtO2 values are reported as relative to baseline values because of large variation at $t=0$. This large
variation is caused by the fact that PbtO\textsubscript{2} varies greatly between brain regions and the probe only samples PbtO\textsubscript{2} in its immediate vicinity. Left and right brain relative pBtO\textsubscript{2} and microdialysis values were not significantly different and were therefore pooled. ICP, pBtO\textsubscript{2}, and brain lactate were the outcome parameters of this study. Spearman’s rho was used to determine correlation between outcome parameters and qEEG parameters. Accuracy of tBSI and MAMP values for diagnosing outcome in respect to ICP was tested using ROC analysis with ICP as a continuous gold standard based on the methods proposed by Obuchowski (11) using the nonbinROC package in R. Animals were further categorized as having either good outcome (low-ICP group, ICP≤20 mmHg at t=240 min) or bad outcome (high-ICP group, ICP>20 mmHg at t=240 min). 20 mmHg was chosen as the cut-off point since in the clinical situation this value is usually regarded as the upper level of normal, above which treatment to lower ICP should be initiated (12). Significance of differences within groups at different time points was calculated using paired tests (paired t-test or Wilcoxon signed-rank test as appropriate), significance of differences between groups was calculated using unpaired tests (unpaired t-test or Mann–Whitney U test as appropriate). Significance of change in qEEG features during the experiments was calculated using a linear mixed model with outcome (high-ICP or low-ICP group), time and outcome by time interaction as fixed effects, using an AR(1) covariance structure to account for repeated measures within the same animal. All tests were two-sided and statistical significance was accepted at p<0.05. Reported confidence intervals are 95% confidence intervals.

<table>
<thead>
<tr>
<th></th>
<th>ICP (mmHg)</th>
<th>rPBrO\textsubscript{2} (%)</th>
<th>brain lactate (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAMP (µV)</td>
<td>-0.817 (p=0.001)</td>
<td>0.725 (p=0.005)</td>
<td>-0.797 (p=0.002)</td>
</tr>
<tr>
<td>ADR</td>
<td>0.463 (NS)</td>
<td>-0.720 (p=0.006)</td>
<td>0.503 (NS)</td>
</tr>
<tr>
<td>SEF\textsubscript{90} (Hz)</td>
<td>0.477 (NS)</td>
<td>-0.724 (p=0.004)</td>
<td>0.476 (NS)</td>
</tr>
<tr>
<td>sBSI</td>
<td>0.665 (p=0.013)</td>
<td>-0.495 (NS)</td>
<td>0.448 (NS)</td>
</tr>
<tr>
<td>tBSI</td>
<td>0.775 (p=0.002)</td>
<td>-0.703 (p=0.007)</td>
<td>0.825 (p=0.001)</td>
</tr>
</tbody>
</table>

Table 1. Correlation of outcome parameters with qEEG features at t=240 min. Values are displayed as spearman’s rho (p-value). NS = non significant.
Results

Of the 16 animals in which air was injected, three were excluded from the analysis because the arterial catheter had dislocated from the ascending pharyngeal artery to the external carotid artery (in two cases), or the catheter had caused thrombo-embolism of the cerebral vessels (one case). Thus, the data presented here is based on the results of 13 animals. Four animals reached the pre-defined endpoint of iso-electric EEG and CPP<30 mmHg before t=240 min. Despite the fact that the same dose of air (in ml/kg body weight) was used in all experiments, we observed a wide variation of results, with ICP at t=240 min ranging from 5 to 67 mmHg.

As illustrated in table 1, only MAMP and tBSI showed strong correlations ($|\rho|\approx0.8$) with the outcome parameters at t=240 min. Figure 2 shows that early levels of MAMP and tBSI correlate with outcome parameters at t=240 min. Using non-binary gold standard ROC analysis, the accuracy of the qEEG parameters to diagnose ICP at t=240 min was determined to be 83% (CI 70–95%) for MAMP, 64% (CI 45–85%) for ADR, 62% (CI 42–91%) for SEF$_{90}$, 75% (CI 60–90%) for sBSI, and 80% (CI 66–94%) for tBSI. After categorization of animals into either high-ICP group (n=5) or low-ICP...
group (n=8), there were no significant differences between these groups in respect to ADR, SEF, and sBSI. MAMP and tBSI changed significantly during the experiments in both groups but the difference was much more pronounced in the high-ICP group (table 2 and figure 3). Figure 4 shows that MAMP and tBSI differed significantly between groups from t=15 min (tBSI) or t=30 min (MAMP) onward.

Discussion

We used a swine model of CAGE to determine the value of several qEEG parameters for diagnosis and prognostication in CAGE. A standardized air embolus led to a large spectrum of brain damage, varying from only slight EEG disturbances to iso-electricity with brain herniation. Thus, our model mirrors the clinical situation where patients with CAGE can present with signs ranging from subtle transient neurological dysfunction to coma (4). The non-invasively obtained qEEG variables MAMP and tBSI could diagnose and predict severe brain damage in our model and may thus be of clinical value.

![Table 2. General parameters in high-ICP group and low-ICP group animals at t=0 min and t=240 min, displayed as value (SD). a = significant difference between t=0 min and t=240 min; b = significant difference between high-ICP group and low-ICP group; MAP = mean arterial pressure.](image-url)
In the high-ICP group we observed a significant increase in heart rate and changes in blood gas values (decrease in $\text{PaO}_2$ and increase in $\text{PaCO}_2$ with decrease in pH) during the experiments. Since such changes did not occur in the low-ICP group we expect these changes to result from the extremely elevated ICP and ensuing hemodynamic and pulmonary alterations (13). For unknown reasons body temperature increased slightly but significantly in the low-ICP group. However, this might have only diminished the observed differences between the groups, since hypothermia is a robust protectant.
MAMP and tBSI showed strong correlation with our outcome parameters. Furthermore, early changes of MAMP and tBSI could predict outcome as judged by ICP, pBtO$_2$, and brain lactate. Although the relation of MAMP to neuronal damage is intuitively clear, the nature of tBSI as well as the related sBSI require more explanation.

sBSI and tBSI were developed by van Putten et al. (10, 15) which group has shown the utility of sBSI and tBSI in determining shunt requirement in carotid endarterectomy (16). Furthermore, they have demonstrated the value of sBSI and a related parameter for monitoring stroke patients (17, 18). sBSI is sensitive to changes in spatial (left-right) EEG changes, while tBSI reflects temporal changes in the EEG spectrum that are not due to changes in spatial symmetry. The main advantage of both parameters is that they are normalized ranging from [0–1]. Results can therefore be easily interpreted and compared between patients, which provides an advantage over the use of non-normalized parameters such as MAMP.

In our experiments sBSI did not significantly correlate with the outcome parameters. This is somewhat surprising, since the air is injected uni-
laterally. However, it is worth mentioning that, as opposed to humans, the pig has a bilateral network of fine arterioles, called the carotid rete, at the base of the brain (19). The air is injected proximal to this carotid rete. The large amount of anastomoses between both retia probably results in bilateral dispersion of the air into the circle of Willis, accounting for the diffuse EEG changes, and explaining the lack of sBSI sensitivity as well as the absence of differences between left and right pBtO2 and brain lactate.

Previous studies have pointed out ADR and SEF90 as being useful in cerebral ischemia (20, 21). Mostly, general slowing of the EEG is described which is reflected by a decrease in high frequency (alpha) and an increase in low frequency (delta) activity, resulting in a decrease of ADR and SEF90. In the present study no significant correlations were observed between ADR or SEF90 and ICP or brain lactate. Both qEEG features were negatively correlated with pBtO2, which is the opposite of the expected outcome. However, when animals were categorized as having either good or bad outcome according to ICP, there was no difference between these groups in regard to ADR, SEF90, and sBSI, while MAMP and tBSI did show a significant difference. Apparently, only the latter two qEEG features have true relationships with our outcome parameters.

Our experiments were performed under general anesthesia with sufentanil, midazolam and ketamine. The former two substances are known to induce dose-dependent changes in EEG pattern, mostly consisting of decrease in high-frequency activity and increase in low-frequency activity (22). Ketamine can induce an active EEG signal with increase in theta and beta activity (23). Overall, the combination of substances used in this study might well result in slowing of the EEG, which may provide an explanation for the lack of sensitivity of ADR and SEF90 to detect cerebral ischemia. However, we did not perform experiments in awake animals to test this hypothesis. Despite the probable changes in EEG due to general anesthesia, detection of CAGE was possible in our model as shown by the changes of MAMP and tBSI after embolization.
This study has some limitations. First of all, we did not correlate our qEEG findings with clinical outcome. We aimed to address this problem by correlating the qEEG results with other clinically relevant outcome measures such as ICP. qEEG findings have been reported to correlate with clinical outcome in human studies of stroke (18). Secondly, the duration of our experiments was only 4 h. It is well known that neuronal damage following stroke develops during several days (24), thus a longer timeframe to test the application of qEEG in CAGE would be interesting. A third limitation pertains to the tBSI, requiring a baseline EEG segment to which later changes in the EEG are compared. Although under many circumstances, such as surgical procedures known to carry a risk of CAGE induction, the definition of a normal baseline EEG epoch is possible, this is not the case in all situations. We believe the results of the present study merit further investigation of the tBSI in a form that does not require supervised definition of a baseline EEG segment. Lastly, a limitation of the employed model is that PbtO$_2$ and microdialysis values as acquired by the cerebral probes only represent the cerebral tissue in the immediate vicinity of the probe. Changes in these values are therefore highly dependent on the dispersion of air in the brain, which might differ between animals. However, we have demonstrated in an earlier study that microdialysis PbtO$_2$ values show a good correlation with ICP when air is injected in the ascending pharyngeal artery, which is the vessel used in this study (7).

CAGE due to pulmonary barotrauma is regarded as one of the most serious risks of diving (2). Although diagnosis of CAGE in the diving situation is usually very well possible based on the clinical situation, the monitoring of non-responsive patients faces the same problems as in patients with iatrogenically induced CAGE. Monitoring is further limited by the fact that hyperbaric oxygen therapy is generally commenced rapidly in these patients, which precludes application of many diagnostic (especially invasive) procedures. Therefore, qEEG might be useful in this patient category. Two abovementioned properties of our study pose difficulties in extrapolating our results to the diving popu-
lation. Firstly, the possible changes caused by the anesthetics we used may limit translation of our results to the awake situation. However, many patients with CAGE due to diving will be under general anesthesia upon arrival at a hyperbaric facility. Secondly, in out-of-hospital CAGE a normal baseline EEG segment as required for the tBSI will not be available, and thus the tBSI cannot be obtained. This difficulty may be overcome by the development of a form of the tBSI that does not require a baseline epoch.

Multiple animal studies on CAGE incorporating EEG have been published. Redo et al. found decrease in fast activity and increase in slow activity after injection of 40 ml of air into the common carotid artery in dogs, followed by decrease in amplitude when increasing amounts of air were injected (25). After injection of 0.5 ml of air into the internal carotid artery of the monkey, severe EEG changes were present which recovered after 10-20 min (26). In another study in monkeys 1-2 ml of air into the internal carotid artery was needed to obtain diffuse slowing, and marked slowing was only observed after injection of 2-4 ml (27). Fritz and Hossmann required only 0.6 ml of blood foam in the innominate artery of the cat to produce a flat electrocorticogram, which recovered in 30–60 min (3). Of note, they observed a larger recovery of fast frequency bands as compared to delta activity, resulting in a faster electrocorticogram during recovery than before embolization. Differences in tolerance to CAGE between these studies might be explained by differences in species, weight, vessel used, and volume of air injection. Drenthen et al. induced CAGE in a model much like the model used in the present study and demonstrated two independent frequency bands in which power was significantly reduced following air embolism (28). The first band, 0.5–7.3 Hz, contains delta plus theta activity while the other band, 26.4–30.3 Hz, corresponds with fast beta activity. Interestingly, the study does not report on the alpha band or ADR, which have been shown to be of significance in other studies on EEG in cerebral ischemia (20). Nevertheless, Drenthen et al. describe EEG as a valuable tool in monitoring the treatment of CAGE by hyperbaric oxygen therapy.
No study demonstrating the acute effects of CAGE on the EEG in humans has been published so far. Ingvar et al. performed EEG measurements in submarine escape trainees, who are at risk of developing pulmonary barotrauma with ensuing CAGE because of the rapid depressurization to which they are subjected (29). They found EEG disturbances, mostly consisting of focal slowing, in seven of nine subjects with subjective and/or objective signs of neurological injury. However, EEG's were performed after treatment with hyperbaric oxygen therapy and therefore do not provide information on the acute effects of CAGE on the EEG.

We believe application of EEG in the clinical situation of a patient at risk for CAGE, for instance during cardiac surgery, may provide advantages over other methods such as transcranial Doppler ultrasonography (TCD) for detection of air bubbles. TCD does only provide information at the acute moment of bubble passage. Although signals from microemboli can be quantified, these results have not proven to correlate well with functional outcome in CPB patients (30). Since EEG provides information on the functional status of the brain, this method may have more relevance to outcome. We are well aware that the present study does not shed light on the correlation between qEEG parameters and outcome at the lower end of the damage spectrum of CAGE, but the sensitivity of the tBSI in other clinical situations (16, 18) suggests that this feature may prove interesting in this area.

The present study demonstrates the diagnostic and prognostic value of qEEG in experimental CAGE. The tBSI seems to be the most interesting parameter and may especially be of use in situations where definition of a normal baseline EEG segment is possible. Further research into a form of tBSI that does not depend on the supervised definition of a baseline EEG segment is necessary to potentiate the use of this parameter in situations where CAGE has been sustained before start of EEG measurement. Human studies are necessary to prove the value of this method in patients.
References

14. Yenari MA, Hemmen TM. Therapeutic hypothermia for brain ischemia: where have we come and where do we go? Stroke 2010; 41:S72-S74.

