Advances in diagnosis and treatment of cerebral arterial gas embolism
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Summary and conclusions
Summary

Chapter 2 provides an overview of all published animal models of CAGE. It describes the aspects that should be taken into account when developing or evaluating an animal model for this disease. The most important of these factors are species, location of air administration, amount of air, outcome parameters, and anesthetic regimen. Many of these aspects, in particular species, amount of air, and outcome parameters, depend on the research question under study. Some general considerations of CAGE animal models are also discussed, for example the necessity to introduce the air as close to the cerebral vasculature as possible, which requires extensive knowledge of cerebrovascular anatomy.

In chapter 3, we discuss an important aspect in the use of the pig (and some other animals) in CAGE models, namely the carotid rete. Since this network of finely entangled arterioles precludes access to the cerebral arteries with a microcatheter, it is imperative to know whether introduction of air upstream of the carotid rete results in cerebral embolism. In order to elucidate this matter, we injected air into the external carotid artery (which is known to result in cerebral embolism because of anastomoses between external and internal carotid territories in the pig) and the ascending pharyngeal artery (which feeds the carotid rete and thus the internal carotid circulation). Although intracranial pressure (ICP) and brain oxygen tension (PbtO₂) after embolization did not significantly differ between the groups, we found an increased brain lactate level after injection into the ascending pharyngeal artery as compared to the external carotid artery. Furthermore, ICP, PbtO₂, and brain lactate correlated significantly after injection into the ascending pharyngeal artery, but not after injection into the external carotid artery. We therefore conclude that air introduced into the ascending pharyngeal artery does indeed pass through the rete into the cerebral arteries, and furthermore that the ascending pharyngeal artery is the most appropriate vessel for air introduction.
The issue addressed in chapter 4 is the use of quantitative electroencephalography (qEEG) for detection of the effects of CAGE on cerebral function. The advantages of EEG are its relatively easy, inexpensive, and non-invasive application, and its high sensitivity for cerebral ischemia. However, traditional qualitative assessment of the signal limits comparison between patients and its use as a research tool. Quantitative assessment of the EEG signal is increasingly used to overcome these disadvantages, and many different methods for analyzing the raw EEG have been developed. In chapter 4, we describe the use of five qEEG features for the acute detection of CAGE, by correlating the values of these qEEG features with the outcome parameters ICP, PbtO$_2$, and brain lactate. The results indicate that mean amplitude and temporal brain symmetry, but not alpha-delta ratio, spectral edge frequency, and spatial brain symmetry index, are useful for the detection of CAGE. This is demonstrated by the good correlation of these two parameters with the other outcome parameters 4 h after air embolism, and the fact that early levels (30 min after CAGE) of mean amplitude and temporal brain symmetry index adequately predict the level of ICP and brain lactate after 4 h. Also, mean amplitude and temporal brain symmetry can distinguish between bad outcome (ICP>20 mmHg) and good outcome (ICP≤20 mmHg), while the other qEEG features cannot.

The study described in chapter 5 further investigates the use of various monitoring modalities to detect CAGE. Apart from qEEG (specifically temporal brain symmetry index), PbtO$_2$, and microdialysis (brain lactate and brain glycerol), which had been used in previous studies, this study introduces measurement of regional cerebral oxygen saturation (rSO$_2$) using near-infrared spectroscopy as a possible method for detecting the cerebral effects of CAGE. Increasing amounts (0.2, 0.4, 0.8, and 1.6 ml) of air were injected in 12 animals, and the mentioned parameters were continuously recorded. The results showed weak correlation of PbtO$_2$ and rSO$_2$, but intermediate to good correlation between all outcome parameters were found when results were condensed to one value per embolization using area-under-the-curve. Furthermore, results indicate that rSO$_2$
and qEEG can detect air boluses almost instantaneously, but with reduced sensitivity as compared to invasive PbtO$_2$ measurement.

Chapter 6 describes a study investigating the maximum delay that can be tolerated after CAGE, before treatment with hyperbaric oxygen therapy (HBOT) must be started. This is an important issue in this disease, since a significant delay is known to occur in many cases of CAGE, and very little data is available on how quickly HBOT must be commenced. Using the knowledge obtained from the studies described in chapters 3 and 4, air was introduced in the ascending pharyngeal artery and titrated to obtain a standardized level of cerebral injury, based on changes in temporal brain symmetry index. Animals were treated with a single session of US Navy Treatment Table 6 after either 2 or 4 h of delay, while control animals were not treated with HBOT. Interestingly, neither of the intervention groups demonstrated improvement of temporal brain symmetry index, ICP, and brain microdialysis values as compared with the control group, despite the fact that significantly higher PbtO$_2$ values were recorded during HBOT in both intervention groups. The results may be due to type II error, since the observed effect size was smaller than expected due to larger variance of the data. The other explanation for our results is that HBOT actually had no positive effect on our animals, which may suggest that the damage inflicted in our model was too severe for a single session of HBOT to be beneficial.

The clinical study presented in chapter 7 regards the use of intravenous lidocaine as a neuroprotective agent in neurological decompression illness (this includes CAGE and neurological decompression sickness). Previous studies have reported conflicting results on this matter, and the study described in this chapter is the first study to investigate the use of intravenous lidocaine in a group of divers with neurological decompression illness. Patient characteristics, injury severity, and neurological outcome were retrospectively analyzed in 14 patients who had received lidocaine, and were compared to a historic cohort of 21 patients who had not received lidocaine. All divers were treated with HBOT according to accepted
protocols. The study failed to demonstrate a positive (or negative) effect of lidocaine on neurological outcome.

Chapter 8 presents a review of a specific category of CAGE, namely CAGE due to hypobaric exposure. While pulmonary barotrauma leading to CAGE is a well-known complication of decompression after initial hyperbaric exposure (e.g., diving), on a theoretical basis CAGE can also be caused by hypobaric activities, such as flying. A literature search resulted in 12 case reports describing this phenomenon, and the pathophysiological, diagnostic, and therapeutic aspects of this form of CAGE are described. The low and slow pressure decrease during most hypobaric activities, among other reasons, accounts for the low incidence of hypobaric CAGE. The diagnosis should be considered in all patients suffering acute central neurological dysfunction during or shortly after pressure decrease. Cerebral and thoracic imaging may reveal findings supporting the diagnosis. The case reports suggest that in a substantial percentage of these patients the mechanism for air entry is rupture of a non-communicating air-filled thoracic cyst during pressure decrease. The review suggests that the most prudent approach in patients with known air-filled thoracic cysts is to deny flying until the cyst is removed.

Conclusions and future research

Diagnosis of CAGE
Our investigations on improving detection of CAGE have focused on non-invasive measurement of cerebral function. Specifically, our attention has been directed towards application of qEEG and measurement of rSO$_2$ using near-infrared spectroscopy. We have demonstrated that qEEG (in our studies specifically using temporal brain symmetry index) is a promising tool in this regard. Although rSO$_2$ was less sensitive than PbtO$_2$ and qEEG in detecting the acute effects of CAGE, it should still be regarded as an interesting modality, not in the last place because of its increasing use in anesthesiological practice.
Both qEEG and rSO\textsubscript{2} are most valuable for monitoring patients at risk for CAGE, as opposed to those patients who first come to medical attention after sustaining CAGE. Thus, the findings of our studies are primarily of interest for the detection (and subsequent treatment) of clinical cases of CAGE, for example during cardiac surgery. This may lead one to conclude that the findings of our studies have no relevance for the diving community. That this is not true, however, is demonstrated by the fact that our results on qEEG have already spawned follow-up studies on the application of this technique in divers. In diving medicine, qEEG may not only be used for follow-up and possible prognostication of diving injuries, but also for research on oxygen toxicity and inert gas narcosis.

In the field of clinical CAGE, our results are mostly relevant for the ongoing debate on postoperative stroke and cognitive dysfunction. While cerebral air embolization certainly plays a role in the etiology of this disorders, the extent of its contribution is not yet elucidated. Multimodal monitoring involving qEEG, rSO\textsubscript{2}, transcranial Doppler, and other techniques may in the future lead to a better understanding of this multifactorial issue, possibly resulting in more clinical awareness of CAGE as a contributing factor to cerebral complications of surgery.

**Treatment of CAGE**

Our study on the effect of HBOT after 2 or 4 h delay in CAGE has produced the interesting result that neither of the intervention groups reacted favorably to the hyperbaric treatment. Above all, this calls for further research into this important subject. Since one of the possible causes for our non-significant results may be that our method of air embolization is not specific enough, ongoing effort should be put in the development of more refined animal models of this disease. Currently, our results should not change accepted policies on HBOT in CAGE, but our study indicates that HBOT – despite its universal acceptance as the only specific treatment for CAGE – needs continuing investigation.

In the first controlled study of lidocaine in decompression illness, we
were unable to demonstrate either a positive or a negative effect of this substance on neurological outcome. This study adds to the body of evidence against the use of lidocaine in decompression illness, despite the promising early results in animal and human studies. Only a large multicenter randomized controlled trial would be able to provide definitive conclusions.

**Animal models of CAGE**

The majority of the studies that form this thesis have been performed in a pig model of CAGE. Also, chapter 2 contains an overview of all animal models used for research of this disease. Our interest in animal models stems from the fact that this type of research plays a significant role in CAGE research, and will probably always continue to do so. This is explained on the one hand by the heterogeneity of the disease and its low prevalence, but also by the fact that HBOT is accepted as the standard treatment modality, despite the lack of level I evidence supporting its use. This situation precludes execution of randomized controlled trials on the use of HBOT in CAGE. Therefore, despite the fact that no single animal model will be able to answer all questions regarding this disease, there should be a continuous effort on the development of more refined animal models. Throughout the research described in this thesis, our own animal model has been continuously updated. This included implementation of a more specific artery for embolization (chapter 3), expanding the modalities to assess cerebral function (chapter 4 and 5), and implementation of more selective application of the air through the use of a balloon catheter (chapter 5 and 6). Despite these efforts and the concurrent increasingly smaller amounts of air used in our studies, one of the main conclusions of our article on HBOT in CAGE (chapter 6) is that the variation of our results is too large. Obviously, future research on this subject should focus on even more selective administration of air, resulting in more standardized effects. A second shortcoming of our studies is the lack of clinical endpoints. No matter how many cerebral parameters the researcher monitors and how elegant they are, none of these can replace clinical examination. Therefore, this should be implemented in future animal models of CAGE.
Military research into CAGE

In the military operational theater, CAGE can occur in various populations. Divers are at risk during their work for salvage diving and mine-countermeasures, pilots and aircrew when rapid decompression occurs during flight, and submarine escapees during disabled submarine disasters. All these populations have in common the lack of nearby decompression facilities and therefore delay in the treatment of decompression sickness and CAGE, which interferes negatively with clinical outcome and operational fitness.

It is of paramount importance to continue animal research on CAGE with the focus on adjuvant therapy, delay of treatment, and the use of other treating gas mixtures, e.g. heliox and trimix. Since investigations on humans are difficult to perform in this uncommon disease, further understanding will have to be based to a large extent on studies in animals.