82991 - NOVEL METHOD TO MEASURE CEREBROVASCULAR REACTIVITY USING MRI AND CO2.

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Introduction: Cerebrovascular reactivity (CVR), defined as a change in cerebral blood flow in response to a vasoactive stimulus, reflects the vasodilatory reserve capacity of cerebral vessels. CVR impairment has shown to be an important prognostic marker of several diseases including stroke. Several techniques have used to measure CVR but the lack of appropriate reproducible stimuli and noninvasive CBF measurement methods limit the routine use of CVR measurement in clinical practice. We have developed a non-invasive method of mapping CVR using a precise targeting of CO2 and BOLD-MRI. Aim of our study was to investigate the feasibility of measurement of CVR using sequential breathing circuit for precise targeting of CO2 in mechanically ventilated patients.

Methods: After IRB approval, patients with known cerebrovascular disease needing general anesthesia for BOLD MRI were included in the study. All patients had standardized general anesthesia care. BOLD-MR imaging was performed in 3.0 Tesla magnet while precise targeting of CO2 was achieved using a custom made sequential breathing circuit and a computer controlled gas blender. Three different PETCo2 targets (normocapnia (baseline resting Co2), Hypercapnia (baseline +10mmHg), and Hypocapnia (baseline -5mmHg) were achieved. MRI and PETCo2 data were imported into custom software (Labview, TX) for creating CVR maps. The BOLD-MRI signal from each voxel was then correlated to the PCo2 and the correlations (positive and negative) were color coded to generate a CVR color maps. In addition, we also measured the changes in CBF under both propofol and sevoflurane anesthesia using ASL–MRI sequence.

Results: We recruited four patients (1 male and 3 female) with mean age of 20 years. All patients had Moyamoya disease with history of previous strokes and cerebral revascularization procedures (EC-IC bypass). All patients had both step and ramp changes in PETCo2 targets were achieved within 2 breaths in all patients. BOLD signal changes correlated with the changes in PETCo2. Impaired CVR with evidence of steal physiology was seen in 3 patients. Under propofol anesthesia, CBF values were lower when compared to sevoflurane (38.4 vs 56.6 in Grey matter and 31.6 vs 42.5 in white matter). In addition, even with hypercapnia, CBF values under propofol anesthesia were lower than the sevoflurane anesthesia under normocapnia.
**Discussion:** Our pilot study showed that using precise targeting of Co2 and BOLD-MRI, measurement of CVR is feasible in mechanically ventilated patients. This combined technique may be complementary in identifying vulnerable brain regions and thus constitute a "Brain Stress test". Non-invasive measurement of CBF is possible using ASL-MRI technique. Cerebral blood flow values (both normocapnia and hypercapnia) were lower under propofol anesthesia compared to sevoflurane.

**References:**

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83115 - SUMATRIPTAN IMPROVES QUALITY OF RECOVERY AFTER CRANIOLOGY

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Background: Microvascular decompression (MVD) is a surgical treatment for trigeminal neuralgia and hemifacial spasms. Current surgical approach is via a small craniotomy which often results in minimal surgical site pain, easily managed with conventional analgesics. However, these patients often experience post craniotomy headache which is a more complex type of pain reminiscent of a migraine headache and is associated with other unpleasant symptoms such as photophobia, nausea and vomiting. This headache may affect the quality of recovery and has the potential for development of chronic pain. Sumatriptan is used to treat migraine-like headaches in various settings. We conducted a randomized controlled study to investigate the effects of subcutaneous sumatriptan administration on post-operative headache and on the overall quality of recovery after MVD surgery.

Methods: This was a single centre, prospective, randomized double blind clinical trial. After REB approval and patient consent, fifty patients who complained of postoperative headache after MVD were randomised to receive a subcutaneous injection of sumatriptan (6 mg) or saline in the post-operative period. The primary outcome was quality of recovery as measured by the QoR-40 score at 24 hours. The QoR-40 is a validated tool to measure quality of recovery and has been used successfully following neurosurgery. The other outcome measures were pain and headache scores, total opioid consumption and hospital discharge times. Statistical analysis were using unpaired t-test, Mann-Whitney test, chi square test or Fischer’s exact test where appropriate. P value < 0.05 was considered significant.

Results: Fifty patients were randomised to the sumatriptan group (n=25) and placebo group (n=25). There were no statistically significant differences in demographics between the two groups. The QoR-40 scores were significantly higher in the sumatriptan group (median 184; interquartile range 169 – 196) than the placebo group (133; 119 – 155, p < 0.01), suggesting higher quality of recovery (table 1). The median scores for the individual aspects of the QoR-40 (physical comfort, emotional state, physical independence, patient support and pain) were all higher in the Sumatriptan group as compared with the placebo group. The sumatriptan group also had...
significantly lower headache scores at 4, 6 and 24 hours postoperatively. There were no significant differences in other secondary outcomes. The median duration of stay was 2 days (range 1 to 3 days) in both groups with no statistical differences ($p = 0.7$). There were no adverse events related to the use of sumatriptan in the study.

**Conclusions:** Our study showed that the use of Sumatriptan improves the quality of recovery as measured by the QoR-40 at 24 hours post-operatively. This may present as a useful alternative treatment for post-craniotomy headache. The precise mechanism remains unknown but may be related to reduction in headache, or mood modulation mediated by a serotonin effect.

**References:**

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84628 - IS SERUM LACTATE A POTENTIAL BIOMARKER OF NON-GLIAL BRAIN TUMORS?

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Introduction: Serum Lactate, an end product of anaerobic metabolism, is used as an indicator of poor tissue perfusion and a measure of severity of the illness. Malignant tumors often switch to aerobic glycolysis for their energy needs producing lactate even in the presence of oxygen. This phenomenon is called Warburg effect. We have shown that increased serum lactate can be used as a potential biomarker of high grade brain tumors (gliomas). The aim of this study was to determine if serum lactate can be used as a biomarker for non-glial cell brain (NGC) tumors.

Materials and methods: After IRB approval and patient consent we conducted a prospective observational study in patients undergoing craniotomy for brain tumors. We collected intra-arterial blood samples after induction of anesthesia and measured serum lactate values. We excluded patients with heart failure, renal or liver dysfunction and those needing inotropic support. Lactate >2 mmol/L was considered as elevated. Statistical analysis was done to calculate the incidence of elevated serum lactate in NGC tumors and to determine the correlation between elevated lactate and tumors of different non glial cell origin.

Results: During the study period (September 2013 to August 2014), we collected data from 121 non-glial brain tumor patients (Meningioma (n=28), Pituitary (37), Metastasis (17) and others (39)). Mean age of study population was 48.7(±13), weight 76.7(±12), M: F 59:62. Overall incidence of elevated lactate in NGC tumors was 34% with varying incidence among the individual tumor groups (meningioma 21%, pituitary 32%, metastasis 70% and others 36%). Patients with metastatic brain tumors had significantly higher baseline serum lactate levels as compared to patients with meningioma and pituitary tumors (p= 0.001, p=0.009 respectively). There was a statistically significant association of metastatic brain tumors with elevated serum lactate (p=0.002, odds ratio=5.4, CI=1.76-16.61, sensitivity 54.5%, specificity 81.8% and PPV 12%.

Discussion: Our study showed that the incidence of elevated serum lactate in NGC tumors was 34%. This finding is similar to variable incidence of brain lactate peak observed on MR spectroscopy of meningioma, pituitary and brain metastatic tumors.
Future studies comparing serum lactate and MR spectroscopic analysis in brain tumor patients are needed to correlate brain and serum lactate. As per our results there is no association between individual brain cell types and baseline serum lactate levels. However brain metastatic tumors had significant association with high baseline serum lactate demonstrating notable Warburg phenomenon. Tracking Warburg effect helps to analyse response to treatment in patients with brain tumors. Hence serum lactate level in non-glial tumor patients may be considered a potential biomarker for quantification of Warburg phenomenon.

References:

Introduction: Awake craniotomy for brain tumors in close proximity to areas of eloquent brain function is performed to minimize neurological injury during resection. The aim of conscious sedation is to have an awake and alert patient during brain mapping. The purpose of this study was to compare the efficacy of propofol-remifentanil (PR) versus dexmedetomidine (Dex) based sedation during awake craniotomy for tumor resection. The primary endpoint was the assessment of ability to perform intraoperative brain mapping and secondary endpoints the incidence of complications and patient satisfaction and outcome.

Materials and Methods: After IRB approval and written informed consent, we conducted a prospective, double blind randomized study. Patients were randomized to the PR or the Dex group. After placement of standard monitors in operating room, each patient received fentanyl 50mcg IV. Group PR received infusions of remifentanil (0.01-0.1mcg/kg/min) and propofol (25-100mcg/kg/min) for 10min, and then titrated to effect. Group Dex received Dex bolus 1mcg/kg for 10min, followed by infusion at 0.2-1mcg/kg/hr and propofol. In both groups additional analgesia and/or sedation when required was with fentanyl 0.5-1.0mcg/kg and/or propofol bolus (20-40mg). Local anesthesia (0.25% bupivacaine and 2% lidocaine with 1:200,000 epinephrine) was injected by the surgeon for pin insertion and infiltration of incision ringblock. At 10min prior to brain mapping, propofol infusion was stopped. Minimal infusion rates of R and Dex were continued. Data collected included intra and postoperative (2hr) hemodynamic and respiratory variables, intraoperative sedation, pain, anxiety and mapping scores, and all complications. At 1hr and 24hr patients were assessed with mental status questionnaire and recall and satisfaction scores. Statistical analysis was performed.

Results: 50 patients (PR (25): Dex (25)) were studied. One patient (Dex) was excluded from analysis due to conversion to general anesthetic at the onset by surgeon’s request.
Demographics and results are in Table. There were no significant differences between the groups with respect to mapping, postoperative complications, and postoperative patient recall and satisfaction scores. Intraoperative heart rate (HR) (80 vs 65, \( p = 0.001 \)) and mean blood pressure (MAP) (89 vs 82, \( p = 0.047 \)) were significantly lower in group Dex. Intraoperative respiratory complications (5 vs 0, \( p = 0.021 \)) were significantly more in the PR group.

**Discussion:** Both PR and Dex based sedation showed good efficacy for intraoperative brain mapping and postoperative patient satisfaction and outcome. Incidence of respiratory complications was more with group PR. In the Dex group overall MAP and HR were lower but did not require treatment. Most of the complications were quickly recognized and easily treated. Optimal dose regimen of sedatives and careful vigilance are the keys for successful conscious sedation for awake craniotomy.

**References:**


2. Annals Pharmacotherapy;2013;47:1391
Introduction: Many patients who undergo surgery with general anesthesia experience memory deficits that persist for days to months\(^1\)\(^2\). However, mechanisms underlying anesthesia-induced memory loss remain poorly understood. Animal models show that memory deficits following anesthesia are associated with a persistent increase in \(\gamma\)-aminobutyric acid type A (GABA\(_A\)) receptor activity\(^3\). The goal of this study was to use a cell culture model to elucidate the molecular mechanisms by which anesthetics increase GABA\(_A\) receptor activity. We hypothesized that glial cells, such as astrocytes, may play a key role in triggering anesthetic-induced increase in GABA\(_A\) receptor activity. Furthermore, since astrocytes express GABA\(_A\) receptors\(^4\), we postulated that anesthetics could exert their action by directly acting on astrocytes.

Methods: The study was approved by the local ethics committee. Cultures of hippocampal neurons, cortical astrocytes, and neuron-astrocyte co-cultures were prepared from embryonic mice. Cells were treated with the anesthetic etomidate (1 \(\mu\)M) or vehicle for 1 h and whole-cell currents were recorded from hippocampal neurons 24 h later. All data are expressed as mean ± SEM and were analyzed by Student’s \(t\)-test or ANOVA (\(p < 0.05\))

Results: Etomidate increased tonic current in neurons that were co-cultured with astrocytes by 75% (Control: 1.1±0.5 pA/pF; Etomidate: 1.9±0.9 pA/pF, \(n = 11\), \(p < 0.05\)) but had no effect in cell cultures containing only neurons. In addition, application of supernatant collected from astrocyte cultures treated with etomidate unto neurons significantly increased tonic current (Control: 1.1±0.2 pA/pF; Etomidate: 1.5±0.2 pA/pF, \(n = 6\), \(p < 0.05\)). This effect was abolished when bicuculline, a competitive GABA\(_A\) receptor antagonist, was co-applied with etomidate in both co-cultures and supernatant paradigms.

Discussion: These findings suggest that astrocytes are necessary for the etomidate-mediated increase in tonic current. Furthermore, these results indicate that activation of GABA\(_A\) receptors on astrocytes triggers the release of soluble factors that subsequently increase tonic current in neurons. Finally, our study provides a new model for understanding the interactions between astrocytes and neurons that are perturbed during general anesthesia.
References:

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Introduction: A quantitative test to diagnose concussion remains elusive. Here we summarize the feasibility and results of a repeatable CO₂ brain stress test employing blood oxygenation level-dependent (BOLD) MRI. This test may potentially aid in management of post-concussion syndrome (PCS).

Methods: Local Ethics Committee approval was obtained. Fourteen adolescent PCS patients and 14 healthy control subjects underwent anatomical MRI and MRI brain stress testing using controlled CO₂ challenge and BOLD MRI. A sequential hypercapnic challenge was delivered using a respiratory gas blender, individualized for each subject using a model-based end-tidal targeting system. Post-hoc processing was by statistical parametric mapping to determine voxel-by-voxel responsiveness of the brain to the CO₂ stimulus (increase in BOLD signal) or the inverse (decrease in BOLD signal).

Results: All subjects received an equivalent CO₂ stimulus, and all studies were well tolerated without any serious adverse events. Anatomical MRI was normal in all subjects. Between group comparisons at the p=0.005 level revealed a mean voxel count of 1745±1208 (PCS group) vs 103±281 (control group) for individual response greater than the control atlas (p=0.042) and a mean voxel count of 219±299 (PCS group) versus 3±6 (control group) for individual response less than the control atlas (p=0.017). Individual analysis confirmed changes in BOLD response for every patient, but with a pattern of abnormalities unique to each individual.

Discussion: The results reported here provide empirical evidence that post-concussion syndrome in adolescents is associated with abnormal cerebrovascular responsiveness. In addition, the resolution of this investigation method revealed that each patient had a unique pattern of abnormal BOLD signal with important regional differences, sometimes
showing simultaneous excessive and diminished responses in different areas of the brain, compared to the control atlas. These abnormalities in cerebrovascular responsiveness can be safely and reliably detected in adolescent PCS patients with the novel MRI brain stress test protocol described here.

The attached figure is a representative example of the second level analysis of a PCS patient to the atlas of normal controls, examined at the p=0.005 level. Voxels with a BOLD response greater than or less than that seen in the control atlas are displayed as hot and cold scale, respectively. PCSS: post concussion symptom score.

References:
2. Neuroimage 2012 2:791-800
Introduction: Anesthetics and sedatives are administered to over 234 million patients each year to allow them to tolerate surgery. Unfortunately, many patients experience memory deficits that persist long after the anesthetic has been metabolized. It was previously shown that the GABAergic anesthetics isoflurane and etomidate cause long-term memory deficits in animal models. However, it is unclear whether benzodiazepines and non-GABAergic anesthetics also cause persistent memory deficits. Anesthetic-induced memory deficits have been attributed to a persistent increase in tonic current mediated by γ-aminobutyric acid type A (GABA_A) receptors. Specifically, brief exposure to etomidate was shown to increase tonic GABAergic current in neuronal culture and ex vivo brain slices as well as induce memory deficits in mice 24 h after treatment. The goal of this study was to determine whether the benzodiazepine midazolam, the non-GABAergic anesthetic ketamine, and the endogenous agonist GABA also trigger a persistent increase in tonic current.

Methods: This study was approved by the local ethics committee. Whole-cell voltage clamp techniques were used to record tonic currents from cultures of hippocampal neurons and neuron-astrocyte co-cultures. Cells were treated with midazolam (200 nM), ketamine (300 µM), GABA (0.5 µM) or vehicle for 1 h and currents were recorded from hippocampal neurons 24 h later. All data are expressed as mean ± SEM and were analyzed by Student’s t-test or ANOVA when appropriate (p < 0.05).

Results: Midazolam increased tonic GABAergic current by 44% 24 h after treatment (Control: 0.9±0.3 pA/pF; Midazolam: 1.3±0.6 pA/pF). In contrast, ketamine and GABA alone had no effect on tonic current (Control: 1.3±0.5 pA/pF; Ketamine: 0.9±0.3 pA/pF; GABA: 1.3±0.3 pA/pF).

Discussion: This is the first evidence that midazolam, but not ketamine, causes a persistent increase in tonic GABAergic current. Considering the widespread use of benzodiazepines, this finding could have significant clinical implications for long-term memory loss after sedation.

References:
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2. Prog Brain Res 2008 169: 409-422
86259 - GABAA RECEPTORS CONTRIBUTE TO DEPRESSIVE BEHAVIORS IN MICE

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Introduction: One of the most exciting recent advances in modern anesthesiology and psychiatry is the discovery that a single low dose of ketamine is effective in treating refractory depression. This discovery has opened the door to the development of newer, faster-acting, and more effective antidepressant drugs. Accumulating evidence suggests that reduced function of the inhibitory neurotransmitter g-aminobutyric acid (GABA) system contributes to the pathogenesis of depression. In particular, the a5 subtype GABA<sub>A</sub> receptor has been implicated in both depression and anxiety-related disorders. Thus, repurposing anesthetics that target a5 subtype GABA<sub>A</sub> receptors is a novel therapeutic target for treating mood disorders. The goal of this study was to determine whether reduced expression of a5 GABA<sub>A</sub> receptors leads to a depressed and/or anxiogenic behavioral phenotype.

Methods: Approval from the local animal care committee was obtained for all experiments. Mice were randomly assigned to one of three experimental groups (n=10 per group): a5 wildtype (a5<sup>+/+</sup>); a5 knockout (a5<sup>−/−</sup>); a5 heterozygous (a5<sup>+/−</sup>). The experiments were designed to assess whether genetic manipulation of the a5 receptor are associated with depression and anxiety states. In addition, animals were assessed on executive function memory tasks, which have been shown to be impaired in depressed patients. Animals were serially assessed in a battery of behavioral tests which included: (1) open field test (OFT); (2) light-dark maze; (3) puzzle box; (4) elevated plus maze (EPM); (5) forced swim test (FST), and; (6) tail suspension test (TST). The same cohort of animals was tested on each behavioral paradigm.

Results: There was a significant group effect in the OFT [F(5,51)=6.94, p < 0.001]. Specifically, a5<sup>−/−</sup> mice displayed a higher rate of defecation in the OFT as compared to a5<sup>+/+</sup> animals, a variable which has been previously associated with high anxiogenic behavior in rodents. Preliminary results indicate that a5<sup>−/−</sup> animals are cognitively impaired compared to a5<sup>+/+</sup> animals in measures of executive functioning such as the puzzle box.

Discussion: A genetic knockdown of extrasynaptic a5 GABA<sub>A</sub> receptors causes an axiogenic phenotype in mice. These results suggest that pharmacological manipulation
of these receptors by positive allosteric modulators such as general anesthetics may alleviate depressive and axiogenic symptoms.

**Clinical Relevance:** Depression is a highly debilitating and pervasive illness which affects over 350 million people worldwide. The monetary costs of depression and related mood disorders that result from reduced productivity, job loss, hospitalization, and drug treatment exceeds well over 40 billion dollars annually. Repurposing anesthetic drugs that selectively act on extrasynaptic α5GABA<sub>A</sub> receptors may provide a novel alternative therapy for patients with depression. This strategy may enable the development of low-cost treatments that can be rapidly scaled up to address the global burden of depression.