

Research Protocol

Impact of CO₂ on cerebral blood flow in infants under 6 months of age during general anesthesia

Principal investigator:

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1. Hypothesis

Optimal cerebral perfusion is an essential objective during anesthesia, especially in infants, whose brains are immature. A number of factors influence cerebral blood flow (CBF) and cerebral oxygenation: arterial pressure, PaCO₂ and hemoglobin.

We previously showed that a mean arterial pressure (MAP) of between 35 and 45 mm Hg was an intraoperative objective for maintaining safe cerebral oxygenation in normocapnic conditions and in the absence of anemia in infants under 6 months of age. (1-3)

CO₂ influences cerebral vascular tone. Hypocapnia causes vasoconstriction, a decrease in CBF and a risk of cerebral ischemia, while hypercapnia causes vasodilation and an increase in CBF. (4)

Mechanical ventilation during general anesthesia changes PaCO₂. Furthermore, mechanical ventilation can be tricky in cases of lung disease in children requiring the use of high-frequency oscillatory ventilation. As well, surgery can influence mechanical ventilation as a result of pressure exerted on the lungs, either directly (thoracotomy or thoracoscopy) or indirectly via the abdomen (laparoscopy). Endoscopic techniques use insufflation with CO₂, a gas that readily diffuses through the pleura or peritoneum to the infant's blood compartment.

Like hypotension, an unsuitable intraoperative PaCO₂ can cause serious neurological sequelae. (5-7)

2. Objectives

Our primary objective is to determine the impact of varying EtCO₂ and, therefore, PaCO₂ on CBF and cerebral oxygenation with a MAP of between 35 and 40 mm Hg in infants under 6 months of age during general anaesthesia

3. Methodology

This will be a prospective study involving infants under the age of 6 months admitted to the surgical suite for surgery requiring mechanical ventilation.

During the anesthesia consultation, explanations will be provided regarding the anesthesia protocol used, with special focus on the following:

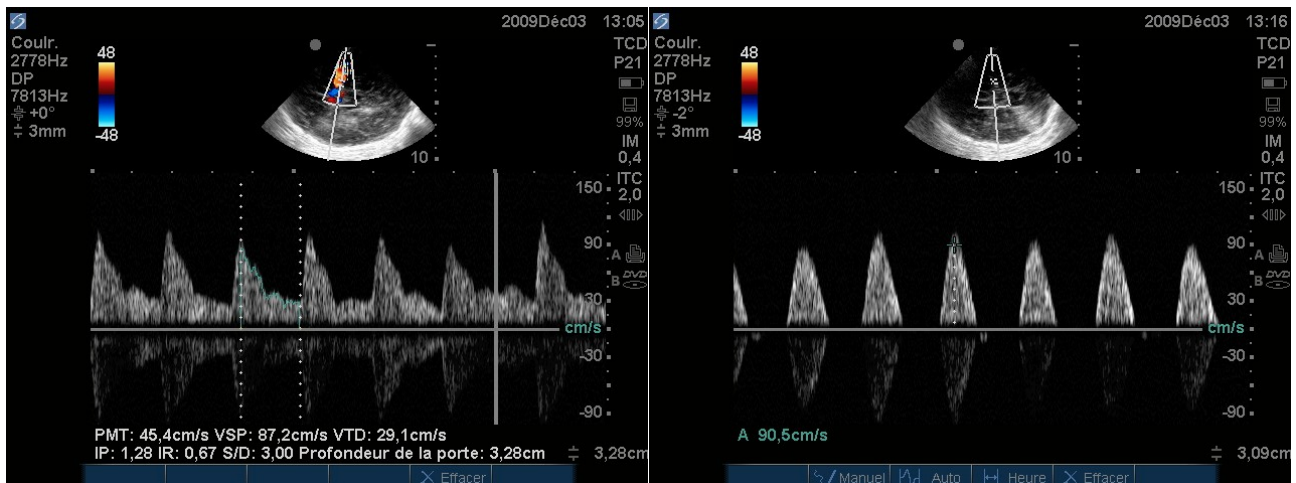
- The standard anesthesia technique, no change in the drugs administered, especially with regard to sedation and analgesia.
- The noninvasive, painless and adverse effect-free technique for evaluating cerebral perfusion.
- Changing cerebral perfusion in the direction of improvement (increase in EtCO₂ and increase in

CBF).

An information and consent form will be drafted using the REB's template (see appendix).

Cerebral perfusion will be evaluated by:

- Measuring the systolic, diastolic and mean velocities in the middle cerebral artery using transcranial Doppler ultrasound (see example below).



Infant awake and then under general anesthesia. Systolic and diastolic flow is observed in the awake infant. This flow disappears after the induction of general anesthesia.

- Measuring cerebral oxygen saturation using a tissue oxygen saturation sensor placed in the frontal region.

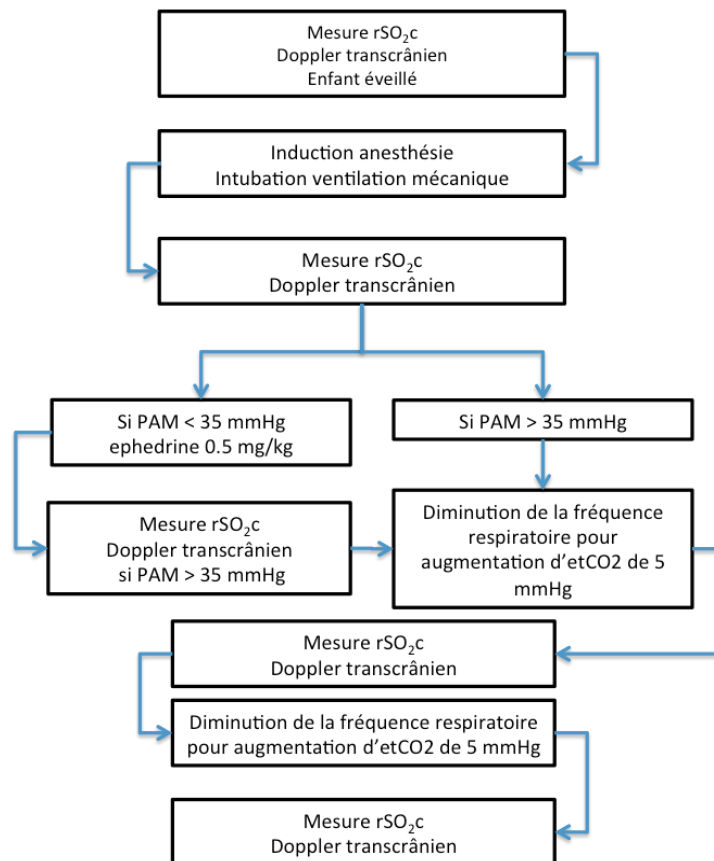


INVOS™ OxyAlert™ NIR Sensors

Near-infrared spectroscopy (NIRS) is used to noninvasively evaluate regional cerebral oxygen saturation (rSO_2c). It reflects the balance between cerebral oxygen supply and consumption (8). A decrease in rSO_2c indicates either an increase in cerebral oxygen consumption ($CMRO_2$) and/or inadequate oxygen supply (decrease in CBF). On the other hand, an increase in rSO_2c could indicate either an increase in CBF or a decrease in $CMRO_2$ caused, for example, by general anesthesia.

Description of study (diagram below)

We will perform a first measurement in the infant while awake. After the induction of general anesthesia and airway control, a series of measurements (Doppler and cerebral oxygen saturation) will be made. The following parameters usually used in anesthesia in infants under 6 months of age will be used for the mechanical ventilation: tidal volume, 8 ml/kg; positive expiratory pressure, 5 mm Hg; and a baseline respiratory rate of 25 to 40 cycles per minute, depending on the infant's age. If necessary, a bolus of ephedrine, 0.5 mg/kg, will be administered if the MAP is less than 35 mm Hg after the induction of anesthesia. Subsequently, two series of measurements with a MAP greater than 35 mm Hg will be made after modifications to the ventilation to effect an increase of 5 mm Hg in the EtCO₂ value. The Doppler and cerebral oxygen saturation measurements and both controlled modifications to the mechanical ventilation are specific to this protocol. All the other aspects of the management are based on standard pediatric anesthetic care.



4. **Description of population**

- Inclusion criteria

This will be a prospective study involving infants under 6 months of age admitted to the surgical suite for surgery requiring orotracheal intubation.

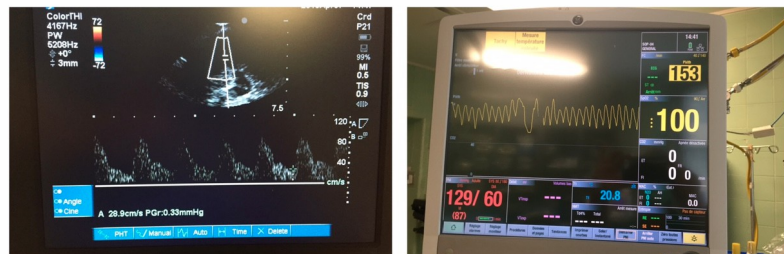
- Exclusion criteria

The exclusion criteria will be as follows: infant over 6 months of age, infant with intracranial pathology or a chronic respiratory disease that causes hypercapnia, parental refusal and surgical emergency.

✓ Anticipated benefits for participants.

The Doppler and cerebral oxygen saturation measurements are noninvasive and painless. The measurements will be made at different CO₂ levels within a range usually observed during general anesthesia in infants (9). In our study, we will vary the CO₂ in the direction of optimizing cerebral perfusion. (Example below with transcranial Doppler: diastolic velocity zero after intubation, and normalization after correcting the MAP and CO₂).

Infant awake



After induction:
EtCO₂ = 29



After increase in
EtCO₂ to 40



5. Statistical analysis

We will analyze the impact of changes in CO₂ on cerebral oxygen saturation and velocities. The Spearman coefficient of correlation will be used to study the correlations between the cerebral perfusion parameters (cerebral velocities and rSO₂c) and EtCO₂. An ANOVA will be performed to determine the significant differences in rSO₂c and cerebral velocities according to EtCO₂.

A change in EtCO₂ of +10 mm Hg could result in a relative increase in rSO₂c of +10%. Therefore, with a mean standard deviation of rSO₂c of 13% observed in the previous studies, we calculate the necessary number of subjects to be 36 (alpha risk = 5%; beta risk = 90%). To ensure that we will be able to analyze 36 patients, we hope to include 60 patients in the study. An interim analysis of the results will be performed after 20 patients have been included.

6. Timetable and funding

For the number of patients to be included (n=60), based on the volume of activity in the CHU Sainte Justine's surgical suite, we estimate that the duration of the study will need to be 18 months (3 to 5 patients a month).

The company Covidien is lending the cerebral oxygen saturation monitor and is providing the 60

sensors needed for the study. We will use the Department of Anesthesiology's sonograph.

Patient recruitment, parent explanations and the signing of the consent forms will be looked after by the anesthesiologist/principal investigator.

7. References

1. Rhondali O, Pouyau A, Mahr A et al. Sevoflurane anesthesia and brain perfusion. *Paediatr Anaesth*. 2015 Feb;25(2):180-5.
2. Rhondali O, Juhel S, Mathews S et al. Impact of sevoflurane anesthesia on brain oxygenation in children younger than 2 years. *Paediatr Anaesth*. 2014 Jul;24(7):734-40.
3. Rhondali O, Mahr A, Simonin-Lansiaux S et al. Impact of sevoflurane anesthesia on cerebral blood flow in children younger than 2 years. *Paediatr Anaesth*. 2013 Oct;23(10):946-51.
4. Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med*. 2002 Jul 4; 347(1):43-53.
5. Weiss M, Vutskits L, Hansen TG et al. Safe Anesthesia For Every Tot - The SAFETOTS initiative. *Curr Opin Anaesthesiol*. 2015 Jun;28(3):302-7.
6. McCann ME, Schouten AN, Dobija N et al. Infantile postoperative encephalopathy: perioperative factors as a cause for concern. *Pediatrics*. 2014 Mar;133(3):e751-7.
7. McCann ME, Schouten AN. Beyond survival; influences of blood pressure, cerebral perfusion and anesthesia on neurodevelopment. *Paediatr Anaesth*. 2014 Jan;24(1):68-73.
8. Bernal NP, Hoffman GM, Ghanayem NS et al. Cerebral and somatic near-infrared spectroscopy in normal newborns. *J Pediatr Surg* 2010; 45: 1306–1310.
9. Hilly J, Pailleret C, Fromentin M et al. Use of near-infrared spectroscopy in predicting response to intravenous fluid load in anaesthetized infants. *Anaesth Crit Care Pain Med*. 2015 Oct; 34(5):265-70.

8. Appendix



INFORMATION ABOUT THE RESEARCH, AND CONSENT FORM

Title: **Impact of CO₂ on cerebral blood flow in infants under 6 months of age during general anaesthesia.**

Persons in charge:

CHU Sainte-Justine: Dr. Ossam Rhondali and Dr. Bruno Greff

Funding source: Department of Anesthesiology. The equipment is being provided by the company Covidien.

WHY ARE YOU BEING INVITED TO PARTICIPATE IN THIS RESEARCH PROJECT?

The CHU Sainte-Justine's Department of Anesthesiology is taking part in research projects aimed at improving the quality of care and the safety of children in the surgical suite. We are today requesting your participation. Please read this information form in order to decide if you are interested in participating in this research project. It is important that you fully understand this form. Please feel free to ask questions. Take all the time you need to make a decision.

In this consent form, "you" refers to you or your child.

WHY IS THIS RESEARCH PROJECT BEING CONDUCTED?

Background and relevance of this research

Brain oxygenation is an essential objective during anesthesia, and a number of factors influence it: arterial pressure, hemoglobin and breathing.

During general anesthesia, your child's breathing will be controlled by a respirator, which, in turn, will be adjusted and controlled by an anesthesiologist. Breathing permits oxygen supply to the body and the elimination of carbon dioxide gas (CO₂).

Carbon dioxide influences oxygen supply to the brain. A decrease in CO₂ causes a decrease in the oxygen supply, while an increase in CO₂ causes an increase in oxygen supply.

Objectives of this research

We are inviting you to participate in this research project, which is aimed at studying the impact of the CO₂ level on cerebral perfusion during anaesthesia.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS RESEARCH PROJECT?

About 60 participants will take part in this project at our facility.

HOW WILL THIS RESEARCH PROJECT PROCEED?

This study involves infants under 6 months of age admitted to the surgical suite for surgery requiring general anesthesia. The management of the anesthesia will be the same as that usually provided in infants under 6 months of age.

What is added in this research project is the evaluation of brain perfusion, which will be done by means of ultrasound and a cerebral oxygen saturation sensor placed on the forehead. Both techniques are painless and noninvasive and are frequently used for neurological monitoring in intensive care and cardiac surgery.

Brain perfusion will be evaluated at different CO₂ levels, which will depend on the ventilation controlled by the anesthesiologist. The anesthesiologist will control the ventilation to maintain the CO₂ values at physiological levels (levels expected for the child).

WHAT IS THE DURATION OF PARTICIPATION IN THIS RESEARCH PROJECT?

Your child will participate in the project during anesthesia but will not require any monitoring or change in his/her postoperative management in connection with his/her participation in the project.

WHAT ARE THE RISKS?

Doppler and brain oxygen saturation measurements are noninvasive and painless. The Doppler ultrasound measurements will be made intermittently and will not involve any risks. Measuring brain oxygen saturation will require the use of a sensor attached to your child's forehead. When the sensor is removed, slight redness of the skin due to the sensor's adhesive may persist. It is the same phenomenon observed when an adhesive bandage is removed. The measurements will be made at different CO₂ levels within a range usually observed during general anesthesia in infants. Furthermore, our study will vary the CO₂ level in the direction of optimizing brain perfusion.

ARE THERE ANY BENEFITS IN PARTICIPATING IN THIS RESEARCH PROJECT?

There would be no direct benefit for your child in participating in this study. However, your participation will help provide us with a better knowledge of the brain and further improve care quality and safety.

HOW WILL CONFIDENTIALITY BE ENSURED?

All the information gathered will remain confidential to the extent permitted by law. Your child's identity will be protected by replacing your name with a research code. Only your hospital's research team will have access to the link between the code and your name. The company Covidien will not have access to the data obtained during this research.

To check that the research is proceeding properly and to ensure your protection, the Hôpital Sainte-Justine Research Ethics Board may consult your research file and your medical record.

If the overall results of this research project are published or presented at scientific conferences, your name and other personal information will not be used.

The research data will be stored in a secure manner for 7 years under the responsibility of the principal investigator at your hospital.

ARE YOU FREE TO PARTICIPATE?

Yes. Participation in this research project is voluntary. You are free to choose not to participate in this research project. If you do not participate in this research project, this would not affect the quality of care provided to your child.

RESOURCE PERSONS

If you have any questions about this research project or experience a problem that you believe is related to your participation in the project, you can contact the investigator in charge of the project at your hospital:

- CHU Sainte-Justine: Dr. Ossam Rhondali, Anesthesiology. 514-345-4733.

For any information about your rights, you can contact the Local Ombudsman and Service Quality Commissioner:

- CHU Sainte-Justine: 514-345-4749.

WHERE CAN I OBTAIN ADDITIONAL INFORMATION?

Clinical Trials (in English only): A description of this clinical trial will be available at <http://www.clinicaltrials.gov> in accordance with the provisions of US and Canadian law. This site will not contain any information by which you could be identified. At most, the site will present a summary of the results. You can search the site at any time.

You can request a summary of the results of this research project. They will be available only after the project is completely finished.

You will receive a signed copy of this form. You can ask the research team questions at any time.

RESEARCH ETHICS BOARD

The Hôpital Sainte-Justine Research Ethics Board has approved this research project and is monitoring it.

CONSENT

Title of research project

Impact of CO₂ on cerebral blood flow in infants under 6 months of age during general anaesthesia

The nature and conduct of this research project have been explained to me. I have read the consent form and have been given a copy of it. I have had the opportunity to ask questions, and they have been answered. After due consideration, I agree to my child participating in this research project.

I authorize the research team to consult my child's medical record in order to obtain information relevant to this project.

In signing this consent form, you are not waiving any of your legal rights. Furthermore, you are not releasing the investigators and the sponsor from their legal and professional liability in the event of a situation that causes you harm.

Your child's name:

Date:

Name of parent or guardian:
(Printed)

Consent (signature)

Date:

I have explained all the relevant aspects of the research to the parents and answered the questions they asked me. I have explained to them that participation in this research project is free and voluntary and that participation can be terminated at any time.

Name of person obtaining consent:
(Printed)

(signature)

Date: