Cerebral blood flow during propofol anaesthesia. Study protocol.

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**Detailed Description:**

**Background**

General anaesthesia reduces blood pressure, but cerebral autoregulation is considered to maintain its blood flow if mean arterial pressure (MAP) is between 60-150 mmHg. Thus, vasoactive medication is administered to treat anaesthesia-induced hypotension if MAP decreases to below approximately 60 mmHg. In young healthy adults, propofol anaesthesia, with limited reduction in blood pressure, decreases cerebral blood flow by approximately 50% by a decrease in neuronal activity. However, it is unknown whether the anaesthesia-induced reduction in cerebral blood flow is affected by a marked decrease in MAP and whether propofol anaesthesia affects the lower level of cerebral autoregulation.

If central blood volume is maintained, cerebral oxygenation may be unaffected by a decrease in MAP to ~40 mmHg whereas a reduction in central blood volume and cardiac output (CO) during orthostasis or bleeding, reduces cerebral oxygenation when MAP is lower than approximately 80 mmHg. Thus, CO may affect cerebral blood flow and the ability to increase CO is likely of importance for maintaining a sufficient cerebral blood flow.

During anaesthesia, cerebral blood flow and MAP may be affected by various factors including release of vasoactive substances. Manipulation of the abdominal organs may induce a so-called mesenteric traction syndrome (MTS) encompassing a triad of flushing, hypotension, and tachycardia in about half of the patients who undergo major abdominal surgery. MTS typically develops 15-20 min after the start of surgery and the haemodynamic manifestations, that appear to be mediated by prostaglandin I2, last for approximately 30 min. The effect of MTS on cerebral blood flow is unknown. Prostaglandin I2 dilates cerebral arteries in vitro but does not affect cerebral blood flow when administered to healthy subjects. In a previous study we found that MTS increases near-infrared spectroscopy determined frontal lobe oxygenation possibly due to an increase in extracranial circulation while there was no effect on middle cerebral artery mean flow velocity as an index of changes in cerebral blood flow.

Propofol anaesthesia appears not to affect the CO₂ reactivity of the middle cerebral artery as determined by transcranial Doppler ultrasonography, but the CO₂ reactivity of the internal carotid artery during propofol anaesthesia is unknown.
Cerebral blood flow during propofol anaesthesia. Study protocol.

Date: 19 November 2017

Objective
The purpose of this study is to evaluate how internal carotid artery blood flow is affected by propofol anaesthesia and related hypotension, and by administration of phenylephrine as standard care to treat anaesthesia-induced hypotension. Further, the study will assess whether internal carotid artery blood flow is affected by development of MTS and whether propofol anaesthesia affects the CO₂ reactivity of the internal carotid artery.

Hypotheses
1) Propofol anaesthesia and related anaesthesia-induced hypotension (MAP < 65 mmHg) reduces internal carotid artery blood flow
2) Treatment of anaesthesia-induced hypotension by administration of phenylephrine increases internal carotid artery blood flow
3) Development of MTS increases near-infrared spectroscopy determined frontal lobe oxygenation due to an increase in forehead skin blood flow and oxygenation with no effect on internal carotid artery blood flow
4) Propofol anaesthesia lowers the CO₂ reactivity of the internal carotid artery

Methods
The study will include thirty patients undergoing oesophageal- or ventricular resection. The study was approved by the Regional Ethical Committee (De Videnskabsetiske Komiteer Region Hovedstaden id: H-16036250) and the Danish Dataprotection Agency. The study lasts from when the patient arrives to the operating room and until two hours after the start of surgery. As part of standard care all patients will be instrumented with arterial and central venous catheters. Anaesthesia will be induced by propofol and maintained by propofol and remifentanil combined with epidural anaesthesia. Development of MTS is defined by flushing within the first 60 min of surgery. Measurements include unilateral internal carotid artery blood flow evaluated by duplex ultrasound, MAP and heart rate as recorded by a transducer connected to the arterial line, central haemodynamics (stroke volume, CO, and total peripheral resistance) evaluated by pulse contour analysis of the arterial pressure curve, frontal lobe and muscle oxygenation as determined by near-infrared spectroscopy, forehead skin blood flow, haemoglobin concentrations, and oxygenation
Cerebral blood flow during propofol anaesthesia. Study protocol.

Date: 19 November 2017

assessed by laser Doppler flowmetry, and depth of anaesthesia determined by Bispectral Index. Arterial blood will be drawn for analysis of the arterial CO₂ tension (PaCO₂).

During the study PaCO₂ will be maintained at the value before induction of anaesthesia by ventilator adjustments. Internal carotid artery CO₂ reactivity before induction of anaesthesia will be determined by evaluations of blood flow and PaCO₂ during normoventilation and during hyperventilation to reduce PaCO₂ by 1.5 kPa as guided by end-tidal CO₂ tension (PetCO₂) and measurements will be conducted when PetCO₂ has been stable for 5 min. The CO₂ reactivity during anaesthesia will be determined by evaluations of internal carotid artery blood flow and PaCO₂ at a PaCO₂ at the value before induction of anaesthesia and 1.5 kPa above and below that value as guided by PetCO₂ and measurements will be conducted when PetCO₂ has been stable for 5 min. The CO₂ reactivity before and during anaesthesia is calculated as the percentage change in internal carotid artery blood flow per kPa change in PaCO₂. Analysis of internal carotid blood flow will be after correction for CO₂ reactivity.

Blood samples for analysis of markers of MTS (6-keto-prostaglandin-F₁, pro-ANP, ACTH, cortisone, IL-1, IL-6, and TNF-α) will be drawn before induction of anaesthesia and 20 and 60 min after the start of surgery. Total amount of blood samples will be no more than 75 ml. Patients will be excluded if the planned surgery is cancelled and excluded patients will be replaced.

Measurements will be conducted and arterial blood drawn at the following time points:
- Before induction of anaesthesia during normoventilation and hyperventilation
- After induction of anaesthesia
- During anaesthesia-induced hypotension (MAP < 65 mmHg)
- After treatment of anaesthesia-induced hypotension by administration of phenylephrine
- 5 min before and after incision and 0, 20, 40 and 70 min after development of MTS and 20, 40, 60 and 90 min after the start of surgery in patients who did not develop MTS
- During normo-, hyper-, and hypocapnia during anaesthesia in random order

Statistics
Trial size: The minimal clinically important difference in internal carotid artery blood flow by treatment of anaesthesia-induced hypotension is considered to be 10%, corresponding to
Cerebral blood flow during propofol anaesthesia. Study protocol.

Date: 19 November 2017

approximately 24 ml/min, and twenty-seven patients were considered required assuming a 42 ml/min SD with a 5% significance level and a power of 80%.

**Outcome Measures**

**Primary Outcome Measures:**

1. Changes in internal carotid artery blood flow by treatment of anaesthesia-induced hypotension
   Time Frame: Two measurements; during anaesthesia
   Designated as safety issue: No
   Unilateral internal carotid artery blood flow [ml/min] assessed by duplex ultrasound as determined during anaesthesia-induced hypotension (mean arterial pressure < 65 mmHg) and after administration of phenylephrine.

**Secondary Outcome Measures:**

2. Changes in internal carotid artery blood flow by induction of anaesthesia
   Time Frame: Two measurements; before and after induction of anaesthesia
   Designated as safety issue: No
   Unilateral internal carotid artery blood flow [ml/min] assessed by duplex ultrasound as determined before and after induction of anaesthesia.

3. Association between changes in internal carotid artery blood flow, mean arterial pressure and cardiac output by treatment of anaesthesia-induced hypotension
   Time Frame: Two measurements; during anaesthesia
   Designated as safety issue: No
   Association between changes in unilateral internal carotid artery blood flow [ml/min] assessed by duplex ultrasound, mean arterial pressure [mmHg] as recorded by a transducer connected to an arterial line, and cardiac output [l/min] evaluated by pulse contour analysis of the arterial pressure curve (Modelflow) as determined before and after treatment of anaesthesia-induced hypotension (mean arterial pressure < 65 mmHg) by administration of phenylephrine.
4. Changes in frontal lobe oxygenation by development of mesenteric traction syndrome
   Time frame: Six measurements; during anaesthesia
   Designated as safety issue: No
   Near-infrared spectroscopy determined frontal lobe oxygenation [%] as compared between those patients who develop mesenteric traction syndrome (defined as flushing within 60 min after the start of surgery) and those who do not as determined 5 min before and after incision and 0, 20, 40, and 70 min after flushing and 20, 40, 60, and 90 min after the start of surgery in those who do not develop mesenteric traction syndrome.

5. Changes in forehead skin blood flow by development of mesenteric traction syndrome
   Time frame: Six measurements; during anaesthesia
   Designated as safety issue: No
   Forehead skin blood flow [PU] assessed by laser Doppler flowmetry as compared between those patients who develop mesenteric traction syndrome (defined as flushing within 60 min after the start of surgery) and those who do not as determined 5 min before and after incision and 0, 20, 40, and 70 min after flushing and 20, 40, 60, and 90 min after the start of surgery in those who do not develop mesenteric traction syndrome.

6. Changes in forehead skin oxygenation by development of mesenteric traction syndrome
   Time frame: Six measurements; during anaesthesia
   Designated as safety issue: No
   Forehead skin oxygenation [%] assessed by laser Doppler flowmetry as compared between those patients who develop mesenteric traction syndrome (defined as flushing within 60 min after the start of surgery) and those who do not as determined 5 min before and after incision and 0, 20, 40, and 70 min after flushing and 20, 40, 60, and 90 min after the start of surgery in those who do not develop mesenteric traction syndrome.

7. Changes in internal carotid artery blood flow by development of mesenteric traction syndrome
   Time frame: Six measurements; during anaesthesia
   Designated as safety issue: No
Cerebral blood flow during propofol anaesthesia. Study protocol.

Date: 19 November 2017

Unilateral internal carotid artery blood flow [ml/min] assessed by duplex ultrasound as compared between those patients who develop mesenteric traction syndrome (defined as flushing within 60 min after the start of surgery) and those who do not as determined 5 min before and after incision and 0, 20, 40, and 70 min after flushing and 20, 40, 60, and 90 min after the start of surgery in those who do not develop mesenteric traction syndrome.

8. Changes in the CO\textsubscript{2} reactivity of the internal carotid artery from before to after induction of anaesthesia
   Time frame: Five measurements; before and during anaesthesia
   Designated as safety issue: No
   Unilateral internal carotid artery blood flow [ml/min] assessed by duplex ultrasound and arterial CO\textsubscript{2} tension (PaCO\textsubscript{2}) [kPa] are evaluated before induction of anaesthesia during normoventilation and hyperventilation to reduce PaCO\textsubscript{2} by 1.5 kPa and during anaesthesia at a PaCO\textsubscript{2} at the value before induction of anaesthesia and 1.5 kPa above and below that value. The CO\textsubscript{2} reactivity before and during anaesthesia is calculated as the percentage change in internal carotid artery blood flow per kPa change in PaCO\textsubscript{2} and the values are compared.

9. Changes in heart rate from baseline
   Time Frame: Continuous measurements before induction of anaesthesia and during anaesthesia
   Designated as safety issue: No
   Heart rate [bpm] as recorded continuously by a transducer connected to an arterial line.

10. Changes in mean arterial pressure from baseline
    Time Frame: Continuous measurements before induction of anaesthesia and during anaesthesia
    Designated as safety issue: No
    Mean arterial pressure [mmHg] as recorded continuously by a transducer connected to an arterial line.
Cerebral blood flow during propofol anaesthesia. Study protocol.

Date: 19 November 2017

11. Changes in cardiac output from baseline
   Time Frame: Continuous measurements before induction of anaesthesia and during anaesthesia
   Designated as safety issue: No
   Cardiac output [l/min] as evaluated continuously by pulse contour analysis of the arterial pressure curve (Modelflow).

12. Changes in stroke volume from baseline
   Time Frame: Continuous measurements before induction of anaesthesia and during anaesthesia
   Designated as safety issue: No
   Stroke volume [ml] as evaluated continuously by pulse contour analysis of the arterial pressure curve (Modelflow).

Inclusion Criteria
- Patients planned for major abdominal surgery that require placement of an arterial line and central venous catheter, including oesophageal- or ventricular resection
  - Age $\geq$ 18 years.

Exclusion Criteria
- No informed consent
- Robotic assisted procedures
- Treatment with anti-inflammatory medication, including NSAID and corticosteroids
- Atherosclerosis of the internal carotid artery that obstructs $\geq$ 30% of the vessel lumen
- Neurologic disease considered to affect cerebral blood flow, including dementia, epilepsy, and apoplexy

Contacts/Locations
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Cerebral blood flow during propofol anaesthesia. Study protocol.

Date: 19 November 2017

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References
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