Protocol - Effect of Sodium Nitroprusside on Cerebral Blood Flow

Brief Title: Effect of sodium nitroprusside on cerebral blood flow
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Sponsor: Rigshospitalet, Denmark
Principal investigator: Niels Damkjær Olesen, MD
Sub-Investigator: Niels H. Secher, M.D., D.M.Sc., Prof.

Contacts/Locations

Central Contact: Niels D. Olesen, MD
Telephone: 0045 35452674
Email: nielsdolesen@gmail.com

Central Contact Backup: Niels H. Secher, M.D., D.M.Sc., Prof..
Telephone: 0045 35452242
Email: niels.secher@regionh.dk

Study Officials: Niels D. Olesen, MD
Study Principal Investigator
Department of Anesthesia, Rigshospitalet 2043, DK-2100 Copenhagen Ø, Denmark

Locations: Department of Anesthesia, Rigshospitalet 2043, DK-2100 Copenhagen Ø, Denmark
Facility contact: Niels D. Olesen, M.D. Tel.: 0045 35452674 e-mail: nielsdolesen@gmail.com

Short Description

The brain has a high energy demand and requires continuous blood flow. The blood flow to the brain appears to be unaffected by small changes in blood pressure, but brain blood flow may be reduced by a large reduction in blood pressure. Large reductions in blood pressure are common during anesthesia or bleeding. It is unclear, however, how a given reduction in blood pressure affects blood flow to the brain.

In this study, medicine called sodium nitroprusside is used to dilate blood vessels and reduce blood pressure in twenty healthy young men. The study will evaluate whether blood flow to the brain is affected when sodium nitroprusside is used to induce a moderate and a large reduction in blood pressure. Blood flow to the brain is evaluated using ultrasound on the neck.

During breathing, oxygen is inhaled and carbon dioxide is exhaled. Carbon dioxide increases brain blood flow whereby changes in respiration can affect the blood flow to the brain. Sodium nitroprusside causes mild hyperventilation, whereby more carbon dioxide is exhaled, which will contribute to a reduction in brain blood flow. Thus, the study will also evaluate how brain blood flow is affected by hyperventilation and by breathing a mix of air and carbon dioxide.

Background

Cerebral autoregulation is generally considered to maintain cerebral blood flow (CBF) if mean arterial pressure (MAP) is between 60 and 150 mmHg. Yet, it is controversial whether there is a plateau for CBF. Thus, blood velocity of the middle cerebral artery (MCA V_{mean}), as an index of CBF, is affected by pharmacological changes in MAP between approximately 40-125 mmHg. In contrast, internal carotid artery blood flow is unaffected by a moderate decrease in blood pressure.

The brain is supplied by the internal carotid and vertebral arteries that have different regulation with higher CO_2 reactivity and larger orthostatic reduction for the internal carotid than the vertebral artery. The different regulation of the two arteries may reflect higher sympathetic innervation of arteries that originate from the internal carotid artery than those of the vertebral artery. The internal carotid artery may contribute to cerebral autoregulation as the vessel dilates during a moderate decrease in MAP while internal carotid artery blood flow is maintained. The arterial CO_2 tension ($PaCO_2$) is an important regulator of CBF and also maintenance of central blood volume and cardiac output is important for regulation of CBF. In the present study, internal carotid and vertebral artery blood flow is evaluated using duplex ultrasound in 20 healthy men when MAP is reduced by sodium nitroprusside, a potent short-lasting vasodilator.

Objective

The purpose of the study is to evaluate whether CBF is affected by 20% and 40% reductions in MAP by sodium nitroprusside. The CO2 reactivity of the internal carotid and vertebral arteries is evaluated in order to control for hyperventilation during sodium nitroprusside induced hypotension. Further, the study will evaluate whether changes in internal carotid and vertebral artery blood flow by a 40% reduction in MAP are different and whether the arteries have different CO2 reactivity. Lastly, the study will evaluate whether the slope of the linear regression of CBF and MAP is higher for the evaluations when MAP is reduced by 40% and 20% than that of the evaluations at baseline and when MAP is reduced by 20%.

Hypotheses

- Sodium nitroprusside-induced reduction in MAP by 40% reduces CBF
- Sodium nitroprusside-induced reduction in MAP by 20% reduces CBF
- Sodium nitroprusside-induced reduction in MAP by 40% causes a larger relative reduction in internal carotid artery blood flow than that of the vertebral artery
- The CO_2 reactivity of the internal carotid artery is higher than that of the vertebral artery
- The slope of linear regression of MAP and CBF at the evaluations when MAP is reduced by 20% and 40% by sodium nitroprusside is higher than that of the evaluations at baseline and when MAP is reduced by 20%

Methods

The study will include 20 healthy men. The experiment lasts for approximately three hours and the subject must be fasting for at least 4 hours, have abstained from alcohol and caffeine for 12 hours and rigorous exercise for 24 hours. Before the start of the experiment, the internal carotid and vertebral arteries are evaluated and in case the vessels can not be visualized, e.g. because of high carotid bifurcation, the subject will not be able to participate in the study. The subject rests in the supine position throughout the study.

Measurements

A catheter is placed in the radial or brachial artery on the non-dominant arm for evaluation of arterial pressure and gas variables. Total volume of blood sampled is less than 25 ml. A long line is placed in a cubital vein and advanced to the subclavian vein for infusion of sodium nitroprusside (Cavafix 20G 32 cm, B. Braun, Melsungen, Germany). The arterial pressure measurement is used for evaluation of stroke volume, cardiac output, and total peripheral resistance by modified pulse contour analysis (Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). Heart rate is evaluated by electrocardiogram lead II. Forehead skin oxygenation and blood flow is evaluated close to the hairline using Laser Doppler flowmetry with an integrated oxygenation sensor at a depth of 1-2 mm in an area of approximately 9 mm^2 (MoorVMS-LDF and MoorVMS-OXY, Moor Instruments, Axminster, UK). Cerebral and biceps muscle oxygenation are evaluated using near-infrared spectroscopy (INVOS 5100C, Somanetics, Troy, MI, USA). Transcranial Doppler is used to evaluate MCA V_{mean} (Multidop X; DWL, Sipplingen, Germany). At a constant diameter of

the MCA, changes in blood velocity reflect those of regional CBF, but the diameter may be affected by changes in MAP and $PaCO_2$.

Changes in central blood volume are evaluated by recording of thoracic electric admittance (C-guard, DanMeter, Odense, Denmark). Central hemodynamics, MCA V_{mean}, electrocardiogram, and skin oxygenation and blood flow is recorded at 100 Hz (Powerlab 16/35 and LabChart 7, ADInstruments, Bella Vista, Australia), cerebral and muscle oxygenation is recorded at 0.1 Hz, and thoracic admittance at 0.25 Hz and saved on a pc.

Internal carotid and vertebral artery blood flow is evaluated unilaterally on the neck using duplex ultrasound (Logiq E, GE Medical System, Jiangsu, China). Evaluation is in the longitudinal section 1-2 cm distal to the carotid bifurcation and the vertebral artery is evaluated between the transverse processes of C2-5 with the head turned approximately 30º to the contralateral side. In order to limit the influence of ventilation, two recordings of approximately 20 s of both arteries are conducted at each level of MAP and the mean is reported. A frequency of 8-12 MHz is used and gain is set as high as possible while vessel lumen is echo-free. The angle-corrected time maximum flow velocity (TAVMAX), that corresponds to twice the mean blood velocity, is evaluated using pulsed-wave Doppler at stable angle ≤ 60º. Diameter is assessed using automatic software to track the vessel wall (Brachial Analyser for Research v. 6, Medical Imaging Applications LLC, Coralville, IA, USA) and blood flow is: 0.125*60*TAVMAX*π*diameter^2 and CBF is the sum of unilateral internal carotid and vertebral artery blood flow.

The CO_2 reactivity of the internal carotid and vertebral artery is: change in blood flow *100 / change in $PaCO_2$ * baseline blood flow using individual linear regression for the evaluations during normo-, hypo-, and hypercapnia. The CO2 reactivity of MCA Vmean and cerebral oxygenation is evaluated similarly and measurements during sodium nitroprusside infusion are corrected for changes in PaCO2 from baseline using the CO2 reactivity to hypocapnia.

Procedures

Baseline evaluation at rest is conducted at least 30 min after placement of catheters. Subsequently, the CO_2 reactivity is evaluated during hypo- and hypercapnia in random order. Hypocapnia is attained by hyperventilation for 6 min to provoke a 0.7-1.2 kPa reduction in $PaCO_2$, and the evaluation is repeated if the reduction in $PaCO_2$ is not within this interval. Hypercapnia is achieved by breathing 6% CO_2 for 6 min.

Thereafter, sodium nitroprusside is infused to reduce MAP by 20% (15%-25%) and 40% (35%-45% and minimally MAP 50 mmHg at a maximal infusion rate of 10 µg/(kg*min)). Sodium nitroprusside is a short-acting, potent vasodilator that activates guanylate cyclase directly or by production of nitric oxide, causing relaxation of smooth muscle cells in arteries and veins. The effect of sodium nitroprusside is attained within 2 min, and the half-life is 2 min whereby the effect is short lasting. Sodium nitroprusside has no direct effect on CBF. Infusion of sodium nitroprusside is by an electronic infusion pump, at 0.25 µg/(kg*min) for one minute and increased by 0.25 µg/(kg*min) each minute. When a level of MAP is reached, MAP is maintained for 120 s where after measurements are conducted during 2-3 min. When evaluations have been done at both levels

of MAP, the infusion speed is reduced gradually in order to avoid so-called “rebound hypertension”. At this time the experiment is finished and catheters are removed.

Statistics

Trial size: In a similar study, sodium nitroprusside-induced reduction in MAP by 43% decreased CBF by 15% after correction for the decrease in $PaCO_2$. A power calculation indicates that at least 14 subjects are required to detect a 15% reduction in CBF with a standard deviation of 18% when MAP is reduced by 40% by sodium nitroprusside with a 5% significance level and a power of 80%.

Inclusion Criteria

- Informed consent
- Male
- Age 18-35 years

Exclusion Criteria

- Alcohol intake ≥ 420 g / week
- Body mass index below 18 kg/m^2 and above 25 kg/m^2
- Smoking
- Beard on the neck
- Chronic cardiac, lung, liver, kidney or metabolic disease that require medication
- Vitamin B12 deficiency
- Anemia
- Leber’s hereditary optic neuropathy
- Tobacco-alcohol amblyopia
- Stenosis that obstructs ≥ 16% of the internal carotid artery
- Intake of sildenafil or vardenafil for 24 hours and tadalafil for 48 timer prior to the experiment

- Intake of monoamine oxidase inhibitors
- Neurologic disease considered to affect cerebral blood flow, including epilepsy and multiple sclerosis

Primary Outcome Measure:

1. Change in cerebral blood flow from baseline to when MAP is decreased by 40% by sodium nitroprusside

Secondary Outcome Measures:

2. Change in cerebral blood flow from baseline to when MAP is decreased by 20% by sodium nitroprusside
3. Relative reduction in internal carotid artery blood flow as compared to that of the vertebral artery from baseline to when MAP is reduced by 40% by sodium nitroprusside
4. The CO2 reactivity of the internal carotid as compared to the vertebral artery
5. Comparison of the slope of linear regression of MAP and internal carotid artery blood flow for the evaluations at baseline and when MAP is reduced by 20% by sodium nitroprusside and that of the evaluations when MAP is reduced by 20% and 40%

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