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ORIGINAL ARTICLE

Cold stimulation of the oral cavity redistributes blood towards the brain in healthy volunteers

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Abstract

Background: The aim of this study was to analyze cold stimulation-induced changes in cerebral and cardiac hemodynamics.

Methods: Upon ingestion of an ice cube, the changes in resistance index, mean flow velocity and flow index of the middle cerebral arteries (MCA) were assessed using transcranial Doppler sonography. Extracranial duplex sonography was used to measure the mean flow velocity and resistance index of the right internal carotid artery (ICA). The change in mean arterial pressure, heart rate, root mean square of successive differences (RMSSD) and end-tidal carbon dioxide pressure were analyzed additionally. These changes were compared to sham stimulation.

Results: Compared with sham stimulation, cooling of the oral cavity resulted in significant changes in cerebral and cardiac hemodynamics. The cold stimulation decreased the resistance index in the MCA (−4.5% ± 5.4%, $p < 0.0001$) and right ICA (−6.3% ± 15.6%, $p = 0.001$). This was accompanied by an increase in mean flow velocity (4.1% ± 8.0%, $p < 0.0001$) and flow index (10.1% ± 43.6%, $p = 0.008$) in the MCA. The cardiac effects caused an increase in mean arterial pressure (1.8% ± 11.2%, $p = 0.017$) and RMSSD (55% ± 112%, $p = 0.048$), while simultaneously decreasing the heart rate (−4.3% ± 9.6%, $p = 0.0001$).

Conclusion: Cooling of the oral cavity resulted in substantial changes in cerebral and cardiac hemodynamics resulting in a blood flow diversion to the brain.

KEYWORDS
autonomic nervous system, cardiovascular physiology, cerebral blood flow, Doppler, physical stimulation

INTRODUCTION

Cooling the face stimulates trigeminal afferent fibers and initiates complex cardiovascular responses. The peripheral body parts (e.g., extremities, skin) receive less blood, heart rate decrease, blood pressure increase and has an oxygen-conserving effect, while oxygen-sensitive organs, such as the brain, are supplied with more blood [1–5].

The aim of the present study was to determine whether cold stimulation of the oral cavity has comparable effects and changes the blood flow towards the brain.

METHODS

Patients

The study examined 77 mainly young, healthy volunteers (aged between 18 and 60 years; mean 26.5 ± 7.7 years; 47/77 women). Exclusion criteria included pregnancy, cerebrovascular disease, brain tumor, primary headache disorder and history of syncope. A parallel study investigated the characteristics of a “headache attributed to ingestion or inhalation of a cold stimulus” [6, 7].

The study was approved by the ethics committee of the Faculty of Medicine at Martin Luther University Halle-Wittenberg and adhered to the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. All participants gave informed written consent before taking part.

Study protocol

Volunteers were asked not to consume caffeine, nicotine or alcohol for 12h before examination. Before the testing, the volunteers relaxed for >5min in a quiet atmosphere. Subjects were asked to breathe normally through the nose and move the head minimally. In order to assess confounding factors, the volunteers were asked to softly press their tongue to their palate for 90s (sham stimulation). For the cold stimulation of the oral cavity, volunteers were told to put an ice cube (temperature −16°C) on their tongue and softly press it to their palate for 90s (ice cube stimulation, see Figure 1a). The area of contact was 3.0×2.5cm on the tongue and 2.5×2.0cm on the palate.

Measurements

Three ultrasound probes were attached to the volunteer's head and neck using a holding device (Figure 1b,a). Two transcranial Doppler probes (2MHz, sample volume 4mm, Multidop X4®, DWL, Sipplingen, Germany) recorded the blood flow envelope of both middle cerebral arteries (MCA) at a depth of approximately 50mm. The Doppler spectra of the MCA were recorded). With an extracranial duplex probe (6MHz, Acuson Sequoia 512, Siemens, Erlangen, Germany) the blood flow in the right internal carotid artery (ICA) around 3cm after bifurcation was quantified.

In addition, the end-tidal carbon dioxide partial pressure in exhaled air (pCO_2) (Capnograph, Drägerwerk AG, Lübeck, Germany) and the mean arterial pressure (SureSign VM6, Philips Medical Systems, Eindhoven, The Netherlands) were measured.

Data analysis

The transcranial doppler MCA envelopes were exported and analyzed using OriginPro® software 9.1.0G (OriginLab Corporation, Northampton, USA). A procedure developed in-house detected the end diastolic velocity (EDV) and the peak systolic velocity (PSV) in the MCA envelope. The mean flow velocity (MFV) and the resistance index were calculated in both MCA and in the right ICA as:

$$\mathrm{MFV} = (\mathrm{PSV} + 2 \times \mathrm{EDV}) / 3.$$

$$\mathrm{Resistence} - \mathrm{Index} = (\mathrm{PSV} - \mathrm{EDV}) / \mathrm{PSV}.$$

The resistance index was used as a parameter for the cerebrovascular resistance, which is mainly controlled by downstream resistance vessels. If there was no side difference, left and right values were combined.

The heart rate and root mean square of successive differences (RMSSD) were calculated from the temporal PSV peak difference. An increase of RMSSD represents a predominance of the parasympathetic system in the heart. Heart rate and RMSSD were calculated from the time difference between the two adjacent systolic peaks and averaged for the resting and stimulation periods.

The procedure also averaged EDV, PSV, MFV, resistance index, heart rate and RMSSD at rest and at the end of the stimulation. The resting period was defined as the last 30 heartbeats, ending 10 heartbeats before the ice cube stimulation. The end of the stimulation period was determined as the last 30 heartbeats of cold stimulation. The procedure compared the relative percentage changes during the end of stimulation period with the resting period.

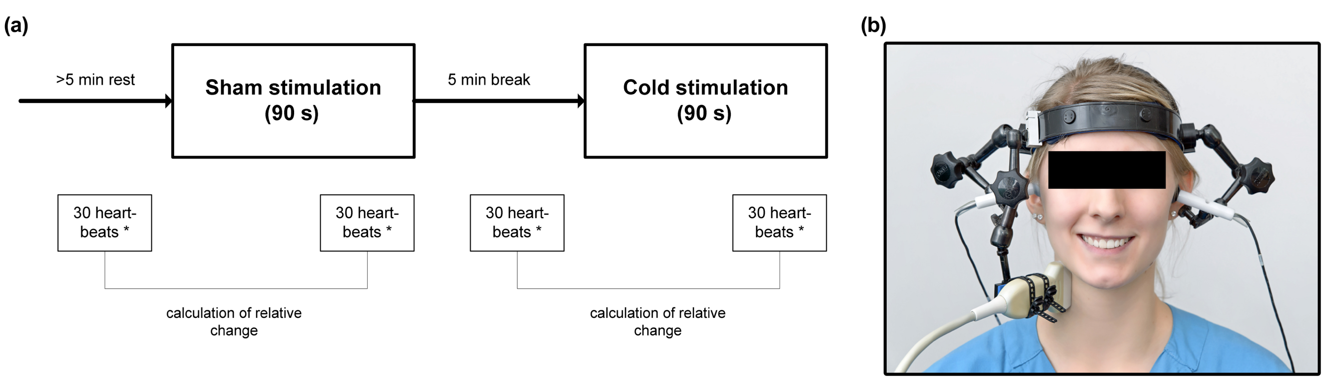

FIGURE 1 (a) A self-constructed, probe-holding device ("Hallesche Halterung") was used, to which two transcranial Doppler probes and an extracranial duplex probe were attached. (b) Study protocol: the volunteers pressed their tongue softly to their palate for 90s (sham stimulation). After a 5-min break, the volunteers put an ice cube on their tongue and softly pressed it to their palate for 90s (cold stimulation). *Measurements of peak systolic velocity (PSV) and end diastolic velocity (EDV) in both middle cerebral arteries and the right internal carotid artery, Doppler spectra of both middle cerebral arteries, mean arterial pressure at the left arm, and end-tidal pCO_2 concentration in exhaled air.

For calculation of the flow index, two heartbeats of the MCA Doppler spectra were extracted. The intensity and velocity of each datapoint in the Doppler spectra was multiplied and the products were summed to give the flow index [8–11]. The relative change in the flow index was calculated in order to estimate the change in cerebral blood flow (CBF) in the MCA.

Appropriate statistical tests (paired, one-sample or two-sample *t*-tests) were used and alpha = 0.05 was established as the significance level.

RESULTS

Compared to sham stimulation, the cerebrovascular MFV, PSV, EDV and flow index in the MCA increased upon cold stimulation of the oral cavity (Table 1). The resistance index in the MCA and right ICA decreased.

There were no differences in the MFV between the right ICA and the right MCA (5.2% ± 24.3% vs. 4.3% ± 7.6%, $p = 0.90$). The resistance index (−6.3% ± 15.6% vs. −4.9% ± 5.2%, $p = 0.48$) did not differ either.

The cardiac parameter heart rate decreased and the RMSSD increased compared to sham stimulation. The mean arterial pressure increased slightly compared to sham stimulation, and end-tidal pCO_2 concentration remained constant (Table 1).

DISCUSSION

The cold stimulation of the oral cavity significantly decreased the cerebrovascular resistance in the MCA and right ICA and increased the CBF in the MCA, thus redistributing the blood flow to the brain.

Transcranial ultrasound is ideal for detecting MFV noninvasively and in real time. However, the change in MFV does not necessarily correlate with the change of CBF because arterial diameter changes at rest or during stimulation [10–13]. Because of this fundamental problem of Doppler sonography, the flow index was analyzed in this study. The flow index is based on the spectral information of the moving particles and correlates more closely with the true CBF change [8–11]. Within the 90-s cold stimulation of the oral cavity, the CBF in the proximal MCA increased significantly by 10.1% ± 43.6%.

CBF in the MCA increases because of dilation of downstream resistance vessels. This is reflected by the decrease of the resistance index in the right ICA and in both MCA. The exact mechanism for this vasodilation is unclear, possibly based on activation of the trigeminal parasympathetic reflex. This is suggested by the simultaneous drop in heart rate and the increase in RMSSD.

However, the increase in blood pressure after cold stimulation of the oral cavity is the result of sympathetic stimulation [14]. The sympathetic and parasympathetic systems are activated simultaneously by stimulation of trigeminal cold receptors; this phenomenon is called the diving reflex [1, 2, 5]. The trigeminal nerve innervates

TABLE 1 Cerebrovascular and cardiovascular effects due to sham and cold stimulation of the oral cavity ($n = 77$).

Parameter	Sham stimulation[a]	Cold stimulation[a]	*P*-value[b]
Middle cerebral artery (bilateral values)			
Peak systolic velocity	−0.9 ± 4.5 ($p = 0.009$)*	1.3 ± 7.4 ($p = 0.016$)*	0.0009*
End diastolic velocity	0.3 ± 7.9 ($p = 0.302$)	7.3 ± 10.2 ($p < 0.0001$)*	<0.0001*
Mean flow velocity[c]	−0.4 ± 5.4 ($p = 0.798$)	4.1 ± 8.0 ($p < 0.0001$)*	<0.0001*
Resistance index[c]	−0.7 ± 5.0 ($p = 0.046$)*	−4.5 ± 5.4 ($p < 0.0001$)*	<0.0001*
Flow index[d]	−1.7 ± 33.0 ($p = 0.738$)	10.1 ± 43.6 ($p = 0.003$)*	0.008*
Right internal carotid artery			
Peak systolic velocity	4.0 ± 24.3 ($p = 0.079$)	0.1 ± 25.3 ($p = 0.489$)	0.332
End diastolic velocity	3.3 ± 26.5 ($p = 0.142$)	15.9 ± 35.4 ($p = 0.0002$)*	0.019*
Mean flow velocity[c]	3.1 ± 22.2 ($p = 0.116$)	5.2 ± 24.3 ($p = 0.037$)*	0.517
Resistance index[c]	2.0 ± 13.3 ($p = 0.101$)	−6.3 ± 15.6 ($p = 0.0005$)*	0.001*
Systemic data			
Mean arterial pressure	−2.3 ± 5.5 ($p = 0.0006$)*	1.8 ± 11.2 ($p = 0.107$)	0.017*
End-tidal pCO_2	−0.49 ± 3.5 ($p = 0.132$)	0.63 ± 4.3 ($p = 0.879$)	0.080
Heart rate[e]	0.8 ± 7.0 ($p = 0.157$)	−4.3 ± 9.6 ($p = 0.0001$)	0.0001*
RMSSD[e]	21 ± 80 ($p = 0.012$)	55 ± 112 ($p < 0.0001$)	0.048*

Abbreviations: pCO_2, carbon dioxide partial pressure in exhaled air; RMSSD, root mean square of successive differences.Values are given as percentages ± standard deviations.

[a]Higher or lower than null by one sample *t*-test.

[b]Different to sham stimulation by paired *t*-test.

[c]Derived from peak systolic velocity and end diastolic velocity.

[d]Derived from the Doppler spectra of both middle cerebral arteries.

[e]Derived from the envelope of the right middle cerebral artery.

*Indicates significant values.

the oral cavity. Oral cooling activates the sympathetic and parasympathetic nervous systems via the trigeminal nuclei, and hemodynamics are redistributed to increase blood flow to important organs such as the brain.

Such redistribution of blood flow can also be seen when there is cooling of other parts of the head. When an individual's forehead, cheeks or nasal cavities are cooled, MFV in the MCA, blood pressure, RMSSD and total peripheral resistance increase, while heart rate and peripheral skin circulation decrease [1, 2, 14–16]. Immersion of the head in water increases blood flow in the common carotid artery by 10%–18% [17] and elevates the arterial oxygen saturation after apnea [5]. Nasopharyngeal cooling with the RhinoChill® device has demonstrated neuroprotective effects and is regularly used during cardiopulmonary resuscitation [18].

It has been suggested that this co-activation of the sympathetic and parasympathetic systems may lead to increased cardiac efficiency [19]. The conservation of oxygen is a result of lower myocardial oxygen consumption during bradycardia, reduced blood flow to peripheral and visceral organs, and lower oxygen depletion in the lungs [5, 20–22]. The combination of decreasing cerebrovascular resistance, increasing perfusion pressure, and reducing peripheral oxygen consumption seems to be an ideal way to preserve the cerebral penumbra. In rats, forehead cooling resulted in a remarkable 30% reduction in infarct volume after MCA occlusion [23]. The feasibility and efficacy of cold stimulation of the trigeminal nerve for cerebral reperfusion therapy or other related conditions such as shock, hypotension, hypovolemia or reduced cardiac output should be studied in depth.

Conversely, the redistribution of blood from the peripheral to the central circulation might be useful during surgical interventions in peripheral organs. The potential risks of such trigeminal cooling should not be overlooked. It can lead to headache [6], cardiac arrhythmias [19], bradycardia [24], a dangerous rise in blood pressure [4, 25], cerebral steal phenomenon [26] or even hypertensive cerebral hemorrhages [27]. In patients with cerebral hemorrhages, it should be noted that cold stimulation of the oral cavity or face might cause further bleeding.

Limitations of the study are that the CBF in the extracranial ICA was not measured directly. The diameter must be correct because the diameter influences the blood flow to the second power. Small changes in the diameter therefore have a relevant influence on the blood flow. Another limitation is that intracranially only the MCA were examined for changes in blood flow. Respiratory rate was not measured. However, the constant end-tidal pCO_2 concentration argues against a relevant influence of respiratory rate on the results. Because predominantly young, healthy volunteers were studied, the effect of blood redirection to the brain may not occur or may occur at a different intensity in elderly or ill people. The determination of RMSSD from Doppler data is new and thus not well established. This measurement may be sensitive to other multiple, external influences (e.g., respiration, excitement) which we attempted to minimize in the present study.

Simple and noninvasive cooling of the oral cavity leads to complex hemodynamic responses, which increase the blood flow towards the brain. These effects of cold stimulation of the oral cavity should be considered and could potentially be used as therapy for various diseases.

AUTHOR CONTRIBUTIONS

Ole Hensel: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; project administration; data curation; resources.

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None.

CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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