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Hypocapnia induced vasoconstriction significantly inhibits the neurovascular coupling in humans ☆

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ABSTRACT

Background/aims: Previous studies proved that vasodilation, caused by hypercapnia or acetazolamide, does not inhibit the visually evoked flow velocity changes in the posterior cerebral arteries. Our aim was to determine whether vasoconstriction induced by hypocapnia affects the neurovascular coupling.
Methods: By using a visual cortex stimulation paradigm, visually evoked flow velocity changes were detected by transcranial Doppler sonography in both posterior cerebral arteries of fourteen young healthy adults. The control measurement was followed by the examination under hyperventilation. Visual-evoked-potentials were also recorded during the control and hyperventilation phases.
Results: The breathing frequency increased from 16 ± 2 to 37 ± 3/min during hyperventilation, resulting in a decrease of the end-tidal CO_2 from 37 ± 3 to 25 ± 3 mm Hg and decrease of resting peak systolic flow velocity from 58 ± 11 to 48 ± 11 cm/s ($p<0.01$). To allow comparisons between volunteers, relative flow velocity was calculated in relation to baseline. Repeated measures analysis of variance revealed significant difference between the relative flow velocity time courses during hyper- and normoventilation ($p<0.001$). The maximum changes of visually evoked relative flow velocities were $26 \pm 7\%$ and $12 \pm 5\%$ during normoventilation and hyperventilation, respectively ($p<0.01$). Visual-evoked-potentials did not differ in the control and hyperventilation phases.
Conclusion: The significantly lower visually evoked flow velocity changes but preserved visual-evoked-potential during hyperventilation indicates that the hypocapnia induced vasoconstriction significantly inhibits the neuronal activity evoked flow response.

1. Introduction

Maintenance of cerebral homeostasis requires dynamic regulation of oxygen and glucose supply so as to match nutrient delivery to metabolic demand of active neurons [1]. This is achieved by a tight spatial and temporal coupling between neuronal activity and blood flow, called neurovascular coupling [2–5]. Although neurovascular research has made significant strides toward understanding how the brain neurovascular unit accomplishes rapid and spatial increases in blood flow following neuronal activation, the exact mechanisms remained unclear. In order to match regional cerebral blood flow with neuronal activity, the cerebral microcirculation was shown to be equipped with control mechanisms, regulated by different mediator systems and cell types such as neurons, endothelial cells as well as astrocytes [6–11]. The regulation involves both vasodilating and vasoconstricting components [12], in which the pH may have a strong effect in both directions. An increase in pH (alkalosis) leads to vasoconstriction and thus decreased flow, whereas an acidosis induces vasodilation and increased cerebral blood flow (CBF).

According to the functional anatomy of the brain, neurovascular coupling can be easily and reliably examined in humans by measurement of the visual stimulation-evoked flow velocity changes in the posterior cerebral arteries [13]. Visual stimulation activates the neurons in the visual cortex, which activation induces vasodilation of arterioles and consequently leads to increase in regional CBF [14,15]. These regional changes result in increased flow and flow velocity in the supplying artery, in this case in the posterior cerebral artery. Transcranial Doppler (TCD) allows to measure the changes of cerebral blood flow velocity in the intracranial arteries, which was shown to be proportional to the changes of regional cerebral blood flow, within one individual [16].

Our previous studies proved that significant vasodilation, caused by either hypercapnia or acetazolamide administration, did not affect the neurovascular coupling since the visually evoked relative flow velocity in the posterior cerebral arteries increased by the same measure under the effect of vasodilating agents as under the control

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condition [13,17]. These data suggest that despite a significant cerebral vasodilation, caused by hypercapnia or acetazolamide, cortical neuronal activation evokes further local vasodilation, maintaining the adaptation of CBF according to neuronal activity.

In the present study, our aim was to examine whether a hypocapnia-(alkalosis-) related cerebral vasoconstriction inhibits the neuronal activation evoked microcirculatory response. In order to determine the effect of the hypocapnia induced cerebral vasoconstriction on the neurovascular coupling, visually evoked flow velocity changes were measured in the posterior cerebral arteries of young healthy subjects during normoventilation and controlled hyperventilation (HV). To obtain a measure of neuronal activity, visual-evoked-potentials (VEP) under conditions of normo- and hyperventilation were also examined.

2. Subjects and methods

Fourteen young healthy adults (7 males, 7 females) between 20 and 35 years of age (mean age: 25 ± 4 years) were included in the study. The study was approved by the local ethics committee, and each volunteer gave written, informed consent. Cerebrovascular risk factors such as smoking habit, arterial hypertension, obesity (body mass index), diabetes mellitus (fasting glucose levels), and hyperlipidemia (levels of total cholesterol, LDL, HDL), as well as history of migraine, coronary or peripheral artery diseases were screened, and subjects with risk factors were excluded. The included subjects did not take any medicine regularly. The study protocol included a complete neurological examination and routine clinical laboratory tests (serum ions, blood urea nitrogen, creatinine, fasting glucose, hepatic enzymes, creatinin-kinase, hemostasis screening test, serum lipids, and inflammatory markers). Blood was drawn after an overnight fast between 8 and 10 a.m.

The functional TCD tests were performed in the morning in a quiet room at about 23 °C while the subjects were sitting comfortably. All volunteers had abstained from caffeine overnight before the study. TCD examinations were always performed by the same examiners (L. O., K.SZ.).

3. Functional TCD study

Two 2-MHz probes were mounted by an individually fitted headband. In all cases, the P2 segment of the PCA was insonated on both sides at a depth of 58 mm. Peak systolic and end-diastolic blood flow velocities were recorded with a Multidop T2 Doppler device (DWL, Überlingen, Germany). The reason for the separated evaluation of systolic and end-diastolic blood flow velocities was that the indices show different time courses in dynamic blood flow regulation. Being less influenced by Doppler artifacts [18], the peak systolic velocity index was used for the following analysis. The other reason for the use of the peak systolic flow velocities in the present study was that this flow parameter reflects most appropriately the dynamic flow regulation [19].

As a stimulation paradigm, we used a news magazine with emotionally neutral text that the volunteers could read freely. This "reading" test has been previously validated against a checkerboard stimulation paradigm [20]. The stimulation protocol consisted of 10 cycles with a resting phase of 20 s and a stimulation phase of 40 s for each cycle. During the resting periods, volunteers were instructed to close their eyes; during the stimulation phases, they opened their eyes and read silently (Fig. 1). Changes between phases were signaled acoustically with a tone.

Beat-to-beat intervals of cerebral blood flow velocity data were interpolated linearly with a "virtual" time resolution of 50 ms for averaging procedures. Within one person, flow velocity data of 10 cycles were averaged. To ensure independence from the insonation angle and to allow comparisons between volunteers, absolute data were transformed into relative changes of cerebral blood flow velocity in relation to baseline. Baseline was calculated from the blood flow velocity averaged for a time span of 5 s at the end of the resting phase, before the beginning of the stimulation phase. With a short time delay at the beginning of the visual stimulation cerebral blood flow velocity increased rapidly, overshooted and then stabilized at a constant but lower level. To analyze the maximum increase of relative flow velcity changes (v_{max}), the highest of the relative values obtained during the overshooting phase was taken from each subject.

After the examination with normocapnia, the same volunteers were taught to hyperventilate at a rate of 35–40 breaths per minute and the visually evoked flow test was repeated under hyperventilation without changing the position of the TCD probes. As a side effect of hyperventilation, the subjects felt dizziness, therefore they were asked to maintain hyperventilation only for 5 min. Since the measurement was started 1 min after the beginning of hyperventilation, only 4 cycles were performed and averaged during the hyperventilation phase (Fig. 1). Relative flow velocities in the control and hyperventilation phases were calculated in each individual and expressed as percent of the control and hyperventilation baseline flow velocity values, respectively.

To control the effectiveness of hyperventilation, end-tidal CO_2 was recorded (Capnograd, Novametrix Medical Systems Corp., Wallingford, USA) during the whole examination period, and capillary blood gasses were checked before and at the end of the hyperventilation phase. Blood pressure was measured noninvasively in the sitting position before and at the end of both normo- and hyperventilation.

Besides visually evoked flow velocities, visual-evoked-potentials (VEP) were also investigated over the occipital cortex under normo- and hyperventilation conditions (Neuropack, Nihon Kohden Corporation, Tokyo, Japan) and amplitudes and latencies of P100 waves were calculated.

4. Statistical analysis

Data were expressed as means $\pm$ standard deviation (SD). Tests for normal distribution were performed, and the homogeneity of the variances was checked by an F test. Results of bilateral measurements were averaged within one subject.

Repeated measures analysis of variance (ANOVA) with Greenhouse–Geisser adjustments for the degrees of freedom was applied to compare absolute and relative changes of visually evoked cerebral blood flow velocities between the normo- and hyperventilation phases. Paired t-test was used to compare the pulse rate, breathing frequency, end-tidal CO_2, resting flow velocity and resting pulsatility index (PI), maximum relative flow velocity change (v_{max}), amplitude and latency of the visual-evoked-potential (P100 wave), and blood gasses before and during hyperventilation. A difference of $p<0.05$ was considered statistically significant.

5. Results

5.1. Effects of hyperventilation on blood gasses, resting flow velocity, and visual-evoked-potential

The breathing frequency increased significantly ($p<0.001$) during hyperventilation and resulted in a significant decrease ($p<0.001$) of the end-tidal CO_2, capillary blood pCO_2, and a significant increase of blood pH and capillary blood pO_2 (Table 1). According to the hypocapnia induced vasoconstriction, the resting flow velocity decreased (Table 1, Fig. 2), while the pulsatility index increased significantly as a result of HV ($p<0.01$). Blood pressure did not change during hyperventilation, however, pulse rate increased significantly ($p<0.001$). Parameters of the visual-evoked-potentials (amplitude and latency of P100 wave) were similar under normo- and hyperventilation (Table 1).

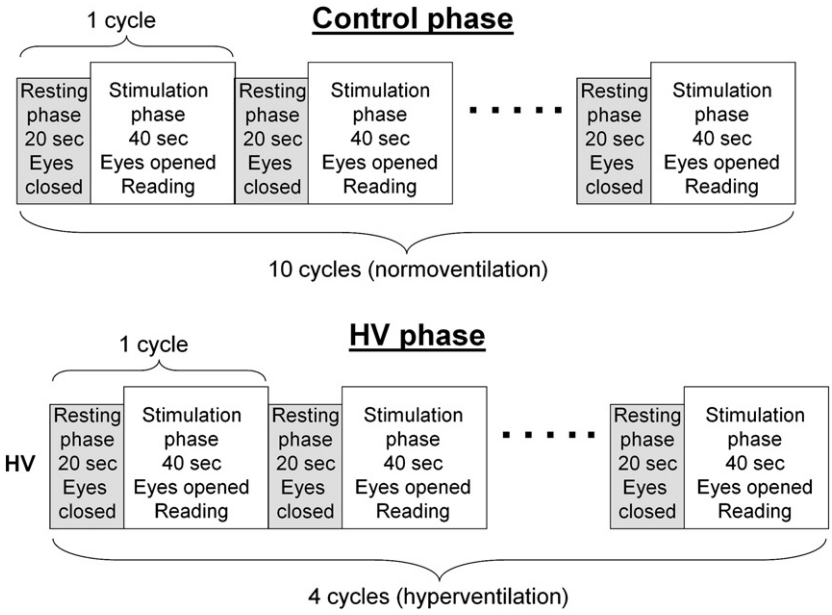

Fig. 1. Experimental protocol. The stimulation protocol consisted of 10 cycles in the control and 4 cycles in the hyperventilation (HV) phases in each individual (n = 14). One cycle included a resting period of 20 s and a stimulation period of 40 s. During the resting periods, volunteers were instructed to close their eyes; during the stimulation periods, they read silently. Between the control and HV phases the position of the transcranial Doppler probes was not changed. Hyperventilation was started one minute before recording the data during the hyperventilation phase. At the end of the examination absolute flow velocity data of 10 cycles during normoventilation and 4 cycles during hyperventilation (HV) were averaged in each individual.

5.2. Effects of visual stimulation on absolute and relative peak systolic flow velocities

Visual stimulation resulted in an increase of peak systolic flow velocity in both the normoventilation and hyperventilation phases (Table 2, Figs. 2, and 3). Absolute changes in velocity of flow (Fig. 2) as well as relative changes (Fig. 3) were analyzed. For absolute values of flow velocity (Fig. 2), repeated measures analysis of variance detected significant group (ie, normo- versus hyperventilation) main effect ($p<0.001$) and significant time-of-measurement main effect ($p<0.001$). This means that during the visual stimulation the peak systolic velocity of blood flow in the posterior cerebral arteries is significantly different between the normo- and hyperventilation phases, and that velocity of flow is significantly different at the different time points of measurement. The group with time-of-measurement interaction was also significant ($p<0.01$), indicating that the pattern of the visually evoked flow velocity time course is different during normo- and hyperventilation.

In order to compare the visually evoked peak systolic flow velocity changes in different individuals and different (i.e., normo- and hyperventilation) phases, relative flow velocities were calculated in the control and hyperventilation phases in relation to the corresponding baseline values (Fig. 3). Repeated measures analysis of variance revealed significant group main effect ($p<0.001$) and significant time-of-measurement main-effect ($p<0.001$) also when relative changes were analyzed during the visual stimulation. It means that not only the absolute, but also the relative changes in flow velocity differ between the normo- and hyperventilation phases and are different at the different time points. The time-of-measurement interaction was significant as well ($p<0.001$), indicating that the pattern of relative changes during visual stimulation is different in the normo- and hyperventilation phases, i.e., the temporal changes of the relative flow velocity during normo- and hyperventilation are not parallel but show different dynamics.

To analyze the maximum increase of relative flow velcity changes, the highest of the values obtained during the 40-second visual stimulation was taken from each subject in both normo- and

Table 1
Characteristics of subjects during normo- and hyperventilation phases.

Feature	Normoventilation (control)	Hyperventilation	p
Breathing frequency (min^{-1})	16 ± 2	37 ± 3	p<0.001
End-tidal CO_2 (mm Hg)	37 ± 3	25 ± 3	p<0.001
Pulse rate (min^{-1})	83 ± 9	98 ± 8	p<0.001
Systolic blood pressure (mm Hg)	113 ± 10	114 ± 12	p = 0.81
Diastolic blood pressure (mm Hg)	74 ± 9	74 ± 11	p = 0.90
Resting flow velocity (cm/s)	58 ± 11	48 ± 11	p<0.01
Resting PI	1.02 ± 0.11	1.45 ± 0.28	p<0.01
Capillary blood pH	7.43 ± 0.02	7.58 ± 0.05	p<0.001
Capillary blood pO_2 (mm Hg)	68 ± 2	83 ± 3	p<0.001
Capillary blood pCO_2 (mm Hg)	35 ± 1	23 ± 2	p<0.001
Amplitude of P100 wave (μV)	7.58 ± 2.08	6.78 ± 1.60	p = 0.39
Latency of P100 wave (ms)	105.00 ± 4.53	108.20 ± 2.96	p = 0.51

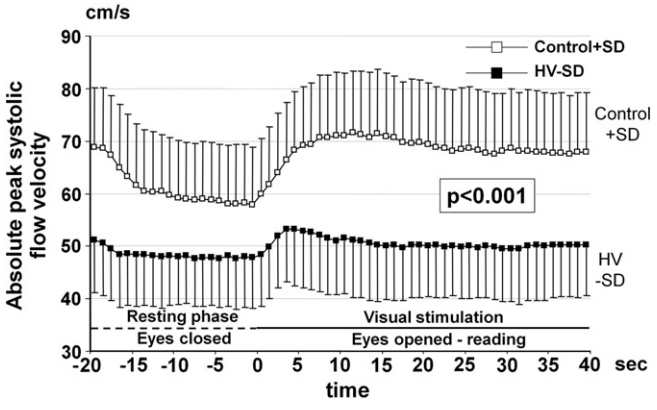

Fig. 2. Absolute peak systolic flow velocity time courses during normoventilation (control; mean + SD; n = 14) and hyperventilation (HV; mean-SD; n = 14). Due to the hyperventilation induced vasoconstriction the absolute flow velocity values were lower during hyper- than normoventilation. Visual stimulation resulted in flow velocity increase during both the control and HV phases, however, the measure and the duration of velocity increase were less during the HV phase. Because the resting flow velocity was smaller in the HV than the control phase, the rate of flow velocity increase can only be compared between the two conditions if relative values are calculated.

Table 2
Absolute and relative baseline peak systolic flow velocity (PSV) values (mean ± SD) in the rest period and maximal peak-systolic flow velocities in the stimulation period of normo- and hyperventilation phases (n = 14).

Features	Normoventilation phase		Hyperventilation phase	
	Baseline PSV (rest period)	Maximal PSV (visual stimulation)	Baseline PSV (rest period)	Maximal PSV (visual stimulation)
Absolute PSV	58 ± 11 cm/s	73 ± 11 cm/s*	48 ± 9 cm/s	54 ± 10 cm/s*
Relative PSV	100 ± 2%	126 ± 7%*	100 ± 1%	112 ± 5%*

(PSV: peak systolic flow velocity.)
* $p<0.001$ compared to the corresponding baseline value.

hyperventilation phases (Table 2). The maximum increases of the visually evoked relative flow velocities were 26 ± 7% and 12 ± 5% during normoventilation and hyperventilation, respectively ($p<0.001$).

6. Discussion

Our results proved that despite the unchanged visual-evoked-potential, the visually evoked relative flow velocity changes were significantly lower during hyperventilation than normoventilation. These findings indicate inhibition of the cortical activation induced flow increase during hypocapnia, in other words, the neuronal activation evoked local vasodilation could not overcome the hypocapnia induced vasoconstriction. To our best knowledge this is the first human study which proves that the hypocapnia induced vasoconstriction significantly inhibits the neuronal activation evoked flow response. Since the flow velocities and the cortical neuronal activity–flow coupling are influenced by hypocapnia, standard conditions are necessary including constant breath rate and pCO_2 during dynamic flow investigations.

The decrease of baseline flow velocity and increase of pulsatility index in the posterior cerebral arteries undoubtedly proved significant vasoconstriction of cerebral microvessels during hyperventilation. Therefore, not surprisingly, the absolute flow velocity changes were much less during hyperventilation than normoventilation (Fig. 2). In order to compare the two phases (normo- and hyperventilation phases), absolute data were transformed into relative changes of flow velocity in relation to the corresponding baseline values. Although the visual stimulation resulted in increase of relative flow velocity in both phases, it was significantly lower during hyperventilation (hypocapnia) than normoventilation (normocapnia), showing that the hypocapnia induced vasoconstriction significantly inhibited the cortical neuronal activity evoked flow changes (Fig. 3). While the visually evoked flow velocity response during hyperventilation (12 ± 5%) was less than 50% of the increase of flow velocity in the control phase (26 ± 7%; Table 2),

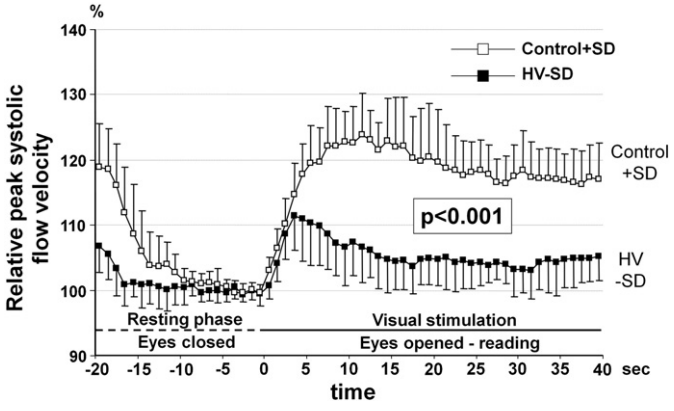

Fig. 3. Relative peak systolic flow velocity time courses during normoventilation (control; mean + SD; n = 14) and hyperventilation (HV; mean-SD; n = 14). Relative values show clearly that the visually evoked flow velocity increase was much lower during the HV than the control phase, indicating disturbance of neuronal activity–flow coupling.

the parameters of the visual-evoked-potentials did not change significantly, indicating preserved visual cortex activity and disturbance of cortical neuronal activity–flow coupling. Our data suggest that about half of the physiological blood flow increase may be sufficient to maintain the same neuronal function during visual stimulation, i.e. such a huge physiological flow increase under normocapnia is not necessary to maintain the normal visual-evoked-potential. In line with findings of Fox et al., Lin et al. and Leithner et al., who showed that cerebral blood flow increases exceeded the cerebral metabolic rate of oxygen by a factor of 2–10 [21–23], our results also indicate that the neurovascular coupling operates with a considerable safety factor under physiological conditions. Nevertheless, stronger reduction of pCO_2 pressure and therefore forced alkalosis may have deleterious effect on neuronal function. Although not in physiological conditions, hyperventilation was shown to induce ischemic areas in patients with closed head injury due to a perfusion lowering effect [24]. Other pathological conditions (e.g. smoking, hypertension, diabetes mellitus) which affect the cerebral vasodilation may also contribute to the potentially deleterious effect of the hypocapnia induced vasoconstriction.

Contrary to the hypercapnia or acetazolamide induced vasodilation, which did not influence the neurovascular coupling, the hypocapnia induced vasoconstriction significantly inhibited the neuronal activity evoked flow response. It cannot be answered by the present study whether vasoconstriction, independent of its induction, generally inhibits the neurovascular coupling, or a special mechanism, namely the hypocapnia induced vasoconstriction is responsible for the inhibition of the cortical activity–flow coupling. It is also questionable whether hypocapnia impairs the neurovascular coupling only by its vasoconstrictive effect or it has an additional direct influence on the coupling too.

Hypocapnia induced vasoconstriction was shown to be mediated by closing the ATP-sensitive potassium channel [25], therefore, one may speculate that this type of potassium channels might be involved in the regulation of neurovascular coupling. Although there is evidence that supports the presence of ATP sensitive potassium channels in parenchymal arteriolar smooth muscle cells, their functional role in regulating parenchymal arteriolar tone has not been known yet [5].

Some potential limitations should be considered in assessing this report. At first, it is questionable whether hypocapnia influences the cerebral oxidative metabolism, although Chen and Pike could not show significant change in global cerebral metabolic rate of oxygen when the end-tidal CO_2 levels were decreased [26]. At second, we presumed that the changes in flow velocity were due to the decrease of the partial pressure of CO_2, however, pO_2 also changed significantly. Although change of pO_2 does not have a significant effect on the vascular tone, it might influence the cerebral blood oxygenation. And finally, besides the blood gasses, there was a significant difference in heart rate as well, being significantly higher during hyperventilation than normoventilation, however, heart rate is known to have no significant effect on cortical activity–flow coupling [27].

In summary, the hyperventilation induced hypocapnia was proved to be a condition in which the neuronal activity evoked flow response is substantially disturbed. Further investigations, including functional

MRI, near-infrared-spectroscopy, and animal experiments, could bring closer to the understanding and interpretation of the disturbance of neuronal activation–flow coupling during hypocapnia [28].

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References

[1] Roy CS, Sherrington CS. On the regulation of the blood supply of the brain. J Physiol 1890;11:85–158.
[2] Dirnagl U. Metabolic aspects of neurovascular coupling. Adv Exp Med Biol 1977;413:155–69.
[3] Koehler RC, Roman RJ, Harder DR. Astrocytes and the regulation of cerebral blood flow. Trends Neurosci 2009;32:160–9.
[4] Filosa JA, Blanco VM. Neurovascular coupling in the mammalian brain. Exp Physiol 2007;92:641–6.
[5] Dunn KM, Nelson MT. Potassium channels and neurovascular coupling. Circ J 2010;74:608–16.
[6] Anderson CM, Nedergaard M. Astrocyte-mediated control of cerebral microcirculation. Trends Neurosci 2003;26:340–4.
[7] Simard M, Arcuino G, Takano T, Liu QS, Nedergaard M. Signaling at the gliovascular interface. J Neurosci 2003;23:9254–62.
[8] Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci 2004;5:347–60.
[9] Mulligan SJ, MacVicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. Nature 2004;431:195–9.
[10] Filosa JA, Bonev AD, Nelson MT. Calcium dynamics in cortical astrocytes and arterioles during neurovascular coupling. Circ Res 2004;95:e73–81.
[11] Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, et al. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat Neurosci 2003;6:43–50.
[12] Metea MR, Newman EA. Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. J Neurosci 2006;26:2862–70.
[13] Rosengarten B, Spiller A, Aldinger C, Kaps M. Control system analysis of visually evoked blood flow regulation in humans under normocapnia and hypercapnia. Eur J Ultrasound 2003;16:169–75.
[14] Fernández-Klett F, Offenhauser N, Dirnagl U, Priller J, Lindauer U. Pericytes in capillaries are contractile in vivo, but arterioles mediate functional hyperemia in the mouse brain. Proc Natl Acad Sci USA 2010;107:22290–5.
[15] Blanco VM, Stern JE, Filosa JA. Tone-dependent vascular responses to astrocyte-derived signals. Am J Physiol Heart Circ Physiol 2008;294:H2855–63.
[16] Brauer P, Kochs E, Werner C, Bloom M, Policare R, Pentheny S, Yonas H, Kofke WA, Schulte am Esch J. Correlation of transcranial Doppler sonography mean flow velocity with cerebral blood flow in patients with intracranial pathology. J Neurosurg Anesthesiol 1998;10:80–5.
[17] Yonai Y, Boms N, Molnar S, Rosengarten B, Bornstein NM, Csiba L, et al. Acetazolamide-induced vasodilation does not inhibit the visually evoked flow response. J Cereb Blood Flow Metab 2010;30:516–21.
[18] Rosengarten B, Aldinger C, Kaufmann A, Kaps M. Comparison of visually evoked peak systolic and end diastolic blood flow velocity using a control system approach. Ultrasound Med Biol 2001;27:1499–503.
[19] Rosengarten B, Kaps M. Peak systolic velocity Doppler index reflects most appropriately the dynamic time course of intact cerebral autoregulation. Cerebrovasc Dis 2002;13:230–4.
[20] Rosengarten B, Aldinger C, Spiller A, Kaps M. Neurovascular coupling remains unaffected during normal aging. J Neuroimaging 2003;13:43–7.
[21] Fox PT, Raichle ME, Mintun MA, Dence C. Nonoxidative glucose consumption during focal physiologic neural activity. Science 1998;241:462–4.
[22] Lin AL, Fox PT, Yang Y, Lu H, Tan LH, Gao JH. Evaluation of MRI models in the measurement of $CMRO_2$ and its relationship with CBF. Magn Reson Med 2008;60:380–9.
[23] Leithner C, Royl G, Offenhauser N, Füchtemeier M, Kohl-Bareis M, Villringer A, et al. Pharmacological uncoupling of activation induced increases in CBF and CMRO2. J Cereb Blood Flow Metab 2010;30:311–22.
[24] Coles JP, Fryer TD, Coleman MR, Smielewski P, Gupta AK, Minhas PS, et al. Hyperventilation following head injury: effect on ischemic burden and cerebral oxidative metabolism. Crit Care Med 2007;35:568–78.
[25] Wei EP, Kontos HA. Blockade of ATP-sensitive potassium channels in cerebral arterioles inhibits vasoconstriction from hypocapnic alkalosis. Stroke 1999;30:851–3.
[26] Chen JJ, Pike GB. Golbal cerebral oxidative metabolism during hypercapnia and hypocapnia in humans: implications for BOLD fMRI. J Cereb Blood Flow Metab 2010;30:1094–9.
[27] Rosengarten B, Budden C, Osthaus S, Kaps M. Effect of heart rate on regulative features of the cortical activity–flow coupling. Cerebrovasc Dis 2003;16:47–52.
[28] Lindauer U, Dirnagl U, Füchtemeier M, Böttiger C, Offenhauser N, Leithner C, et al. Pathophysiological interference with neurovascular coupling—when imaging based on hemoglobin might go blind. Front Neuroenergetics 2010;2:25.