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Role of cerebrovascular and cardiovascular CO_2-reactivity in the pathogenesis of arterial hypertension

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Abstract

Intense emotions cause arousal of the central nervous system, sympathetic activation, blood pressure (BP) increase and hyperventilation. Continuous negative emotions coming with hyperventilation lead to increase in CO_2-chemosensitivity that keeps chronic hypocapnia constant and results in BP dysregulation and stable arterial hypertension (AH). The key mechanism of a hypertensive effect of chronic hyperventilation probably lies in sensitivity changes of CO_2-chemoreceptors. Respiratory training with periodic hypercapnia has potential therapeutic effect in HTN by restoring CO_2-chemoreceptor sensitivity and increasing antioxidant activity. Hypocapnia violates autoregulation mechanisms. Cerebral blood vessels lose their ability to neutralize BP surges, which negatively affects chemoreceptor-related processes of respiratory and BP regulation. With the HTN progression, cerebrovascular dysregulation occurs depending on the BP level. Moreover, hypocapnia is accompanied by the reduction of intracranial venous tone which can lead to increased intracranial pressure and problems with BP regulation in the brain. The threshold level of cardiovascular CO_2-reactivity is normally higher than the threshold level of cerebrovascular CO_2-reactivity. The changes in cardiovascular CO_2-reactivity occur already in the initial period of HTN. Compared to healthy people, hypertensive patients develop slower BP reaction to hyper/hypocapnia, and hypercapnia induced low BP does not restore to the baseline level that can result from the BP dysregulation. In general, cerebrovascular CO_2-reactivity is decreased in HTN patients. However, the cerebrovascular vasodilator function is preserved better than the vasoconstrictor reserve demonstrating that cerebral vessel remodeling in HTN is characterized by luminal narrowing due to the vascular wall hypertrophy.

Key words: arterial hypertension, hypocapnia, hypercapnia, cerebrovascular reactivity, cardiovascular reactivity

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Цереброваскулярная и кардиоваскулярная CO_2-реактивность в патогенезе артериальной гипертензии

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Резюме

Выраженные эмоции вызывают возбуждение центральной нервной системы (ЦНС), симпатическую активацию, подъем артериального давления (АД) и гипервентиляцию. При продолжительных отрицательных эмоциях, сопровождающихся гипервентиляцией, хемочувствительность к CO_2 повышается, что поддерживает хроническую гипокапнию и приводит к нарушению регуляции АД и стабилизации артериальной гипертензии (АГ). Ключевым механизмом гипертензивного эффекта хронической гипервентиляции является, вероятно, изменение чувствительности хеморецепторов к CO_2. Респираторные тренировки с периодической гиперкапнией имеют существенный терапевтический потенциал при АГ, восстанавливая чувствительность хеморецепторов к CO_2 и усиливая антиоксидантную активность. Гипокапния нарушает ауторегуляцию, и мозговые сосуды утрачивают способность нивелировать скачки АД, что оказывает неблагоприятное воздействие на связанные с хеморецепторами процессы регуляции дыхания и АД. При прогрессировании АГ возникает зависимое от степени повышения АД нарушение церебральной ауторегуляции. Также при гипокапнии снижается тонус внутричерепных вен, что может быть причиной повышения внутричерепного давления и нарушения центральной регуляции АД. Порог кардиоваскулярной CO_2-реактивности в норме выше порога цереброваскулярной CO_2-реактивности. Кардиоваскулярная CO_2-реактивность изменяется уже на начальном этапе развития АГ. В отличие от здоровых лиц, у больных с АГ реакция АД на гипер/гипокапнию развивается медленнее, и величина АД не восстанавливается после его снижения на гипокапнию, что может отражать нарушение механизма контроля АД. Цереброваскулярная CO_2-реактивность при АГ в целом снижается. При этом вазодилатационный резерв мозговых сосудов сохраняется в большей степени, чем вазоконстрикторный, что отражает характер ремоделирования мозговых сосудов при АГ, для которого характерно сужение просвета за счет гипертрофии стенки.

Ключевые слова: артериальная гипертензия, гипокапния, гиперкапния, цереброваскулярная реактивность, кардиоваскулярная реактивность

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Introduction

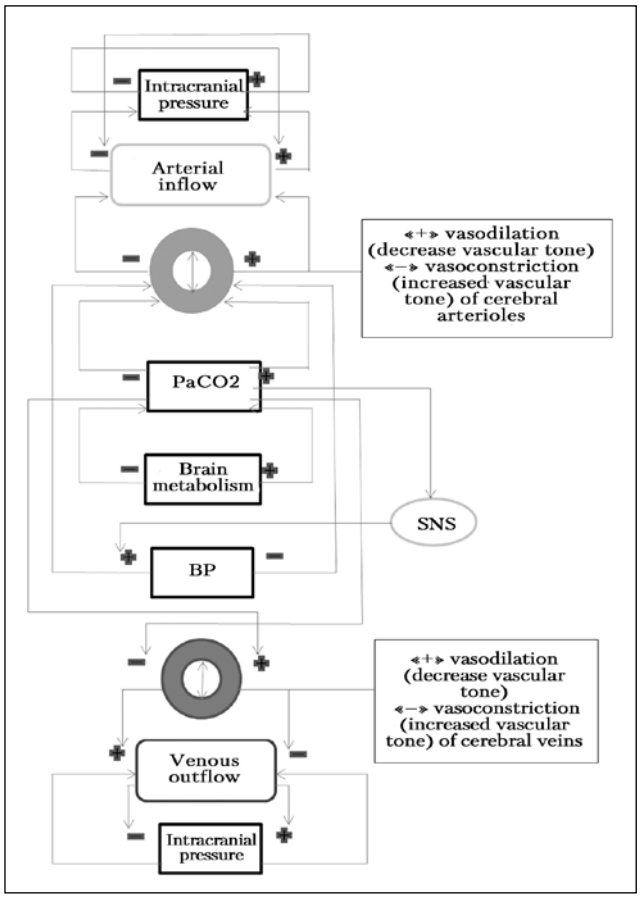
Arterial carbon dioxide tension ($PaCO_2$) plays a crucial role in the regulation of cerebral blood flow. $PaCO_2$ rise (hypercapnia) leads to the dilation of cerebral arterioles and precapillary sphincters, which reduces regional vascular resistance and stimulates cerebral blood flow (CBF), whereas a decrease in $PaCO_2$ (hypocapnia) leads to the narrowing of resistive cerebral arteries followed by a decrease in CBF [1,2]. The vasodilator mechanism of resistive cerebral blood vessels in hypercapnia is connected with CO_2-dependent decrease in extracellular pH [3, 4], activation of K^+ channels in vascular smooth muscle cells [5, 6], and enhancement of the synthesis of endothelial and neuronal NO-synthases with NO and cGMP accumulation [7, 8]. Those listed above will finally reduce the concentration of intracellular calcium and result in the relaxation of smooth muscles and a drop in the vascular tone. Unlike hypercapnic vasodilatation, the vasoconstrictive effect of hypocapnia is considered to be dependent exclusively on the alteration of pH and an increase in the concentration of intracellular Ca^{2+} in the smooth muscle cells, which induces an increase in vascular tone [9].

It is also well known that carbon dioxide effectively changes systemic arterial pressure (AP). Hypercapnia causes increased AP due to the activation of sympathetic nervous system (SNS) through the excitation of central and peripheral chemoreceptors and, as a consequence, increased vascular tone and cardiac output [10, 11]. Correspondingly, arterial pressure decreases in hypocapnia [12].

It follows, therefore, that carbon dioxide has a double effect upon vascular tone. With its direct impact upon the smooth muscle cells, CO_2 is a vasodilator. But on the systemic level, it is a vasoconstrictor, mediating its effect due to SNS activation. The basic mechanisms of control of cerebral circulation are shown in figure 1.

It seems to be obvious that having such pronounced effects on vascular tone and systemic hemodynamics, CO_2 must play a significant part in the pathogenesis of arterial hypertension (AH). Nevertheless, modern pathophysiological concepts of AH pay little attention to carbon dioxide. In the meantime, chronic hyperventilation and hypocapnia are extremely widely spread, considering the expansion of stress and neuroses. Respiratory failures with hypercapnia can induce hyperventilation and hypocapnia between the attacks, as, for example, in the case of bronchial asthma or sleep apnea [13]. Such

Fig.1. The basic mechanisms of control of cerebral circulation

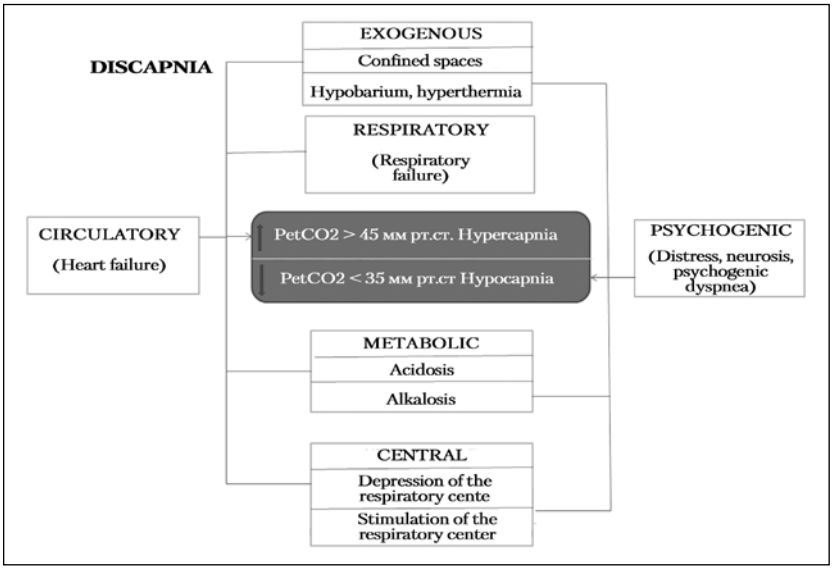


Note: BP — blood pressure; $PaCO_2$ — pressure of CO_2 in arterial blood; SNS – sympathetic nervous system.

changes in $PaCO_2$ can play a significant part in the pathogenesis of AH. For instance, obstructive sleep apnea with chronic intermittent hypoxia (CIH) is an independent risk factor of AH [14]. At the same time, CIH is characterized not only by recurring hypoxia but also by alternation of hypercapnia and hypocapnia.

We have introduced the term "dyscapnia" to refer to widely spread deviations in $PaCO_2$. ***Dyscapnia*** is a standard pathological process characterized by stable or recurring deviations from the state of normocapnia towards an increase (hypercapnia) or decrease (hypocapnia) in $PaCO_2$. The level of CO_2 in the body is known to be characterized by three states: normocapnia, hypercapnia, hypocapnia, unlike oxygen, for which under natural conditions there exist only two states — normoxia and hypoxia — due to close to 100 % normal blood oxygen level. Pathophysiological variants of dyscapnia is shown in figure 2. Similar to hypoxia, dyscapnia develops under changes of the atmospheric pressure and partial pressure of the breathing gas (exogenous), in respi-

Fig. 2. Pathophysiological variants of dyscapnia



Note: PetCO2 — partial pressure of CO2 in alveolar air.

ratory and cardiac failure (respiratory, circulatory), in metabolic disorders (hypercapnia in metabolic acidosis and hypocapnia in alkalosis), in the depression (hypercapnia) and stimulation (hypocapnia) of the respiratory center (central). Among them stands out widespread psychogenic dyscapnia, which develops as a result of hyperventilation under stress and neuroses, and is characterized by hypocapnia and normoxia.

The current work presents reported data and researches earlier published by us, which, in our opinion, may prove the involvement of dyscapnia in the pathogenesis of primary AH.

Psycho-emotional stress, hypocapnia, and arterial hypotension

Regarding the participation of dyscapnia in the pathogenesis of AH, first of all, we refer to the mechanisms of AH connected with psycho-emotional excitation. Proceeding from the famous 'neurogenic theory' of G. F. Lang and A. L. Myasnikov, psycho-emotional stress has been traditionally considered to be the most important link in the pathogenesis of primary arterial hypertension [15]. Psycho-emotional tension is treated as one of three essential pathophysiological mechanisms of AH in Folkow's concept as well [16]. Recently published results of meta-analysis confirm the role of chronic psycho-emotional tension as a risk factor of AH [17]. This research shows that psychological stress is associated with the excess risk of AH development (OR = 2.40, 95 % CI = 1.65–3.49), and hypertensive subjects have a higher level of psychosocial stress as compared to normotensive patients (OR = 2.69, 95 % CI = 2.32–3.11). Modern conclusive researches state that stress induces unfavourable changes in hemodynamics and stress reactivity, which lead to AH, cardiovascular diseases, and their complications [18, 19].

However, it is not taken into consideration that stress is always followed by hyperventilation and hypocapnia. In a healthy person at sea level, the volume of pulmonary ventilation is regulated by $PaCO_2$, by comparing the preset level in the respiratory center (preset value) with the incoming information from the chemoreceptors, and maintains its level at 35–45 mm Hg [20]. Expressed emotions (fear, panic, aggression) are accompanied by CNS arousal, sympathetic activation, an increase in AP, and hyperventilation. Hyperventilation is maintained due to temporary neglect of the preset value of $PaCO_2$ induced by the CNS arousal [21]. Anxiety, fear, and panic cause accelerated and deeper breathing with a decrease in $PaCO_2$ down to respiratory alkalosis [22]. Prolonged negative emotions, anxious disorders, and bronchial asthma enhance chemosensitivity to CO_2, which maintains constant hyperventilation and chronic hypocapnia [23–25].

As mentioned previously, hypocapnia leads to a decrease in blood pressure and can be a physiological factor preventing a dangerous rise and stabilization of high AP under stress-induced sympathetic activation. However, prolonged stress causes hyperventilation syndrome with chronic hypocapnia and alkalosis, which, on the contrary, can lead to metabolic disturbances, AP regulation disorders, and stabilization of AH.

A key mechanism of hypertensive effect of chronic hyperventilation may be a change in the sensitivity of chemoreceptors to CO_2, O_2, and H^+, similar to what happens when stress hyperventilation is formed [24]. Increased sensitivity of carotid chemoreceptors to oxygen is experimentally established under CIH with the activation of carotid chemoreflex and an increase in sympathetic tone, which leads to hypertension [14]. According to the authors' opinion, it can relate to sympathetic hyperactivity and cardiorespiratory hyper-reactivity to hypoxia in patients and animals subjected to intermittent hypoxia. Increased sensitivity of central chemoreceptors to CO_2 is a key factor of the hypersthenia of the sympathetic nervous system, hyperventilation, and high AP in spontaneously hypertensive rats [26]. There exists a distinct connection between enhanced afferent signalling from carotid chemoreceptors and sympathetic overactivity in heart failure [27]. The author point out that the ventilatory response value at the activation of the peripheral chemoreceptors is proportional to the level of heart rate (tachycardia) and blood pressure (hypertension). More and more experimental evidence proves the concept of a decisive contribution of abnormally high sensitivity of carotid chemoreception to overactivation of the sympathetic nervous system and the development of cardiometabolic disease [28, 29]. It is shown that selective carotid body ablation increases the survival rate in the experimental models of cardiac failure [30, 31], prevents the development of insulin resistance and arterial hypertension in rats exposed to a high fat diet [32], and relieves CIH-induced hypertension in a rat model of obstructive sleep apnea [33].

Carotid body ablation was suggested as a treatment for severe and resistant arterial hypertension in humans [29]. However, there are technical difficulties and safety problems of intervention in carotid bodies [27]. Therefore, respiratory exercise can be promising. Their task is to restore the sensitivity of chemoreceptors to CO_2 [13]. Earlier, we demonstrated a decrease in cerebrovascular CO_2 reactivity under regular respiratory exercise with hypercapnic hypoxia in people [34], which can be explained by a reduced sensitivity of the respective chemoreceptors under the influence of recurring hypercapnia. Therapeutic efficiency of hypercapnic hypoxia, created by the Buteyko method or a hardware-based rebreathing technique, can as well be connected with the restoration of the sensitivity of chemoreceptors [13]. We can assume that a key role in this effect belongs to hypercapnia. Thus, it was demonstrated that hypercapnia has a more pronounced effect upon the increase in the brain tolerance to ischemia/hypoxia, as compared to hypoxia, whereas their combined application (hypercapnic hypoxia) is significantly more efficient than independent [35, 36]. Furthermore, the response of cerebral blood flow to combined hypoxia and hypercapnia is known to be mainly determined by $PaCO_2$ level and not by the deficiency in PaO_2 [37].

The assessment of the degree of AP reaction to hyper-hypocapnia (cardiovascular reactivity, CVR-CO_2) can become important for diagnostics, prognosis, and the choice of therapy at the initial stage of AH development, similar to the examination of cerebrovascular reactivity to CO_2 ($CVRCO_2$), is a trustworthy test for cerebral blood flow disturbances. In Niewinski's opinion [27], examination of cardiovascular reactivity to hypercapnia and hypoxia can be important to control and eliminate hyper-sympathicotomy when treating cardiac failure, especially since all the responses to the activation of the peripheral chemoreceptors (pulmonary ventilation, heart rate, and AP) can be measured by non-invasive, safe, and reproducible methods.

Another important mechanism of the hypertensive effect of chronic hyperventilation and hypocapnia may be the enhancement of oxidative stress, which plays a substantial role in the pathogenesis of AH provoking endothelial injury and endothelial dysfunction [38]. The point is that carbon dioxide considerably enhances antioxidant activity [39], activating superoxide dismutase, stabilizing transferrin–iron complex, neutralizing active forms of oxygen, combining with peroxynitrite and then transforming into nitro-carbonate, and, when combined with water, generating a carboxy anion and a nitoxide anion [40–42].

In the experiment modeling the impact of hypoxia and hypercapnia upon invertebrates [43], it was demonstrated that these two factors at a moderate rate facilitates activation of the antioxidant defense system protecting cells from damage, increasing transcription of the genes of cytoplasmic Mn superoxide dismutase, glutathione peroxidase and peptide methionine sulfoxide reductase. This antioxidant activity of CO_2 can have a significant therapeutic potential for AH, as, for example, high efficiency of hypercapnic hypoxia in the experimental stroke, which we demonstrated earlier [44].

Hypocapnia, cerebral autoregulation, and arterial hypertension

As we see it, cerebral blood flow and the disturbed $CVRCO_2$, as well as dyscapnia, are not generally given enough importance in the pathogenesis of AH. Not only a relatively large but, more important, constant volume of perfusion is vital for the brain. Only thus can brain functions be provided, including the work of vasomotor center, carotid chemoreflex, and neurogenic regulation of AP. As is well known, neurons are extremely sensitive to hypoxia arising during the reduction of arterial blood flow to the brain (ischemia). However, hyperemia is equally destructive for the brain closed inside the skull as it provokes intracranial hypertension and cerebral perfusion disturbances (Fig. 1). Stability of cerebral perfusion is maintained due to a unique mechanism of cerebral blood flow autoregulation. As it is known, cerebral autoregulation consists of maintaining a constant volume of cerebral blood flow under the conditions of mean hemodynamic pressure altering within the limits of 50–170 mm Hg [45]. In response to an increase in the systemic AP, the tone of cerebral resistance vessels rises, which protects the brain from hyperfusion and hyperemia. When AP drops, brain vessels, on the contrary, dilate, resistance goes down, which prevents cerebral perfusion failure. The mechanism of cerebral autoregulation is not fully determined. An important role in this mechanism, apparently, belongs to myogenic regulation of vascular tone (the Bayliss effect) [46]. The main problem lies in the fact that the change of $PaCO_2$ beyond normocapnia makes autoregulation inefficient [47, 48]. Because of a pronounced vasomotor effect of CO_2, under dyscapnia, cerebral blood vessels lose the ability to level the leaps in AP and maintain stable perfusion at the same time. Thus, CBF disturbance, caused by dyscapnia, can lead to disorders in the functions of vasomotor center and AP control. In support of this, we can provide the results of a research that showed CBF autoregulation disturbance dependent on the degree of AP rise in patients with AH [49]. Disorders in cerebrovascular function, caused by dyscapnia, impact the chemoreceptor regulation of breathing and AP. Thus, $PaCO_2$-associated change in pH at the level of central chemoreceptors causes changes in CBF, which, in its turn, influence central control of breathing [50, 51]. The researches showed correlation of a decreased $CVRCO_2$ with the emergence of central sleep apnea in patients with congestive heart failure [52], as well as with obstructive sleep apnea [53].

Cerebral venous CO_2 reactivity and arterial hypertension

Recently determined, higher as compared to arterial, cerebral venous reactivity to CO_2 [54] does not allow neglecting a possible important role of venous circulation under dyscapnia in the pathogenesis of AH. Cerebrovascular CO_2 reactivity is considered almost exclusively from the point of view of regulation of arterial blood flow to the brain. Apparently, to prevent destruction of the brain hyperemia, an increase in the inflow requires an increase in the outflow. Hence, an expressed reaction of cerebral venous hemodynamics to hypercapnia can be expected.

We studied the reaction of the blood flow in the veins of the brain to hypercapnia [54]. Typical reaction of the blood flow in the basal veins to hypercapnia consisted of a significant increase in blood flow velocity. The reactivity coefficient was 60 ± 22.7% (CI 52.9–67.2%), which is more than two times higher than the reaction of arterial blood flow in the middle cerebral artery. Such a pronounced increase in blood flow velocity in the intracranial veins under hypercapnia is impossible to explain only by passive reaction of the outflow to the increase in the inflow. Presumably, alongside with the passive mechanism, hypercapnia enables an active mechanism of venous outflow stimulation in the form of vein constriction. The principal possibility of CO_2-induced vein constriction was demonstrated in an experiment on animals [55]. Another piece of evidence can be the results of the study of cerebral venous CO_2 reactivity in objects with brain concussion accompanied by cerebral venous dystonia [56]. The results of the study showed that the reaction of the blood flow in the basal vein to hypercapnia in the patients with brain concussion, unlike that in healthy objects, did not exceed that of the middle cerebral artery. This result can be explained by the loss of active CO_2-induced vein constriction caused by brain concussion, while preserving only the passive reaction of venous outflow to an increase in the arterial inflow.

Expressed cerebral venous reactivity to CO_2 implies a disorder in venous outflow from the brain under hyperventilation and hypocapnia, which can cause an increase in intracranial pressure and disturbance of the functional state of the brain, including its participation in AP control.

Cerebrovascular and cardiovascular CO_2 reactivity in normal subjects

Research methodology of the effects of dyscapnia upon cerebral and systemic hemodynamics consist of simultaneous synchronous real-time monitoring of cerebral blood flow velocity, AP, and CO_2 partial pressure in the alveolar air ($PetCO_2$), as it was earlier described in detail [57].

Cerebral blood flow velocity in segment M1 of the middle cerebral artery (MCA) was registered through transcranial Doppler (TCD) with 2 MHz pulsed wave sensors (Angiodin Universal, BIOSS, Russia). The sensors were fixed in the region of the middle temporal acoustic windows on both sides with the help of a special helmet. TCD measures linear blood flow velocity in MCA and not cerebral perfusion as such. However, studies show that linear blood flow velocity in MCA represents a reliable and effective cerebral perfusion index [58–60]. Moreover, TCD allows conducting bilateral examination of CBF, as well as possesses a sufficient time resolution for the assessment of cerebrovascular reactivity.

When studying CBF and systemic AP, we carried out capnographic control with the assessment of $PetCO_2$ (end-tidal partial pressure of CO_2), which differs from $PaCO_2$ only by 1–2 mm Hg and adequately represents its value [61]. Capnographic control was carried out throughout the whole examination (OEM module, Oridion, USA).

During the whole examination, we monitored mean AP (mean arterial blood pressure, MAP, in mm Hg) by means of the digital photoplethysmographic method, using uninterrupted beat-to-beat non-invasive measurement at the left middle and index fingers (CNAP Monitor 500, CNSystems, Austria).

Arterial oxygen saturation (SpO_2,%) was measured by pulse oximetry (BPM-200, Biosys, Korea).

As many other authors, we used rebreathing through a breathing circuit to create hypercapnia [62, 63]. The use of a breathing circuit does not require any additional equipment or gas mixtures. Rebreathing provokes not only hypercapnia, but also hypoxia. However, CBF reaction to the combined impact of hypoxia and hypercapnia is mostly determined by $PaCO_2$ level, and not by PaO_2 deficiency [37]; therefore, we chose rebreathing to assess the impact of hypercapnia upon CBF velocity. To create hypocapnia, we used the method of arbitrary hyperventilation at a rate of one respiratory cycle per 2 sec for 2 min.

Volunteers underwent three stages of the examination: baseline, rebreathing, and hyperventilation. At the first stage, the subjects breathed room air for 5 min (normocapnia). The second stage was rebreathing, which created hypercapnia. To achieve that, a breathing circuit was attached to the mask (Carbonic, Russia); it possessed additional 1000 ml of dead space volume, and the subjects breathed through it for 10 min. Thus, an increase in $PetCO_2$ by 10–15 mm Hg was provided. Rebreathing was followed by a 5-min rest during which hemodynamic parameters and capnogram restored their initial values. Then, there was the hyperventilation stage, which created hypocapnia with a decreased $PetCO_2$ by 10–15 mm Hg.

Hypercapnia and hypocapnia initiated by rebreathing and hyperventilation include a wide range of $PetCO_2$. However, we chose not to create a gradual increase in CO_2 from hypocapnia to hypercapnia, as in Duffin rebreathing tests [64], as we consider it to be more physiological to increase and reduce $PaCO_2$ starting from normocapnia.

At rest, mean (SD) $PetCO_2$ for all samples was 33.6 (3.1) mm Hg, which was a little lower than in the classical concept of normocapnia (35–45 mm Hg). Besides, mean (SD) $PetCO_2$ in women was 31.8 (1.2) mm Hg, whereas in men, mean (SD) $PetCO_2$ was 35.1 (3.5) mm Hg. Such a decrease in $PetCO_2$ during quiet breathing in healthy women can be explained by peculiarities of ventilation depending on the menstrual cycle phase. We tested women at the luteal and at the beginning of the follicular phase of menstrual cycle, when oestrogen levels are the lowest, to minimize the impact of increased oestrogen background upon cerebrovascular reactivity [65]. At the same period of menstrual cycle, functional hyperventilation and a decrease in $PaCO_2$ by 2.5–3 mm Hg are known to be reported [66].

Linear blood flow velocity data in the right and left MCA (MCAv left and right), $PetCO_2$, mean AP (MAP), and SpO_2 were averaged during a 5-min period of normocapnia for each test subject. On this basis, mean values (M ± SD) of the given parameters were calculated for all samples. Maximum alterations of all the parameters under rebreathing and hyperventilation as compared to the resting state (Δ), their absolute value, and the percentage were calculated. MCAv data for every 10 sec of rebreathing and hyperventilation were transformed into a percent change of the mean value at rest (%MCAv left and right). Then,%MCAv left and right were compared

to $PetCO_2$. Absolute change in CBF velocity was standardized by 1 mm Hg $PetCO_2$.

For the assessment of cerebrovascular reactivity to CO_2, the index of cerebrovascular reactivity to hypercapnia ($CVRhyperCO_2$) and hypocapnia ($CVRhypoCO_2$) were calculated according to Lindegaard et al. [67] from the formula:

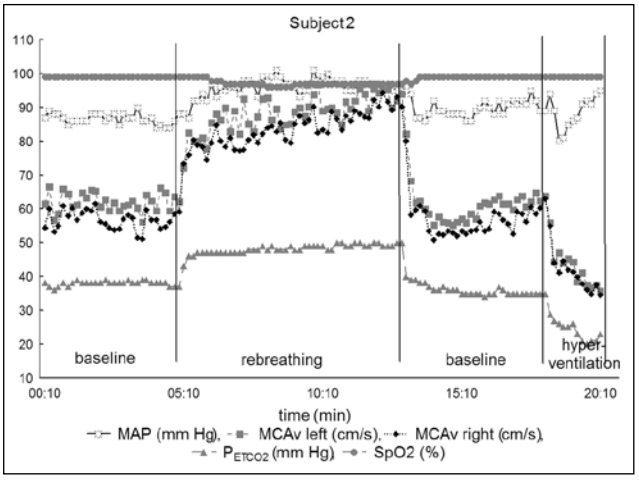
$CVRhyperCO_2$ = (Δ MCAv hyper/MCAv norm)/Δ $PetCO_2$ hyper × 100,

where MCAv norm is MCAv value under normocapnia, Δ MCAv hyper (Δ MCAv hypo) is the change in MCAv under hypercapnia (hypocapnia) as compared to MCAv norm, Δ $PetCO_2$ hyper (Δ $PetCO_2$ hypo) is the change in $PetCO_2$ under hypercapnia (hypocapnia) as compared to PetCO2 under normocapnia.

$PetCO_2$ alteration range in healthy young people during rebreathing and hyperventilation, according to our data [57], was from 19 to 48 mm Hg (Fig. 3). Maximum increase in CBF velocity at that was 185% (from 35 to 100 sm/sec).

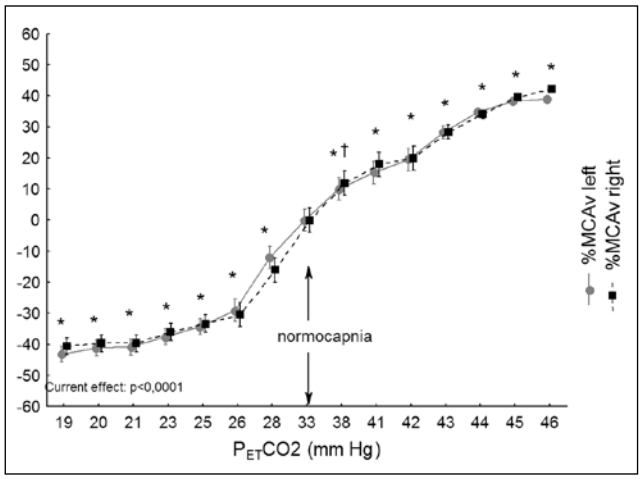
Changes in CBF velocity as compared to normocapnia ($PetCO_2$ 33 mm Hg) occurred at $PetCO_2$ 38 mm Hg during rebreathing and a decrease in $PetCO_2$ to 28 mm Hg during hyperventilation (Fig. 4). Therefore, a change in $PetCO_2$ even by 5 mm Hg towards a decrease or an increase provokes reaction of CBF velocity.

Fig. 3. Typical reaction of the parameters under study (subject 2) at rest, in rebreathing, and hyperventilation [57]



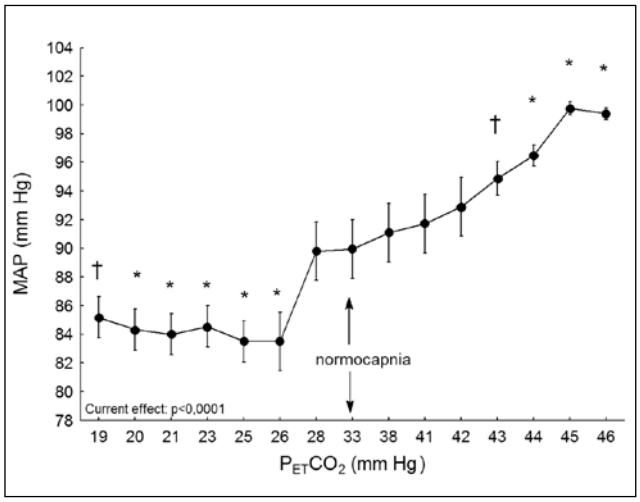
Note: MAP (mm Hg), MCAv left (sm/sec), MCAv right (sm/sec), PetCO2 (mm Hg), SpO2 (%).

Fig. 4. Impact of PetCO2 level upon% MCAv left and right [57].



Note: Values%MCAv left and right are expressed as least mean squares for each value of $PetCO_2$. Vertical lines represent 0.95 confidence intervals. *$p < 0.01$ and †$p < 0.05$ for%MCAv left and right at the corresponding values of $PetCO_2$ of hypercapnia and hypocapnia as compared to%MCAv left and right under normocapnia 33 mm Hg $PetCO_2$.

Fig. 5. The impact of PetCO2 level upon MAP value [57]



Note: MAP data are expressed as least mean squares for each value of $PetCO_2$. Vertical lines represent 0.95 confidence intervals. *$p < 0.01$ and †$p < 0.05$ for MAP at corresponding $PetCO_2$ values as compared to MAP under normocapnia 33 mm Hg $PetCO_2$.

Hypercapnia resulted in a natural increase in MAP, whereas hypocapnia resulted in its decrease (Fig. 5). A significant growth of MAP under hypercapnia appeared when $PetCO_2$ reached 43 mm Hg. In the study carried out by Battisti-Charbonney et al. [68], the threshold value of $PetCO_2$ for MAP in rebreathing was 44.4 mm Hg, which is practically identical to our results.

Threshold value of $PetCO_2$ for MAP under hypocapnia, apparently, has not been studied before. Our research has discovered a significant decrease in MAP upon achieving threshold value of $PetCO_2$ of 26 mm Hg (Fig. 5). During further decrease in $PetCO_2$, MAP remained decreased.

Our research has discovered a significant alteration of the indices of cerebrovascular reactivity to CO_2 upon achieving the thresholds reaction rates of arterial pressure [57]. Thus, $CVRhyperCO_2$ changes at the increase in $PetCO_2$ level. At $PetCO_2$ 38–43 mm Hg, mean (SD) $CVRhyperCO_2$ was 2.3 (1.4)%/26 mm Hg, whereas at $PetCO_2$ over 43 mm Hg, $CVRhyperCO_2$ increased to 3.3 (1.2)%/mm Hg ($p < 0.01$). Since $PetCO_2$ threshold for MAP also made up 43 mm Hg, it becomes obvious that, namely, increased cerebral perfusion pressure at the background of increasing MAP and hypercapnia-induced CBF autoregulation failure contributed to a greater growth of CBF velocity by 1 mm Hg, $PetCO_2$ upon achieving $PetCO_2$ threshold of 43 mm Hg.

Similar to hypercapnia, cerebrovascular reactivity to hypocapnia was also connected with the threshold value of $PetCO_2$, which involved a reaction from MAP [57]. Thus, $CVRhypoCO_2$ considerably increased at $PetCO_2$ 26 mm Hg, and then decreased, whereas at 23 mm Hg, $PetCO_2$ and its further decrease down to 19 mm Hg, $CVRhypoCO_2$ did not change. The given results can be caused first by the limits of the contraction of cerebral vessels under hypocapnia. Maximum contraction of the resistance vessels presumably occurred during the decrease in $PetCO_2$ to 23 mm Hg, since during a greater decrease in $PetCO_2$ $CVRhypoCO_2$ did not change. Secondly, CBF velocity and $CVRhypoCO_2$ can be also influenced by decreased MAP with a corresponding decrease in cerebral perfusion. Maximum decrease in MAP occurred at 26 mm Hg, $PetCO_2$ (Fig. 5), maximum $CVRhypoCO_2$ was observed at the same value. Mean (SD) $CVRhypoCO_2$ at 28 mm Hg, $PetCO_2$ made up 3.6 (2.5)%/mm Hg, whereas at 26–25 mm Hg, $PetCO_2$, it was 5.9 (3.9)%/mm Hg ($p < 0.01$).

In the present study [57], we have determined the threshold values of $PetCO_2$ for MAP under hypercapnia, which made up 43 mm Hg. The result appeared to be practically identical to that in other works. We have first determined $PetCO_2$ threshold for MAP under hypocapnia, which made up 26 mm Hg. We have also discovered $PetCO_2$ threshold for $CVRCO_2$. During rebreathing, $CVRhyperCO_2$ remained constant up to 43 mm Hg $PetCO_2$; then, it increased. During hyperventilation, $CVRhypoCO_2$ considerably changed with the decrease in $PetCO_2$ down to 26 mm Hg. $PetCO_2$ thresholds for $CVRCO_2$ and MAP during rebreathing and hyperventilation coincide.

Thus, there have been established threshold levels that differentiate cerebral blood flow (CBF) and arterial pressure (AP) reaction to CO_2. CBF is more sensitive to the alteration of CO_2 pressure within the alveoli ($PetCO_2$). A change in $PetCO_2$ even by 5 mm Hg towards decrease or increase provokes a response from CBF velocity. Reaction of the systemic AP is initiated by more considerable deviation of CO_2 concentration from normocapnic level. The threshold of hypertensive response corresponds to an increase in $PetCO_2$ by 9 mm Hg, whereas the threshold of hypertensive response corresponds to its decrease by 7 mm Hg. Within the threshold values of $PetCO_2$ from 26 to 43 mm Hg, AP does not change; hence, CBF velocity and $CVRCO_2$ are determined by cerebral vessels reaction to CO_2, reflecting "genuine" cerebrovascular CO_2 reactivity, independent of AP. Upon overcoming of the threshold values of $PetCO_2$ for AP response, there occurs an increase in $CVRCO_2$ indices, which indicates cerebral autoregulation failure.

Cerebrovascular and cardiovascular CO_2 reactivity under arterial hypertension

Peculiarities of CBF and AP response to hyperhypocapnia have been studied on volunteers with diagnosed essential AH and with an increased, at the moment of the examination, systolic AP over 139 mm Hg, at normal or increased diastolic AP over 89 mm Hg [69]. At the moment of the examination, mean AP (MAP, Me (25; 75‰)) in patients with AH was 109.7 (105.3; 112.8) mm Hg, which was significantly higher than in healthy volunteers-85.6 (80.7; 90.0) mm Hg ($P < 0.001$).

In spite of the difference in AP value, in our study, the groups of healthy subjects and those with AH [69] did not differ in blood flow velocity in the MCA. Lack of differences in the parameters of blood flow in the MCA in patients with AH as compared to healthy subjects was also noted by other researchers [70,71]. Such differences, mainly in the form of increased vascular resistance in the intracranial arteries, occur in progressive AH [49].

Lack of differences in the parameters of hemodynamics in the intracranial arteries in AH at rest,

especially at the initial stage of the disease process, can be explained by the mechanism of cerebral autoregulation functioning, maintaining stability of cerebral blood flow under conditions of changing systemic AP [45]. During AH, the cerebral autoregulation curve is known to shift towards higher AP values [72], protecting the brain from hyperfusion but making it more vulnerable to decreased perfusion pressure. Earlier, we reported on cerebral autoregulation disturbance dependent on the degree of AP growth [49].

The main mechanism of such a "shift" of the autoregulation in AH is represented by wall remodelling of cerebral arteries, which results in thickening of the vessel wall and vascular lumen narrowing [73]. At rest, hypertensive remodeling of cerebral vessels manifests itself as an increased cerebrovascular resistance [49].

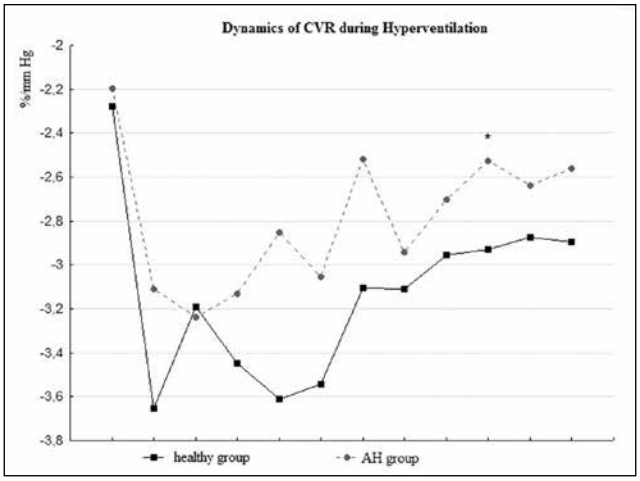
MAP considerably increased by 40 sec in patents with AH during rebreathing, whereas in the group of healthy objects, by 30 sec. A distinctive feature of the response to hypocapnia in patients with AH, as compared to healthy objects, was MAP non-restoration in patients with AP after its decrease, whereas in healthy objects MAP decreased considerably from 20 to 90 sec and then restored. It means that even at the initial stage of AH development in young patients, cardiovascular reactivity changes. Generally, these changes can be characterized as a reduced AP lability under dyscapnia.

In our research, cerebrovascular reactivity to hypercapnia in patients with AH [69] did not differ from that in healthy subjects. Generally, it is typical of young patients with AP [12], as well as of patients with minimal cerebrovascular disorders. Other researches reported decreased $CVRCO_2$ to hypercapnia in AH [75,76,77,78,79]. These contradictions may be associated with a concurrent cerebrovascular disease in patients [75] and the use of different methods of cerebrovascular reactivity assessment. Thus, besides rebreathing used to create hypercapnia [76], the acetazolamide challenge test was also applied [75].

However, in our research $CVRCO_2$ to hypocapnia in AH [69] was lower as compared to healthy objects (Fig. 6). A similar decrease was demonstrated in the work by Settakis et al. [80].

In general, the given results indicate a decrease in $CVRCO_2$ in AH, wherein the vasodilator reserve of the cerebral vessels is likely to remain more stable than vasoconstrictor. It appears logical if we take into consideration the nature of cerebral vessel remodeling in AH, which is characterized by the lumen narrowing due to hypertrophy of the walls [73]. One of the most important manifestations of remodeling of the cerebral vessels in AH is increased vascular resistance in the intracranial arteries at rest in patients during 2–3 degrees of AP increase [49]. Naturally, such remodeling, first of all, reduces vasoconstrictor reserve.

Fig. 6. Dynamics of cerebrovascular reactivity to hypocapnia ($CVR\ hypoCO_2$) during 10 min of rebreathing in the healthy group and in the AH group [69]



Note: The values of $CVR\ hypoCO_2$, corresponding to every 10 sec. of hyperventilation. $*P < 0.05$ as compared to the healthy objects.

Conclusion

Strong emotions cause excitation of CNS, sympathetic activation, increased AP, and hyperventilation. Long-lasting negative emotions lead to an increase in CO_2 chemosensitivity, which maintains stable hyperventilation and chronic hypocapnia. Hypocapnia provokes a decrease in blood pressure and, apparently, can be a physiological factor preventing dangerous rise and stabilization of high AP during stress-induced sympathetic activation. However, positive stress causes hyperventilation syndrome with chronic hypocapnia and alkalosis, which, on the contrary, can lead to disorders in AP regulation and stabilization of arterial hypertension (AH). A key mechanism of the hypertensive effect of chronic hyperventilation is, apparently, change in the CO_2 sensitivity of chemoreceptors. Respiratory exercise with recurring hypercapnia possesses considerable therapeutic potential in AH, restoring

CO_2 sensitivity of chemoreceptors and enhancing antioxidant activity.

Stability of cerebral perfusion during the changes in systemic AP is achieved due to the cerebral autoregulation mechanism. However, exit beyond the limits of normocapnia disturbs autoregulation, and cerebral vessels lose their ability to level AP jumps. This cerebrovascular disorder has an adverse effect upon the processes of respiratory and AP regulation associated with chemoreceptors.

Under hypocapnia, cerebral venous tone is reduced, and cerebral venous outflow velocity decreases, which can cause increased intracranial pressure and disturbances in the participation of brain in AP control.

Threshold levels have been established, differentiating CO_2 reaction of the cerebral blood flow (CBF) and AP. CBF is more sensitive to the alterations in CO_2 pressure in the alveoli ($PetCO_2$). A change in $PetCO_2$ even by 5 mm Hg towards decrease or increase causes CBF response. Systemic AP response is initiated at a more significant deviation of CO_2 concentration from the normocapnic level. The threshold of hypertensive response corresponds to an increase in $PetCO_2$ by 9 mm Hg, whereas the threshold of hypotensive response corresponds to its decrease by 7 mm Hg. Within the limits of $PetCO_2$ threshold values from 26 to 43 mm Hg, AP does not change, which means that CBF velocity and $CVRCO_2$ are defined by CO_2 reaction of cerebral vessels, which represents "genuine" cerebrovascular CO_2 reactivity independent of AP. Upon exceeding $PetCO_2$ threshold values for AP response, there occurs an increase in $CVRCO_2$ indices, which indicate cerebral autoregulation failure.

CBF parameters in patients with AH at rest, especially at the initial stage of the development of the disease, do not differ considerably from those in healthy objects, which indicates intactness of the cerebral autoregulation mechanism. AH development is accompanied by a shift of the autoregulation curve to the right to higher AP values and increased cerebrovascular resistance due to the vascular remodeling with thickening of the vessel walls and lumen narrowing. During progressive AH, there occurs a cerebral autoregulation disturbance, dependent on the degree of AP rise.

Cardiovascular CO_2 reactivity changes even at the initial stage of AH development. Unlike in healthy objects, AH response to hyper/hypocapnia develops more slowly in AH patients, and AP value does not restore after its decrease under hypocapnia. Generally, these changes can be characterized as decreased AP lability under dyscapnia, which can indicate disturbances in the mechanism of AP regulation.

Cerebrovascular CO_2 reactivity in AH generally decreases. Together with that, vasodilator reserve of cerebral vessels remains more stable than vasoconstrictor as $CVRCO_2$ mostly decreases under hypocapnia. It seems logical, considering the peculiarities of cerebral vessels remodeling in AH, which is characterized by lumen narrowing due to the hypertrophy of the walls.

According to our hypothesis, AH development includes hyperventilation and hypocapnia as an inevitable typical response to psycho-emotional stress, which causes increased sensitivity of the central and peripheral chemoreceptors, as well as hyperactivation of SNS, cerebral autoregulation disorder, and disturbance in the participation of the brain in AP regulation. All those mentioned above contribute to a rise and stabilization of increased AP. We fully realize the extraordinary complicacy and an enormous volume of the studies necessary to check the findings. However, the facts quoted in the present article, in our opinion, at least partially prove the proposed hypothesis.

Conflict of interest
The authors declare no conflict of interest.

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