THE REGULATION ROLE OF CAROTID BODY PERIPHERAL CHEMORECEPTORS
IN PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL CONDITIONS

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Summary
Introduction. The major oxygen sensors in the human body are peripheral chemoreceptors, also known as interoreceptors-as connected with internal organs, located in the aortic arch and in the body of the common carotid artery. Chemoreceptor function under physiological conditions. Stimulation of peripheral chemoreceptors during environmental hypoxia causes a reflex-mediated increased ventilation, followed by the increase of the muscle sympathetic activity, aiming to maintain tissue oxygen homeostasis, as well as glucose homeostasis. Besides that, peripheral chemoreceptors interact with central chemoreceptors, responsible for carbon dioxide changes, and they are able to modulate each other. Chemoreceptor function in pathophysiological conditions. Investigations of respiratory function in many pathological processes, such as hypertension, obstructive sleep apnea, congestive heart failure and many other diseases that are presented with enhanced peripheral chemosensitivity and impaired functional sympatholysis ultimately determine the peripheral chemoreceptor role and significance of peripheral chemoreceptors in the process of those pathological conditions development. Considering this, the presumed influence of peripheral chemoreceptors is important in patients having the above mentioned pathology. Conclusion. The importance and the role of peripheral chemoreceptors in the course of the breathing control is still controversial, despite many scientific attempts to solve this problem. The main objective of this review is to give the latest data on the peripheral chemoreceptor role and to highlight the importance of peripheral chemoreceptors for maintaining of oxygen homeostasis in patients with hypoxia caused by either physiological or pathological conditions.

Key words: Carotid Body; Chemoreceptor Cells; Anoxia; Ventilation; Exercise; Hypertension; Oxygen; Homeostasis

Sažetak
Uvod. Periferni hemoreceptori glavni su senzori za kiseonik u ljudskom telu, a takođe su poznati i kao interoreceptori jer su povezani sa unutrašnjim organima koji se nalaze u luku aorte, kao i u telu a. carotis communis. Uloga perifernih hemoreceptora u regulaciji fizioloških stanja. Žna se da stimulacija perifernih hemoreceptora u eksperimentalnim uslovima hipoksi, fizičkog napora, pa čak i tokom nekih bolesti izaziva refleksno posredovano pojačanje ventilacije, koje prati povećanje mišićne simpatičke aktivnosti, sa ciljem održavanja tkivne homeostaze kiseonika, kao i homeostaze glukoze. Osim toga, periferni hemoreceptori interagiraju sa centralnim hemoreceptorima koji su odgovorni za promene u nivou ugljen-dioksida i one se međusobno nadopunjuju. Uloga perifernih hemoreceptora u regulaciji patoloških stanja. Istraživanja respiratorne funkcije u mnogim patološkim procesima, kao što su hipertenzija, opstruktna slip-apnea, konstestivna srčana insuficijencija i mnoge druge bolesti i stanja, a koja se odlikuju povećanom perifernom hemosenzitivnošću i poremećajem funkcije simpatičkog nervnog sistema, jednoglasno naglašavaju ulogu perifernih hemoreceptora tokom ovih procesa. Imajući prethodno navedeno u vidu, uloga perifernih hemoreceptora je važna kod pacijenata sa navedenim bolestima. Zaključak. Značaj perifernih hemoreceptora u kontroli disanja je i dalje neznatni, uprkos brojnim naučnim pokušajima da se reši ovo pitanje. Glavni cilj ovog rada bio je sažet prikaz najnovijih istraživanja o značaju hemoreceptora, osvetljajući njihovu ulogu u održavanju homeostaze kiseonika kod bolesnika sa hipoksiom uzrokovanim hlo fiziološkim ili patofiziološkim stanjima.

Ključne reči: Karotidna telašca; hemoreceptorske čeličke; hipoksi ja; vežbanje; hipertenzija; kiseonik; homeostaza

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Introduction

Respiration, as measured with pulmonary ventilatory rate (volume per minute), is controlled voluntarily and involuntarily. Voluntary control depends on the brain condition (emotional state, temperature, free will, etc) and is provided by cerebral cortex.

Involuntary control mechanisms of the ventilatory pattern are not yet fully understood, thus involving convergence of signals coming from the respiratory control centers located in the medulla oblongata and pons, being integrated in the anterior horn cells of the spinal cord. Involuntary ventilatory rate is determined by pH-sensing central chemoreceptors of the surface of medulla oblongata and by oxygen- and carbon dioxide-sensing peripheral chemoreceptors, with the impulse transferred to the glossopharyngeal nerve (nervus IX) and the vagus nerve (nerves X). The other way of the involuntary ventilation regulation is by mechanoreceptors located in the airways and parenchyma.

Peripheral chemoreceptors (PC), located in the body of the common carotid artery and the aortic arch, are the major oxygen sensors in the human body [1]. They are essential in low-oxygen-characterized situations, prompted to increase in their number and size by low access to oxygen. Although the mechanism is not completely understood yet, it is believed that type II cells, previously thought to have only a supportive role, retain properties of the stem cells, able to differentiate into type I transducer cells [2]. The specific signal of transduction comes through depolarization, caused by inhibition of the potassium channels. The AMP-activated protein kinase (AMPK) opens and closes potassium channels via phosphorylation in oxygen sensing of the type-I cells [3]. PC work along with central chemoreceptors (CC), which monitor the blood carbon dioxide (CO$_2$) level in the cerebrospinal fluid around the brain. Allogether, in low-oxygen situations, they send nerve signals to the medullar vasomotor center.

Stimulation of PC causes a reflex-mediated increase in ventilation, followed by the increasing of the muscle sympathetic activity (MSNA), with the non-contracting skeletal muscles, gut and kidneys vasoconstriction, aiming to redirect the peripheral blood into the active muscles [1, 4]. It is a well-known fact that environmental hypoxia, exercise or some pathophysiological conditions can lead to the rapid changes in oxygen (O$_2$) supply or demand. Cardiorespiratory reflex plays the important role in maintaining the tissue O$_2$ homeostasis [5]. The importance and the role of PC in the breathing control is still controversial, regarding previous studies of the respiratory function during hypoxia, exercise and some particular diseases. There have been many attempts at solving this question, but the exact role of the PC in the breathing control is still unclear.

Bearing all of the above mentioned in mind, the main objective of this article is to overview recent PC studies, as well as to highlight the importance of PC for the maintainence of the O$_2$ homeostasis during hypoxia associated both with physiological and pathological conditions.

The electronic database MEDLINE was searched from January 1982 to July 2014, with the following keywords: peripheral chemoreceptors, carotid body, hypoxia, ventilation, exercise, hypertension and chronic heart failure, by choosing articles with different-aged human subjects, between 16 and 74 years of age. This systematic review included healthy, physically inactive people, then people with mild hypertension, congestive heart failure, obstructive sleep apnea and people who underwent therapeutic carotid body resection, as well as professional athletes.

After the preliminary literature search by the selected keywords, there were 2,164 references identified in MEDLINE. The advanced search scan produced 114 potentially relevant studies, which were thoroughly analyzed. Finally, after thorough review and consideration, the total number of papers included in this article was 43.

Function of Chemoreceptor under Physiological Conditions

The Relative Contribution of the PC to the Hypoxic Ventilatory Response

Sympathetic activity is increased during physical activity, leading to redistribution of the blood flow from the inactive muscles and vascular beds into the active muscles [4]. Previous studies have shown enhanced sensitivity of PC during exercise [6, 7], but PC contribution to the muscle blood flow redirection in the terms of hypoxia in humans is still questionable.

Stickland et al. conducted a study on seven healthy participants who were exposed to short and repeated bouts of hyperoxia to demonstrate the role of PC on MSNA at rest and during rhythmic dynamic handgrip exercise [1]. They showed that transient PC inhibition reduced ventilation, but had no effect on either the femoral blood flow or the arterial pressure, neither at rest nor during leg extension exercise. Besides, low-dose dopamine inhibits peripheral chemoreceptors and attenuates the hypoxic ventilatory response (HVR) in humans. However, it is unknown whether it also modulates the hemodynamic reactions to acute hypoxia, cardiac baroreflex sensitivity (BRS) and if there is any effect of dopamine withdrawal [8].

Although there are limited results of the PC involvement during hypoxia, the important role of PC in the skeletal muscles blood flow regulation has been demonstrated during normoxic state of exercise [1]. Furthermore, an advanced study performed by Stickland et al. with similar methodology as the...
previous one was conducted on 13 healthy subjects (9 men, 4 women), evaluated at rest and during constant rhythmic handgrip exercise [9]. PC were inhibited using hyperoxic gas inhalation, whereas hypoxic gas inhalation was used for its activation.

Their results pointed at the PC contribution to the regulation of the skeletal muscle blood flow during normoxic exercise. On the other hand, PC stimulation seems to be withdrawn under hypoxia by local vasodilatory factors, confirming once again the limited role of PC in conditions characterized by hypoxia. In addition, afferent signals from the skeletal muscles in contraction are the important source of the brain stem neural input during exercise. These exercise-induced signals are generated by the activation of group III (predominantly mechanically sensitive A-δ fibres) and group IV (predominantly metabolically sensitive C fibres) skeletal muscle afferents which reflexively increase the arterial blood flow pressure (ABP) and the heart rate. Hemodynamic regulation by this reflex loop, termed as the exercise pressor reflex, is primarily mediated by the increased efferent sympathetic nerve activity [9].

Series of studies conducted by Stickland et al. (2008, 2011) have shown the sensitization of PC during exercise. Transient PC inhibition occurring in healthy individuals during physical activity leads to the inhibition of muscle sympathetic nerve activity, leading to blood vessels vasodilatation as a consequence [1, 10].

A similar study done by Housienne et al. with simultaneous metaboreflex and chemoreflex activation was conducted on 13 healthy participants randomized into three groups: group I had PC activation with isocapnic hypoxia, group II had isometric handgrip exercise in normoxia and group III had metaboreflex activation in exercise during hypoxia [11]. The achieved results showed that metabo- and chemoreceptors exert different effects on sympathetic response during hypoxic exercise. More potent stimulus for MSNA was the exercise alone, as compared to PC alone.

Gujic et al. have come to a similar observation, by examining 15 healthy, physically inactive young males. Three-minute tests were performed in 4 different conditions: during normoxic test, normoxic exercise, hypoxic exercise and hypoxia at rest. The results have confirmed the previously reported data on sympathetic baroreflex sensitivity, mostly determined with metaboreceptor activation, while PC was shown to be mainly responsible for the time between two consecutive R waves in the electrocardiogram (R-R) interval operating point shortening [12].

Previous studies have shown oscillation in PC activity, with the influence on breathing [13]. Moreover, recent studies have demonstrated enhancement of human hypoxic ventilatory response (HVR) during short-duration intermittent hypoxia [14]. HVR is also associated with higher PC response to acute hypoxia [15]. However, it still remains controversial, unresolved and unclear whether there are differences in PC sensitivity between short-duration intermittent hypoxia and long-duration intermittent hypoxia. Foster et al. examined 17 healthy male participants who were randomly exposed either to short- or long-term duration of intermittent hypoxia. Their results showed that increased HVR has no functional significance on PC sensitivity.

There are only a few studies on the role of PC in older adult humans, one of them was conducted by Yovk et al. [16]. They compared 3 groups with 5 members in each of them, representing young men and women, only young males and five older males. They were re-exposed to brief hypoxic pulses after 20 minutes of sustained eucapnic hypoxia. Their results were in compliance with investigational data from Smith et al., showing that HVR characteristics are unwavering by age in healthy and active people [17].

Peripheral Chemoreceptors and Exercise
The main characteristic of a professional athlete is the possibility to achieve series of physiological adaptations, enabling better performance [18]. Exercising muscles are in need of a prompt, but very precise response of the respiratory and cardiovascular system in order to provide fine matching of the blood perfusion to metabolic demands [19–22]. PC reflexes are involved in ventilatory stimulation during exercise [23]. Changes of ventilation are passed through the following 3 phases: a rapid increase in ventilation that occurs at the exercise (I), an exponential increase in ventilation that follows afterwards (II) and a steady state coming at last (III) [24, 25]. During an exaggerated near-maximal and maximal physical activity, the ability of the respiratory system to maintain homeostasis is challenged. Therefore, this kind of physical activity leads to arterial hypoxemia which can be the limiting factor for exercise in that case [26].

Blood flow through intrapulmonary arteriovenous anastomoses (IPAVA) is increased with exposure to acute hypoxia and has been associated with pulmonary artery systolic pressure (PASP). The principal stimulus ultimately responsible for regulating IPAVA recruitment is unknown; however, the literature suggests that pulmonary blood flow, pressure or alveolar hypoxia is a probable mediator. In humans, progressive hypoxia appears to promote a graded increase in the magnitude of microbubble passage despite a small increase in PASP indicating that alveolar hypoxia may be more important than the pulmonary vascular pressure [27].

These responsiveness mediator mechanisms are complex and, though they have been much elucidated in the previous literature, the PC contribution to autonomic exercise response, especially in the population of professional athletes, has not received much attention [28].

There are few studies aimed at this relatively new concept in the exercise physiology. Data from previous studies have emphasized the PC role in the ventilatory stimulation during phase I and III [29–33]. A study done by Stulbarg et al. has shown the decreased ventilatory response to exercise in subjects with carotid body (CB) resection [30].

In addition, those studies have shown that, as compared to the untrained individuals, well-trained endurance athletes have lower peripheral chemosensitivity and lower ventilation per minute in the
course of the exercise [34–38]. Specific mechanism of the reduced peripheral chemosensitivity in physically active individuals still remains the key question in the exercise physiology.

McMahon et al. examined the effects of respiratory muscle training (RMT) on peripheral chemosensitivity [31] in 20 trained male cyclists, randomized into the RMT group and the control group. Peripheral chemosensitivity was reduced significantly in RMT group as compared to the controls (-5, 8±6, 0% vs. 0, 1±4, 6%, p<0, 5). This reduction in chemosensitivity was not significantly correlated with the exercise ventilation or the cycling endurance. They suggested the possibility that PC role in the ventilation control in the course of exercise was not so important. A study done by Levine et al. has also found no significant change in PC response due to hypoxia at rest [32].

According to the above listed studies, the influence of physical activity on PC is not clear enough, as supported by controversial results. It is still not clearly known whether peripheral chemosensitivity differs at the normal and higher level of physical activity, as presented in professional athletes. Ventilation during exercise is a particular challenge- still not resolved, debating on the excitatory or inhibitory role of the PC (pointing out that they are not the only oxygen sensing cells that can respond in the stress periods) [33].

**Function of Chemoreceptor in Pathophysiological Conditions**

Previous studies have shown the increased sympathetic activity in many pathological processes, such as hypertension, obstructive sleep apnea, congestive heart failure and many other diseases, which throws new scientific light on the future studies which should be aimed at determining the PC role and significance in those pathological conditions.

The main characteristics of the majority of cardiovascular and other diseases are enhanced peripheral chemosensitivity and impaired functional sympatholysis [35, 36]. Considering this, the presumed influence of the PC on the exercise tolerance level is important in patients with the above mentioned pathology.

According to several studies examining pathology of cardiovascular and other diseases, there is a number of potential explanations for the pathophysiology of the exercise tolerance. Izdebska et al. examined the PC reflex reactivity in young mildly hypertensive men (HTS) [37, 38]. Being the first in this field, they compared mildly hypertensive men and normotensive male controls before the dynamic exercise physical therapy and 3 months after it; their results confirmed the enhanced PC drive in hypertensive patients [39–43], allowing the possibility of important clinical conclusion, as the pressure chemoreceptor reflex contributes to a possible effect of the regular physical activity on arterial hypertension treatment.

A single bout of mild to moderate exercise can lead to a postexercise decrease in blood pressure in hypertensive individuals, called postexercise hypotension. It can last for up to 13 hours in humans, and could be an effective non-pharmacological anti-hypertensive strategy. Despite the well-documented blood pressure-lowering effect of the exercise, the central neuronal mechanisms have only recently been revealed [44].

Lately, Ilsini et al. have found out that reduced sympathetic activity in hypertensive patients by PC deactivation immediately decreases blood pressure in humans [39].

Literature data about the role of the peripheral chemosensitivity in serious cardiovascular disorders and pathophysiological conditions are also available. Previous studies have shown that the patients with chronic heart failure (HF) have an increased sympathetic nerve activity, leading to the highest mortality [45]. Some authors have also speculated on the augmented peripheral chemosensitivity underlying the increased sympathetic nerve activity. Nunes Alves et al. have studied autonomic control and PC role in HF patients lately, showing that systemic hypoxia PC stimulation in HF patients leads to an increase in the sympathetic nerve activity. They have found increased MSNA control by PC, even in mild changes of the oxygen saturation [46].

Seventy years ago it was thought that PC were responsible for asthma, so CB resection was one of therapeutic interventions in asthma. Moreover, scientists conducted physiological studies on human subjects over 20 years of age after CB surgical removal. Kimura et al. conducted such a study on bronchial asthma patients who underwent therapeutic CB resection [45]. Unilateral CB resected patients showed biphasic ventilatory response pattern, while bilateral CB resected patients did not demonstrate the same ventilatory response. Once again, the important PC influence on ventilation stimulation and HVR control was highlighted.

Studies conducted by Paton et al. and Ribeiro et al. emphasized the idea that inhibition of PC caused by denervation or even surgical removal might represent the advanced method of treatment for those disorders [47, 48].

Although there is a significant attenuation of hypoxic ventilatory response in CB resected subjects as reported by previous studies, there are some precariousness that should be noted. Available data about the non-carotid body chemoreceptors mechanism involved in upregulation are scarce. Almost every cell in our body has chemoreceptors, since they need to control local pO2 and PCO2 tonically. As the existing skeletal muscles have chemoreceptors that drive the exercise pressor reflex, massive sympathoexcitation is driven during exercise.

It still remains unresolved whether the above mentioned attenuation comes as a consequence of asthma, or due to non-carotid body chemoreceptor compensatory upregulation, or deficiency.

Regulation of breathing sleeping disorders, such as the obstructive sleep apnea (OSA), has frequently been studied recently. Narkiewicz et al. have studied male OSA patients, emphasizing the striking HVR augmentation [49]. Similar results have also been obtained in Cistulli and Sullivan's studies [50]. Increased peripheral chemosensitivity could be explained by augmented HVR. Contrariwise, a number of studies have shown depressed HVR in those patients [51, 52].
It is possible that increased peripheral chemosensitivity leads to enhancement of ventilatory response in the early stages of this breathing disorder. This initial increase is followed by PC desensitization with insensitivity to hypoxia. Bearing in mind the above mentioned facts, further examination of PC desensitization during intermittent hypoxia should be done.

**Conclusion**

Chemoreceptors are powerful modulators of the ventilatory and circulatory response in terms of hypoxia, not only in certain physiological conditions, but also in some health disorders. Studies reviewed in this paper evaluated the role of peripheral chemoreceptors in hypoxia-induced ventilation stimulation. In addition, the peripheral chemoreceptors role in stimulation of breathing during exercise is undoubtedly important; however, as reviewed, the condition including human subjects have only yielded the indirect peripheral chemoreceptors function. As we are unable to get information from live, physically active humans, we must rely on indirect evidence, with the hope that more advanced techniques are going to give us more information.

We should bear in mind additional chemoreceptors, called “paraganglions”, representing tissues similar to peripheral chemoreceptors, placed in the thorax and abdomen. In the population with surgically removed carotid body in order to treat pulmonary diseases, which is characterized by chronic absence of peripheral chemoreceptors, hypoxic ventilatory response maintenance is upregulated by non-carotid body chemoreceptors. The exact mechanisms for this regulation are poorly investigated, waiting to be examined in the future. Though available evidence suggests increased peripheral chemosensitivity in the early stages of a number of pathophysiological conditions (such as obstructive sleep apnea, chronic heart failure or certain forms of hypertension), the precise mechanisms still remain to be explored. There is a potential protective role of peripheral chemoreceptors in the course of the disease progression. The underlying mechanisms for maladaptive responses are unclear. A new avenue for research has been opened by this review, which should clarify further the peripheral chemoreceptors role in subtle tuning between the blood flow and the peripheral chemoreceptors affection. The future for the upcoming studies lies in the new imaging techniques, capable of introducing fine communication relationships between the peripheral chemoreceptor cells and the sensory nerve endings. By revealing peripheral chemoreceptors and hypoxic ventilatory response regulation interaction, the successful completion of those future surveys would certainly produce a deeper vision of the peripheral chemoreceptor-linked pathophysiological process and possible therapeutic approaches.

**References**


