

Specifics of Ventilatory and Heart Rate Chemosensitivity Related to Special Endurance Capacity in High Performance Alpinists and Endurance Athletes

DOI: 10.2478/v10131-009-0011-z

Authors' Contribution:

A – Study Design
 B – Data Collection
 C – Statistical Analysis
 D – Data Interpretation
 E – Manuscript Preparation
 F – Literature Search
 G – Funds Collection

Viktor Mishchenko^{1 (A,B,D,E,F)}, **Anatoly Pavlik**^{2 (B,C,F)},
Andrzej Suchanowski^{1 (A,D,F)}

¹Jedrzej Sniadecki Academy of Physical Education and Sport in Gdansk, Poland

² National University of Physical Education and Sport, Kiev, Ukraine

Key words: *alpinists, endurance athletes, cardiorespiratory response, hypoxia, hypercapnia, special work capacity*

Abstract

Background: *The aim was to compare ventilatory and heart rate chemosensitivity to hypoxia and hypercapnia in homogenous groups of high performance alpinists and endurance athletes and its relation to special work endurance.*

Material/Methods: *Thirty-two male best national alpinists (30.7±2.7 yrs, VO_{2max} 63.7±1.9 ml.kg⁻¹.min⁻¹, 14.3±2.4 yrs of experience) and 24 high performance male road cyclists of national team (25.7±1.1 yrs, VO_{2max} 74.5±1.5 ml.kg⁻¹.min⁻¹, 11.2±1.4 yrs of experience) were examined by isocapnic progressive hypoxia and CO₂ rebreathing tests. Maximal oxygen uptake, lung ventilation and heart rate peak responses were measured in an incremental ergometric test at sea level. Special work capacity of 23 alpinists was evaluated as the best time of non complicated mountain climbing between the point at 3,290 and 4,300 m above the sea level. Special work capacity of cyclists was evaluated as the best time of the individual 50 km race at the sea level.*

Results: *The results showed no significant differences of the hypoxic ventilatory response in groups of alpinists and cyclists ($p>0.05$) But circulatory response evaluated by response of HR increase in answer to a decrease in O₂ arterial blood saturation (SaO₂) in alpinists was lower ($p<0.05$). Results showed that the evaluation of ventilatory and heart rate chemosensitivity in addition to measure of aerobic power may give important information for prevision of specific working capacity of high performance alpinists. Maximal oxygen uptake (ml/kg body mass) of the four best alpinists did not differ from the values of other alpinists. Special work capacity of alpinists was significantly related to tidal volume increase for the hypoxia test ($r=-0.60$) and to CO₂ sensitivity ($r=-0.67$).*

Conclusions: *The long-term exposure to environmental hypoxia and hypocapnia in alpinists generates specific changes in respiratory control. To evaluate special work capacity potential possibilities in a homogenous group of high performance alpinists first of all heart rate response sensitivity to hypoxia as well ventilatory response sensitivity to CO₂ had to be taken into account, but only an alpinist's aerobic power.*

Word count: 2 851

Tables: 3

Figures: -

References: 20

Received: November 2009

Accepted: November 2009

Published: December 2009

Address for correspondence:

Prof. Viktor Mishchenko

Academy of Physical Education and Sport, Department of Theory of the Olympic Sport, 80-336 Gdańsk, Poland, ul. K. Górskiego 8

Phone: +4858 554-73-66, e-mail: vmishch@awf.gda.pl

Introduction

Oxygen delivery and efficiency of O₂ utilization are of tremendous importance for the realization of energy processes during adaptation in alpinists and endurance athletes. Under conditions of specific training loads the above occurs along with the increase in the body oxygen regime tension [1,2]. However, specific control mechanisms of realizing this kind of adaptation effect are not yet clear [3]. Some data indicate that the response mechanisms of the ventilatory control system are not static but depend on afferent input and exhibit a large degree of restoration or plasticity [4].

It is known that a possible degree of shifting homeostasis parameters may permit making judgements about the “reserves of homeostasis” [2,5]. If one could easily determine the level of homeostatic reserves, it would become the most precise quantitative expression of the specific adaptation degree. In alpinist and endurance training the most important is respiratory homeostasis. One may suppose that any optimum value of above indicated parameters of the cardiorespiratory system response (or, its optimum reactivity) may only provide the most favorable for energy metabolism respiratory homeostasis. At such a direction of adaptation regulatory mechanism analysis attention is accentuated at the account of cardiorespiratory response sensitivity to the hypoxic and CO₂-H⁺ shifts of the internal environment (homeostatic regulation) [3,6].

For the analysis of adaptation to high physical activity in high altitude hypoxic environment one should take into account the fact that in the process of respiratory system adaptation to a specific factor of high physical activity (hypoxia and metabolic acidosis), reduction of total amount of afferent impulses occurs [2,7,8]. Therefore, the decrease in the total amount of afferent impulses may be one of the important criteria for optimization of respiratory system adaptation.

Specific mechanisms indicating peculiarities of alpinists' training status are not yet clear. We supposed that respiratory response hyposensitivity to hypoxia and hypercapnia may be essential factors of high specific adaptation, and therefore, in this study we aimed to compare ventilatory and heart rate chemosensitivity to hypoxia and hypercapnia in homogenous groups of high performance alpinists and endurance athletes. Its relation to special work endurance was evaluated also.

Material and methods

Thirty two male best national male alpinists (30.7±2.7 yrs, BMI 24.31±0.51 kg/m², VO_{2max} 63.7±1.9 ml.kg⁻¹.min⁻¹, 14.3±2.4 yrs of experience) and 24 high performance male road cyclists of national team (25.7±1.1 yrs, BMI 24.03±0.43 kg/m², VO_{2max} 74.5±1.5 ml.kg⁻¹.min⁻¹, 11.2±1.4 yrs of experience) were examined by isocapnic progressive hypoxia and CO₂ rebreathing tests [9,10]. Measurements were provided at the sea level (32 alpinists, 24 cyclists) and at 3,700 m above the sea level (23 alpinists) 7–8 days after arrival to an alpinist base camp (the Pamir Mountains). Morning rest ventilatory and heart rate responses to hypoxia were evaluated as the slope of regression between oxygen desaturation and ventilation and heart rate [11]. The ventilatory response to normoxic hypercapnia was analyzed by a linear regression. The time of rebreathing test procedure was 5–6 min. Maximal oxygen uptake, lung ventilation and heart rate peak responses were measured in an incremental ergometric test at the sea level. The test was performed using an incremental grade bicycle exercise protocol 8–10 days prior testing of special work capacity and 2–3 days after the last high-load training session. All subjects were familiarized with the bicycle exercise (Monark, Sweden) and gas analysis procedures prior to the study. The test was terminated when the subjects could no longer continue pedaling at rate of 50/min. VO₂

max was determined from the measurement of the fractional concentrations of O₂ and CO₂. To achieve a true VO₂ max, subjects had to meet two of the following criteria: plateau in VO₂ max and RER>1.1, or HR within 5 beat per min of individual HR max, measured previously. Special work capacity of alpinists was evaluated as the best time of non complicated mountain climbing between the point at 3,290 and 4,300 m above the sea level (it required about 32–42.5 min). The test was provided in a competitive condition as a component of athlete's selection in team for a Himalayan expedition. Special work capacity of cyclists was evaluated as the best time of the individual 50 km race at the sea level. The four best alpinists and endurance athletes were selected from the complete group as a result of coaches' ranking. Statistical analyses were performed using a statistical software package (SYSTAT). An analysis of variance (ANOVA) was used to determine the significance of differences between groups. Values were presented by means ± standard deviations, and significance was set at the p<0.05 level.

Results

There were no significant differences of the hypoxic ventilatory response in groups of alpinists and cyclists (p>0.05) But circulatory response evaluated by response of the HR increase in answer to a decrease in O₂ arterial blood saturation (SaO₂) in alpinists was lower (p<0.05) (Table 1).

Tab. 1. The cardiorespiratory response to hypoxia and hypercapnia in homogeneous groups of high performance endurance athletes (n=21) and alpinists (n=17) in the competitive period of training. Mean and SD

Characteristics	Alpinists		Endurance athletes	
	Complete group (A)	4 best athletes	Complete group (E)	4 best athletes
Body mass, kg	76.7±3.1	73.5±1.9	77.6±2.1	75.1±1.4
BMI, kg/m ²	24.31±0.51	23.89±0.32	24.03±0.43	23.81±0.20
Vital capacity, l	5.56±0.31	5.47±0.25#	6.21±0.21	6.30±0.25#
ΔV _E /ΔSaO ₂ , l.min ⁻¹ per 1% decrease	0.22±0.06	0.20±0.08	0.23±0.05	0.17±0.03
V _E at SaO ₂ 84%, l.min ⁻¹	8.55±0.56	8.67±0.79	9.61±0.40*	7.63±0.15*
ΔV _T /ΔSaO ₂ , l.min ⁻¹ per 1% decrease	0.209±0.09	0.176±0.08#	0.159±0.04*	0.041±0.009*#
ΔHR/ΔSaO ₂ , beat.min ⁻¹ per 1% decrease	0.57±0.08*#	0.48±0.09*	0.85±0.08*#	0.49±0.09*
ΔV _E /ΔP _A CO ₂ , l.min ⁻¹ per 1 mm Hg increase	2.52±0.27*#	1.67±0.31*	1.16±0.10#	1.10±0.09

- difference of groups A and E was significant at p<0.05;

* - Difference of 4 best athletes and complete group was significant at p<0.05

Four best alpinists were significantly differed by higher tidal volume response to hypoxia in comparison with cyclists although their vital capacity was significantly lower. Differences in chemosensitivity of ventilatory response between 4 best alpinists and the complete group of alpinists consisted in lower sensitivity to CO₂ of best alpinists (p<0.05).

Special work capacity of alpinists was significantly related to tidal volume increase for hypoxia test (r=-0.60) and to CO₂ sensitivity (r=-0.67). The best cyclists in comparison with the complete

group differed in lower ventilatory and circulatory responses to hypoxia. Special work capacity of cyclists was related to complex characteristic of ventilatory and circulatory response to hypoxia.

Maximal oxygen uptake (ml/kg body mass) of the four best alpinists did not differ from the values of other alpinists (Table 2).

Tab. 2. Maximal oxygen uptake (ml/kg body mass), lung ventilation and heart rate peak responses at VO₂ max test in complete groups and the four best alpinists and endurance athletes at the s.l. Mean and SD

Characteristics	Alpinists		Endurance athletes	
	Complete group (A)	4 best athletes	Complete group (E)	4 best athletes
VO ₂ max, l.min ⁻¹	4.88±0.19#	4.79±0.12	5.78±0.21#	5.90±0.14
VO ₂ max, ml.kg ⁻¹ .min ⁻¹	63.7±1.9#	65.2±1.4	74.5±1.3* #	78.6±1.1*
V _E max, l.min ⁻¹	138.6±3.3*	130.7±2.1*#	143.2±4.1	144.7±3.7#
HR max, beat.min ⁻¹	183.4±1.5	180.2±1.1	186.7±2.0	184.3±1.7

- Difference of groups A and E was significant at $p < 0.05$;

* - Difference of 4 best athletes and complete group was significant at $p < 0.05$

In endurance athletes maximal oxygen uptake was significantly higher than in alpinists. In the best endurance athletes maximal oxygen uptake (ml/kg body mass) was higher in comparison to the complete group. Lung ventilation peak responses at VO₂ max test in 4 of the best endurance athletes was higher than in 4 of the best alpinists. In complete group of alpinists V_E max was higher than in 4 of the best alpinists. There were no significant differences in peak response of the heart rate.

At the next stage of analysis all alpinists were divided into two groups which differed in special work capacity (time of non complicated mountain climbing). Special work capacity in group 1 was comparatively lower than in group 2. The comparison of rest CRS response and sensitivity to hypoxia and hypercapnia at 3,700 m above the sea level were made (Table 3).

Tab 3. Comparison of morning rest CRS response and chemo sensitivity at 3700 m above sea level (PiO₂=101 mm Hg) in group of high performance alpinists with relatively lower (group 1) and higher (group 2) special work capacity (by time of non complicated mountain climbing), Mean and SD

Characteristics	Group 1; n=20	Group 2; n=12
P _A O ₂ , mm Hg	59.5±1.1	58.8±1.2
P _A CO ₂ , mm Hg	29.6±0.41	28.7±0.51
Lung ventilation, l.min ⁻¹	10.7±0.31*	8.4±0.52*
Tidal volume, l	1.03±0.08*	0.85±0.09*
V _E at P _A O ₂ 40 mm Hg, l.min ⁻¹	16.5±0.35*	13.4±0.41*
Lung ventilation increment at P _A O ₂ 40 mm Hg, l.min ⁻¹	5.80±0.31*	5.00±0.28*
A – sensitivity to hypoxia (relation V _E -P _A O ₂), l.min ⁻¹ mm Hg ⁻¹	47.3±0.63*	40.7±0.51*
Heart rate increment at P _A O ₂ 40 mm Hg, bt.min ⁻¹	13.6±0.85*	10.9±0.65*
S – sensitivity to increasing P _A CO ₂ (ΔV _E /ΔP _A CO ₂), l.min ⁻¹ mm Hg ⁻¹	2.60±0.23	2.74±0.31
Lung ventilation at P _A CO ₂ 50 mm Hg, l.min ⁻¹	44.4±0.95	40.0±1.05

* - Difference group 1 and 2 was significant at $p < 0.05$

The data in Table 3 showed that groups with relatively lower and higher special work capacity differed by levels of hyperventilation and sensitivity of ventilatory and heart rate responses to hypoxia at 3,700 m above the sea level. Group 2 (higher special work capacity) was characterized by lower rest lung ventilation, tidal volume, lung ventilation increment at $P_{A}O_2$ 40 mm Hg, ventilatory and heart rate sensitivity to hypoxia. In group 2 there was also a tendency for lower lung ventilation at $P_{A}CO_2$ 50 mm Hg. Furthermore, this data demonstrated an important role of ventilatory response sensitivity to hypocapnia and alkalosis for a higher level of special work capacity in the group of alpinists.

The results of correlation analysis showed that special work capacity of alpinists was related first of all to heart rate response sensitivity (but not to ventilatory response) for a hypoxic stimulus ($r=-0.56$) and to ventilatory response to hypercapnic stimulus ($r=-0.49$) ($p<0.05$). Special work capacity of cyclists was related to ventilatory response sensitivity to hypoxia ($r=-0.51$) as well as to ventilatory response to hypercapnia ($r=-0.57$) ($p<0.05$). Heart rate response sensitivity to hypoxia in cyclists was related to special work capacity also ($r=-0.57$). Special work capacity was significantly related to body mass in group of alpinists only ($r=-0.47$).

Discussion

The results showed no significant differences in the hypoxic ventilatory response in groups of alpinists and cyclists. But the circulatory response evaluated by response of HR increase in answer to a decrease in O_2 arterial blood saturation in alpinists was lower. In endurance athletes maximal oxygen uptake (ml/kg body mass) was significantly higher than in alpinists. In the best endurance athletes maximal oxygen uptake (ml/kg body mass) was higher in comparison to the complete group. Maximal oxygen uptake of the four best alpinists did not differ from the values of other alpinists. Special work capacity of alpinists was significantly related to tidal volume increase for the hypoxia test and to CO_2 ventilatory sensitivity. The high importance of the cardiorespiratory chemo sensitivity to respiration was related to their role in adaptation to the lack of oxygen in high intensity exercises and in different types of hypoxia [1,3,6,11]. It is known that human breathing is regulated by feedback and feed-forward control mechanisms, allowing a strict matching between metabolic needs and the uptake of oxygen in the lungs [1,3,5]. The most important control mechanism, the metabolic ventilatory control system, is fine-tuned by two sets of chemoreceptor, the peripheral chemoreceptor and the central CO_2 chemoreceptor in the ventral medulla [3,4]. It is well known that chemoreceptor mediated hypercapnic and hypoxic stimulation of the respiratory centre is the principle mechanism which establishes correspondence of pulmonary ventilation to the intensity of metabolic processes [3]. One of the major regulators of homeostatic responses is carbon dioxide and closely connected with it concentration of H^+ . The influence of numerous factors which either stimulate or inhibit human ventilatory or circulatory responses may be described by alteration of response to CO_2 - H^+ -complex [11,12,13]. Some studies suggest that alveolar PCO_2 oscillations provide a feedback signal for the respiratory control, independent of changes in mean PCO_2 , suggesting that natural PCO_2 oscillations drive breathing in exercise at sea the level and at high altitude [14]. Ventilatory acclimatization to hypoxia consists of a progressive increase in ventilation and a decrease in end-tidal PCO_2 . Underlying ventilatory acclimatization to hypoxia, there are also increases in the acute ventilatory sensitivities to hypoxia and hypercapnia [7]. There was a significant increase in the acute ventilatory sensitivity to hypoxia after exposure to mild hypoxia, and a significant decrease in sensitivity to hypoxia after exposure to mild hyperoxia. So hypoxic ventilatory sensitivity is increased during ventilatory acclimatization to hypoxia in awake goats, resulting in a time-dependent increase in expired ventilation [13]. The presented study shows that it

may be related to working capacity. Some study showed interrelation sensitivity to hypoxia and CO₂ – acute ventilatory response to hypoxia in the presence of hypercapnia is increased after exposure to episodic hypoxia [15]. Therefore, long-term exposure to environmental hypoxia and hypocapnia in alpinists and endurance athletes generates specific changes in respiratory control [13,16]. In endurance athletes long-term exposure to specific hypoxia of exercise takes place (O₂ deficit, accumulated O₂ deficit). It is related to an interaction of exercise hypoxia and metabolic acidosis [16,17]. In both cases changes in respiratory chemo sensitivity to hypercapnia and hypoxia stimuli differently affect sympathetic activity, cardiovagal and sympathetic baroreflex function in a manner related to ventilatory chemoreflex sensitivity [18]. So it may be related to working capacity.

Regulation of the process of oxygen demand meeting through closely conjugated with it process of control for elimination of CO₂ and the level of pH is highly reliable and perfect. It is also known that parameters of PCO₂, PO₂, pH of arterial blood are adequate irritants of circulatory responses as well. As ventilatory and circulatory responses ensure the same processes of gas mass transfer and gas exchange in lungs, it is quite natural that the character of their adjustment should have common features [3]. As the presented data showed, a long period of respiratory adaptation in alpinists and in endurance athletes induced some specific response of lung ventilation and heart rate to increment hypoxia. Specific changes in chemo sensitivity of alpinists and in endurance athletes may be related to “setting” meanings of pH or PCO₂ according to which the ventilation is regulated, or assigned by a special enzyme or any other factors within tissue of a chemoreceptor [3,11]. Recent evidence suggests that ATP is a mediator of central (within the ventral surface of the medulla) and peripheral (within the carotid body) chemosensory transduction [19].

Thus, during an analysis of possible changes in CRS response sensitivity under physical load and environmental condition the key point is availability of alterations in chemoreceptor apparatus “tuning” (status). Notions of the theory of automatic control are sometimes used in the above analysis. In particular, characteristic of respiration control apparatus as a “regulator of variable reinforcement” is applied [2].

The results showed that a reduction of respiratory system response sensitivity to hypoxia and its greater stability are an important factor of work capacity under conditions of sustained, strenuous physical load. The analysis demonstrated that these changes have been largely connected with the dynamics of blood acidosis shifts [5,16]. An increase in response sensitivity to CO₂-H⁺ stimulus at the background of acidosis has been observed, as a rule, during a low level of acidosis as well as at the initial part of the load [8]. Therefore, such an increase in response sensitivity is a peculiar for relatively short total duration of load of the given intensity [6]. At a high level of acidosis expression as well as at the end of the load, sensitivity of response could decrease significantly [2]. Both exercise and hypoxia increase pulmonary ventilation. However, the combined effects of the two stimuli are more than additive, such that exercise may be considered to potentate the acute ventilatory response to hypoxia [20]. These data contribute to a better understanding of important aspects of alteration of respiratory system reactive features in the process of sustained physical loads which are closely connected with special work capacity manifestation under different environmental conditions.

Respiratory response hyposensitivity to hypoxia and hypercapnia may be essential factors of high specific adaptation. Results showed that evaluation of ventilatory and heart rate chemo sensitivity in addition to measure of aerobic power may give important information for prevision of specific working capacity of high performance alpinists. In endurance athletes measuring of

changes in ventilatory and heart rate chemo sensitivity to hypoxia and hypercapnia stimulus (in addition to measure of aerobic and anaerobic power) may give important data for evaluation and prevision of the adaptation process in long-term training.

Conclusion

We concluded that special work endurance was related to ventilatory and heart rate chemo sensitivity to hypoxia and hypercapnia in homogenous groups of high performance alpinists and endurance athletes. To evaluate special work capacity potential possibilities in a homogenous group of high performance alpinists, first of all heart rate response sensitivity to hypoxia as well ventilatory response sensitivity to CO₂ had to be taken into account, not only an alpinist's aerobic power. In the case of evaluation of special work capacity potential of high performance endurance athletes, besides aerobic power, we also have to consider complex ventilatory and heart rate characteristics of cardiorespiratory response sensitivity to hypoxia and hypercapnia. High physical activity in mountain hypoxic environment was connected with some specific characteristics of chemo sensitivity. The high special endurance capacity of high performance alpinists was related to sensitivity not only to hypoxia and hypocapnia but also to hypercapnia. Its may be used as additional criteria of the specific training status of alpinists and preview of their special work capacity. Still it requires a special additional research.

References

1. Forster HV, Pan LG. Breathing during exercise: demands, regulation, limitations (review). *Adv Exp Med Biol* 1988;227:257-326.
2. Mishchenko V. Cardiorespiratory reactivity and adaptation of athletes. Kiev: Scientific world; 2007.
3. Mines AH, Respiratory physiology. New York: Raven Press; 1993.
4. Dahan A, Nieuwenhuijs D, Teppema. Plasticity of central chemoreceptors: effect of bilateral carotid body resection in central CO₂ sensivity. *PLoS Med* 2007 Jul 24;4(7):239.
5. di Prampero PE. Factors limiting maximal performance in human. *Eur J Appl Physiol* 2003;90(3):420-429.
6. Mishchenko VS, Bulatova MM. Effect of endurance physical training on cardio-respiratory system reactive features (mechanisms of training load accumulation influence). *J Sports Med Phys Fitness* 1993;33(2):95-106.
7. Donoghue S, Fatemian M, Balanos GM, et al. Ventilatory acclimatization in response to very small changes in PO₂ in humans. *J Appl Physiol* 2005 May;98(5):1587-1591.
8. Tomiak T, Lysenko E, Zasada M. Fast kinetics and sensitivity of cardiorespiratory responses in athletes of different sport events. *Research Yearbook* 2005;11:25-29.
9. Rebuck AS. Measurement of ventilatory response to CO₂ by rebreathing. *Chest* 1976;70:118.
10. Chua TP, Coats AJ. The reproducibility and comparability of tests of the peripheral chemoreflex: comparing the transient hypoxic ventilatory drive test and the single-breath carbon dioxide response test in healthy subjects. *Eur J Clin Invest* 1995;25(12):887-892.
11. Kara T, Narkiewicz K, Somers VK. Chemoreflexes - physiology and clinical implications. *Acta Physiol Scand* 2003;177(3):377-384.
12. Kato T, Tsukanaka A, Harada T, Kosaka M, Matsui N. Effect on hypercapnia on changes in blood pH, plasma lactate and ammonia due to exercise. *Eur J Appl Physiol* 2005;95(5-6):400-408.
13. Dwinell MR, Janssen PL, Pizarro J, Bisgard GE. Effects of carotid body hypocapnia during ventilatory acclimatization to hypoxia. *J Appl Physiol* 1997 Jan;82(1):118-124
14. Collier DJ, Nickol AH, Milledge JS, van Ruiten HJ, Collier CJ, Swenson ER, Datta A, Wolff CB. Alveolar PCO₂ oscillations and ventilation at sea level and at high altitude. *J Appl Physiol* 2008 Feb;104(2):404-415.
15. Mateika JH, Mendello C, Obeid, Badr MS. Peripheral chemoreflex responsiveness is increased at elevated levels of carbon dioxide after episodic hypoxia in awake humans. *J Appl Physiol* 2004 Mar;96(3):1197-2205.

16. Chicharro JL, Hoyos J, Lucía A. Effects of endurance training on the isocapnic buffering and hypocapnic hyperventilation phases in professional-cyclists. *Brit J Sports Med* 2000; 34:450-455.
17. Ohyabu Y, Usami A, Ohyabu I, Ishida Y, Miyagawa C, Arai T, Honda Y. Ventilatory and heart rate chemosensitivity in track-and-field athletes. *Eur J Appl Physiol Occup Physiol* 1990;59(6):460-464.
18. Steinback CD, Salzer D, Medeiros PJ, Kowalchuk J, Shoemaker JK. Hypercapnic vs. hypoxic control of cardiovascular, cardiovagal, and sympathetic function. *Am J Physiol Regul Integr Comp Physiol* 2009;296(2):402-410.
19. Spyer KM, Dale N, Gourine AV. ATP is a key mediator of central and peripheral chemosensory transduction. *Exp Physiol* 2004 Jan;89(1):53-59.
20. Wood HE, Fatemian M, Robbins PA. Prior sustained hypoxia attenuates interaction between hypoxia and exercise as ventilatory stimuli in humans. *Exp Physiol* 2007 Jan;92(1):273-286.