ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 3 Issue 5 May 2019

Research Article

The Role of Lungs in Regulation of Cortisol in Arterial Blood Stream of Healthy Athletes

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Received: March 25, 2019; **Published:** April 29, 2019

Abstract

It is known that the lungs have a variety of metabolic functions, but most studies have been carried out on experimental animals. Accordingly, the role of the lungs in the regulation of hormones under various physiological conditions and the effects of physiological stress has not been studied. The survey was carried out on qualified karate athletes and donors. It should be noted that the equilibrium zone was at an average concentration of the hormone in the venous blood of 350.0 nmol/l. With an increase in this level of cortisol in the blood inflowing the lungs, hormone retention in the small circle was detected, and with a decrease in the level below this value, there was an ejection from the lungs ($r=-0.87$, $p<0.001$). After physical exertion, the equilibrium zone shifted toward a rise in the concentration of the hormone in the venous blood (700.0 nmol/l), but even under these conditions, hormone retention in the venous blood resulted in hormone retention, and with a decrease in this level. The obtained data may indicate a possible involvement of the lungs in the regulation of the level of the adaptive hormone cortisol in the arterial bed under physiological stress.

Keywords: Lungs; Hormone; Cortisol; Physical Activity; Metabolism

Introduction

The large endothelial surface of the lungs suggests the active role of the small circle of blood circulation in the metabolism of biologically active compounds, including hormones. Taking into account the diverse functions of the endothelium, such as participation in the metabolism of biologically active compounds by the lungs, is obvious. The presence of various and numerous enzymatic systems of receptors in the lungs [1,2] makes justified such a conclusion. This conclusion is confirmed by the facts of the presence of receptors in the lungs to a number of biologically active compounds, as well as to their synthesis and inactivation: glucocorticoids [3,4], enkephalin [5], leptin [6], sex hormones etc. [7-9]. A generalization on this issue was presented by Gillis [10].

The statements about the presence of the endocrine system in the lungs, which are widely reported in recent reviews 11, are very convincing.

Unfortunately, most of the studies presented in the literature were performed in model experiments on animals, but for humans, such studies were practically not carried out. Accordingly, the role of the lungs in the regulation of hormones under various physiological conditions and the effects of physiological stress has not been studied. Further study of the metabolic functions of the lungs in relation to specific hormones is of fundamental and applied importance. In this respect, data on the regulation of the level of stress hormone cortisol in the systemic circulation are of particular interest.

Methods

The analyzed groups are represented by 14 qualified karate sportsmen and unrelated donors (n=18) aged 17-39 years, without hereditary complications and clinical manifestations of chronic lung diseases. The study was conducted in compliance with the written consent of all participants in the experiment. In order to study the metabolic activity of the lungs in relation to cortisol, the arteriovenous difference (ABp) method was used for cortisol in the inflowing and outflowing (arterial) the lungs blood. For the purity of the experiment, venous blood was sampled from the right side of the heart by means of a catheter inserted through a cubital vein using 'the catheter-catheter' technique (14G Medicevent catheter with 12G cannula). The capillary blood was used as the arterial blood taken from a deep puncture of a finger. The concentration of cortisol from the obtained blood plasma samples (nmol/l) was determined by the method of enzyme immunoassay ("Steroid IFA-cortisol" kits by CJSC "Alkor-Bio" St. Petersburg, StatFax-1200 device). Blood sampling was taken every 12-15 hours. Blood sampling of some sportsmen was taken twice: before and after having the dosed submaximal physical activity (75% of the maximum heart rate). The results were processed by a statistically non-parametric Mann-Whitney method, as well as the Spearman correlation analysis and regression analysis. Differences were assumed to be significant at a confidence level of $p<0.05$.

Results

The analysis of AB-difference (ABp) had shown that the indices of AB-difference were positive at 18 of 32 examined men, however the rest of the 14 examined men had negative ones (table 1). There had been no differences in concentrations in the inflowing and outflowing blood throughout the entire study summation (group 1). In this regard, the levels of hormones in arterial and venous blood have been analyzed depending on the direction or sign of the arteriovenous difference.

In the group with a positive AB-difference (group 2), a significant difference was found between the concentration in the blood inflowing the lungs and the blood flowing out of the lungs (293.6 ± 65.3 nmol/l and 460.8 ± 63.4 nmol/l, $p<0.05$). However, in the group 3 with a negative AB-difference, the concentration of cortisol in the blood flowing out of the lungs did not significantly differ from the index in the blood inflowing the lungs. Despite the absence of statistically significant differences in the concentration indices between the study groups, the AB-difference indices for the second and third studied groups significantly differed (156.3 ± 37.4 nmol/l and -109.4 ± 39.0 nmol/l; $p<0.001$). The ABp indices of each group (number 2 and number 3) separately differed significantly (table 1) with the indices of the total study population (group 1).

The presence of the differences between the blood inflowing the lungs and the blood outflowing the lungs in the group with a positive ABp gave a reason to conduct a correlation analysis between the concentration of the hormone in the blood inflowing the lungs and the arteriovenous difference.

Group	Group Concentration of the Hormone, nmol/l			p
	In the Artery	In the Vein	ABp	
1. Whole Group (n=32)	409.4 ± 43.1	363.3 ± 52.3	38.9 ± 35.7	$p^1<0.035$ $p^2<0.01$
2. Positive ABp (n=18)	460.8 ± 63.4	293.6 ± 65.3	156.3 ± 37.4	$p^3<0.001$
3. Negative ABp (n=14)	343.3 ± 52.7	452.9 ± 81.5	-109.4 ± 39.0	$p^4<0.001$

Table 1: The concentration of cortisol in the arterial and venous blood, depending on the sign (+/-) of the arteriovenous difference.

Notes: ABp-arteriovenous difference; *- reliability of differences between: concentration in the artery and vein: p^1- of the whole group and a group with a positive ABp; p^2 is the whole group and the group with negative ABp; p^3-group with positive ABp and negative ABp; p^4-group with negative ABp and positive ABp.

The graphical relationship between the AB-difference to the exertion and the concentration in the venous blood (Figure A.1) was expressed in the form of a parabola, and the dependence itself was expressed mathematically in the following Form. (A.1).

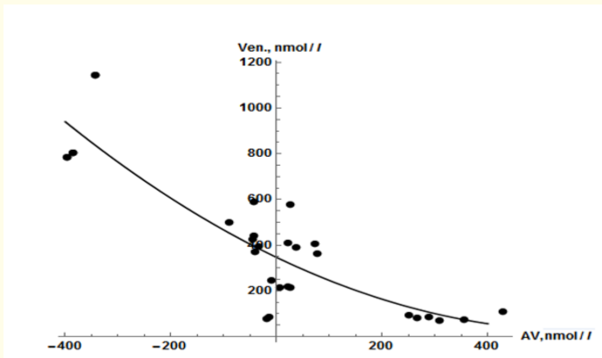

Figure A.1: Dependence between the AB-difference in cortisol (along with the axis "X", nmol/l) and the level of cortisol (along with the axis "Y", nmol/l) in the blood inflowing to the lungs at rest.

$$\textbf{AB - difference} = 346.14 - 1.098x + 0.000968424x^2,$$

where x is the concentration of cortisol in the venous blood.

Form. (A.1) The equation of dependence between the AB-difference before the physical exertion.

The revealed dependence and its graphic expression allow assuming the fate of cortisol when passing the small circle either cortisol is retained in the small circle of blood circulation, or it releases into the arterial bed of the large circle of blood circulation.

In addition, it was detected that when the concentration of hormones in the venous blood more than 380.0-400.0 nmol/l – the arteriovenous difference could equally be both positive and negative. This peculiar "optimum zone" of hormone concentration under conditions of relative rest. The zero value of the ABp-index corresponded to the concentration of 350.0 nmol/l in the graph. Further increase of the hormone in the blood inflowing the lungs was accompanied by its seizing and binding, as it was evidenced by the negative value of the AB-difference. This fact means that the hormone is seized by the lung at initially high concentrations, or in situations accompanied by an increase in the concentration of cortisol in the venous blood above these values, and its concentration in the arterial blood-flow becomes smaller. On the contrary, at low concentrations of cortisol, these indices increase in the arterial bed, immediately after passing the small circle in the blood inflowing the lungs (range: 200.0-220.0 nmol/l). This pattern was confirmed by the presence of the significant negative correlation between the level of the hormone in the venous blood and the AB-difference (r=-0.87, p <0.001).

Thus, we can talk about the regulation of the concentration of cortisol at the level of the small circle of blood circulation, carried out in the lungs. The physiological meaning of this regulation, apparently, is to optimize the body's reactions associated with the stress of the glucocorticoid function of the adrenal gland and to maintain the level of the stress hormone in physiologically adequate concentrations for a particular situation.

It is notable that healthy individuals have a high degree of variability in the level of the hormone in the venous and arterial blood, which led us to take other options for analyzing the results. In particular, it was decided to analyze the relationship between the concentration of the hormone in the venous and arterial bed and the degree of "seizure" or "ejection" of the hormone from the small circle. Accordingly, the patients were divided into groups according to the degree of the seizure of the hormone or its ejection from the small circle of blood circulation (table 2).

Analysis of these concentrations in the arterial blood had shown that the level of the hormone in the group with a large seizure was significantly higher than in the group with moderate seizure (group: 3-4, table 2). In other cases, the concentration in the arterial blood flow did not differ between the study groups, including those with moderate and large hormone ejection. In contrast, the level of the hormone in the venous blood determined the direction of the arteriovenous difference, both in absolute value and in sign (or the seizure of the hormone, or its ejection). Thus, the level of the hormone in the group with a big AB-difference (gr.1) was significantly lower and differed from the level of cortisol in the venous blood in the group with a moderate ejection (gr.2) (p <0.001), with a large (gr.3) (p <0.001) and moderate (gr.4) (p <0.003) seizure. Comparing the indices of groups 2 and 4, it can be assumed that at the average values of the hormone concentration (290.5-353.1 nmol/l) indicated in the table, both hormone ejection and its seizure can occur.

Group	Group Concentration of Hormone, nmol/l		
	In the Artery	In the Artery	AB-difference
1. With a large ejection (n=8)	414.2-72.6 ± 27.4 $p^1<0.2$	86.0-13.5 ± 5.1 $p^2<0.001$	330.0-62.1 ± 21.9
2. With a moderate ejection (n=10)	353.1-161.5 ± 53.8	349.3-128.0 ± 45.2 $p^3<0.001$	36.5-22.6 ± 7.1 $p^3<0.001$
3. With a large seizure (n=3)	537.3-28.9 ± 132.1 $p^4<0.05$	912.0-01.6 ± 116.4 $p^1<0.001$	-347.2-27.9 ± 16.1 $p^1<0.001$ $p^4<0.001$
4. With a moderate seizure (n=11)	290.5-160.3 ± 48.3 $p^4<0.05$ $p^5<0.5$	327.8-179.5 ± 54.12 $p^4<0.001$ $p^5<0.5$ $p^6<0.003$	-40.8-24.6 ± 7.7 $p^1<0.001$ $p^4<0.001$

Table 2: Concentration of cortisol in arterial and venous blood of healthy patients who have different degrees of seizure or ejection of hormones from the lungs.

Notes: ABp-arteriovenous difference; reliability of differences: p^1 - between a group with a large ejection and a large seizure; p^2 - between the artery and the vein; p^3 - between the groups with a large ejection and a moderate ejection; p^4 - between the groups with a large seizure and a moderate seizure; p^5 - between the groups with a moderate ejection and a moderate seizure; p^6 - between the groups with a large ejection and a moderate seizure.

When the level of the hormone increases in the blood inflowing the lungs (group III), active hormone uptake was being detected, as it was evidenced by negative values of the ABp. Despite the small number of observations in the group III, it once again confirms the reliability of the established inverse correlation between the hormone level in the blood inflowing to the small circle and the arteriovenous difference.

As it turned out, the dependence (Figure B.1) was being maintained for sportsmen after physical exertion ($r=-0.74$, $p<0.008$). This group includes 12 sportsmen who are constantly engaged in karate. The established dependence was expressed by the Form. (B.1).

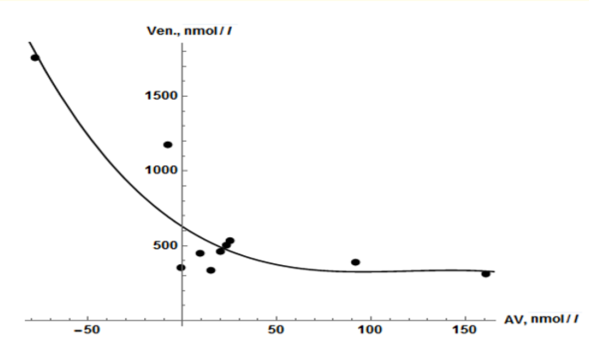

Figure B.1: The relationship between the AB-difference (along with the axis "X", nmol/l) and the level of cortisol in the flowing to the lungs (along with the axis "Y", nmol/l) blood after physical exertion.

$$\textbf{AB - difference} = 685.6 - 9.91x + 0.048x^2,$$

where x is the concentration of cortisol in the venous blood.

Form. (B.1) The equation of dependence between the AB-difference after the physical exertion.

According to the presented graph (Figure B.1), it is detected that, in contrast to the data in Figure A.1, the curve shifts upwards along with the "Y" axis, and the intersection level with the "Y" axis corresponds to a value of 700.0 nmol/l (zero ABp). In other words, under conditions of physical exertion, which was carried out mainly by constantly exercising individuals, the zone of the optimum was being shifted in the direction of increasing. At values of 500.0-600.0 nmol/l of the hormone in the venous blood, an additional ejection of cortisol into the arterial bed was detected, as evidenced by the positive arteriovenous difference. With an increase in the concentration of cortisol in the venous blood of more than 700.0 nmol/l, the hormone "was being seized" by the lungs, - the fact had been confirmed by negative values of the AB-difference. At the same time, the inverse correlation is being observed between the concentration of the hormone in the inflowing to the lungs blood and the AB-difference ($r=-0.74$, $p<0.008$).

It should be noted that a moderate rise in the concentration of cortisol was detected during physical exertion, although no significant differences were observed either in the venous blood or in the arterial blood (table 3). We attribute this fact to the large variability in the initial level of the hormone in different sportsmen's bodies, although the trends towards increasing the concentration, both in the venous blood and the arterial blood, were detected.

Group #	The Concentration of Hormone, nmol/l		
	In the Artery	In the Vein	ABp
1. Before physical exertion (n=11)	528.1 ± 95.9	482.5 ± 76.9	45.5 ± 31.7
2. After physical exertion (n=11)	677.6 ± 138.4	666.3 ± 151.1	25.7 ± 21.3
p*	p<0.5	p<0.2	p<0.6

Table 3: The concentration of cortisol in the arterial and venous blood before and after the physical exertion.

Note: ABp-arteriovenous difference.

We performed statistical treatment depending on the direction of the arteriovenous difference and its sign for more detailed analysis of the obtained data (table).

According to the results obtained in table, it was detected that the concentration of cortisol did not differ significantly in the arterial bed in the group with the positive ABp (gr.1) and the negative ABp (gr.2), – both before and after the exertion. However, in the study group with the positive ABp before the exertion, in comparison with the group with a negative ABp value, the hormone concentration in the venous blood had statistically significant differences (table). At high values of cortisol in the venous blood after performing physical work, the ABp changed the sign to the opposite and became negative, which can be treated as a "seizure" of the hormone by the lungs. This comparison confirms the revealed reliable inverse correlation between the level of the hormone in the inflowing to the lungs blood and the arteriovenous difference.

Taking into account the revealed regularity, we can say that in situations accompanied by increasing cortisol in venous blood (in this case, with physical exertion), a new level of regulation of the hormone in the arterial blood flow is established at the level of the small circle. This level is characterized by the fact that the concentration at the output of the small circle decreases at high concentrations of the hormone in the blood inflowing the lungs, and, on the contrary, it increases at low concentrations.

Discussion

In light of the foregoing, we assume that the lungs act as a regulator of the level of cortisol in the outflowing from the lungs blood and, accordingly, the lungs can regulate the nature and the intensity of the response to stressful effects. The presence of such a regulation system in the body is biologically expedient, taking into account the negative effects of high concentrations of cortisol on the neurons of stress-responsive brain structures [11]. Especially it can be manifested with repeated stress or chronic stress. Reducing the concentration of cortisol in the arterial bed with the excessive response of the body to the stress factor can be considered as a manifestation of the functioning of the stress-limiting system, and the lungs themselves – a component of this system.

Specific mechanisms of the seizure of cortisol and its ejection from the lungs have not been clarified completely, although we can assume several options. On this mission, first of all, the endothelium of the lungs can claim [12,13], which contains specific enzymes for the synthesis and degradation of glucocorticoids. Moreover, enzymatic systems for the synthesis of glucocorticoids with the expression of the corresponding genes are activated during development and maturation of the lung embryo [14].

It is possible that the form elements of blood can play a role in this process, the surface of which can be used as an additional transport system. An example is the red blood cells transporting, including glucocorticoid hormones [15]. In the case of a change in the physiological parameters of the hypothalamic-pituitary system, the biophysical properties of the transport systems of blood cells can change. In the studies of Kunitsin and Panin [16], the dependence of hemoglobin oxygenation, Na+/K+-AT-Phase activity, membrane microviscosity from the level of cortisol on the erythrocyte membrane was shown. In turn, the delivery to the lungs of hormones, their seizure or ejection can depend significantly on the parameters of the external respiration, oxygen saturation, carbon dioxide, the concentration of hydrogen ions, the degree of erythrocyte deformation during the passage of the microcirculatory bed of the lungs.

Changes in breathing parameters under stress, perhaps, display the correction of the level of stress hormone by the restructuring of breathing patterns. The possibility of participation of the endocrine system of the lungs is not excluded with prolonged responses to stress [11]. In turn, the endocrine system of the lungs is capable of introducing corrective effects on intracellular processes. It should be emphasized that there remain many unresolved issues in this problem, but this study substantiates the important role of the lungs in the overall adaptive response to various stimuli and stressful effects. Corrective effects of the lungs are displayed either with excessively active or with the insufficient reaction of the adrenal glands. Apparently, we can talk about the physiological system of "lungs-adrenals" and its participation in the overall adaptive response of the body to stressful effects.

Conclusion

1. Lungs are the key element of the physiological system of the “lungs-adrenal glands” in regulating the level of cortisol in the arterial bloodstream, the biological meaning of which is to optimize stressful hormonal responses sufficient for realizing an adaptive response to a physiological stimulus.
2. The orientation of the regulatory reactions of the small circle and lung tissue to maintain the “optimum zone” at rest or under physical exertion depends on the concentration of cortisol in the blood inflowing to the lungs, followed by its deposition or ejection of the hormone into the arterial bed.

Practical Implications

1. Obtained data significantly expand the understanding of the metabolic functions of the human lungs, in particular, the mechanism of regulation of the level in the arterial blood of the stress hormone cortisol.
2. This makes an additional contribution to the fundamental science and ideas about the physiology of human lungs.
3. It opens the possibility of studying the regulation of human stress response by changing the parameters of external respiration, which can be used in health technologies and in the preparation of special professional groups.

Conflict of Interest

The author has no conflict of interest.

Funding

The article is executed without the use of grants or other sources of funding.

Acknowledgements

The authors express their gratitude to Muzhenya Dmitry for assisting in the registration and submission of the article.

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Volume 3 Issue 5 May 2019
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