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Adaptation to hypoxia in the treatment of anemia in the rehabilitation of dysfunctional uterine bleeding in adolescent girls

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Abstract. Twenty two of 35 girls (aged 12-15 years) have received a course of interval hypoxic training (IHT) (10-12 daily séances) and conventional during treatment for juvenile

dysfunctional uterine bleedings (JDUB) white the other 13 girls have received the drug treatment (control group). Clinical examination proved the IHT course a beneficial effect. A positive clinical effect was obtained after 5 séances; bleeding stopped in all patients after 8 séances of the IHT. The hemoglobin concentration significantly increased; oxygen consumption and body oxygen regimen (BOR) were normalized; the working capacity increased. Increases were observed in urine pregnandiol and in the amount of keratosic cells in vaginal smears. It was suggested that the IHT beneficial effect on patients with JDUB depended-both-on- the general stimulating influence of low oxygen partial pressure in the inhaled (p_IO_2) on the function of oxygen supply *system* and on the specific effect of low p_IO_2 on the hypothalamic-hyphophysis-ovarian *system.*

The juvenile dysfunctional uterine bleedings (JDUB) make 10% of menstrual function disturbances in the girls of pubertal age [10]. Women's childbearing function depends in many respects upon the character of puberty: 28.2% of women with JDUB in the reproductive age suffer from menstrual dysfunctions, 35.5% of women are primary (hormonally) sterile, 35% have abortions [15]. The girls born by the mothers with the disturbed reproductive system often have physical development disorders.

The period of puberty is one of the most critical periods in the life of the women [6, 7, 8]. In European peoples, especially in the northern countries, the period of puberty in closes 12-15 years [7]. During this very important period the rearrangements of nervous and humoral regulation of the vitally important functions take place [5, 10].

The etiology and pathogenesis of the JDUB are not yet clear. Many factors contribute to the development of the pathology of this type: hypovitaminoses (B_1, A, B_6, E), acute chronic infections, psychic traumas, overloads, stresses associated with the feedback disordered steroid-hypothalamic mechanism when the adrenal steroids suppress the function of the cyclic center of the hypothalamic area responsible for the menstrual function [10]. The endocrine glands interrelation is being maintained via the "long way" (hypophysis - peripheric endocrine glands), the "short way" (hypothalamus-hypophysis) and the "ultrashort way" (self regulation of the glands secreting several hormones). A complex interrelation between the endocrine glands function can be the cause of frequent disturbances of sexual development under the dysfunction of either gland causing the changes in the whole endocrine system [10].

The "vulnerability" of the hypothalamus - hypophysis - ovarium- uterus system during pubertal development is of a great significance for occurring the JDUB. In most JDUB cases the hypothalamic centers are not ready to function because of their insufficient maturity, the changed function of the anterior part of this area, or production of the disordered liberins providing hormonopoesis of the hypophysis [3, 10].

According to the clinical-morphologic features, the JDUB are divided into ovular and anovular types. In the period of puberty more anovular acyclic dysfunctional uterine bleedings because of persistence or atresia of the follicles occur more frequently. During the anovularitory uterine bleedings ovulation is absent and so is the lutein phase. In case of follicle persistence the matured follicle continues producing large quantities of estrogens which affect the hormone-dependent organs, the uterus, in particular.

As the result of reduced hormonal activity there develops endometrium plethora with trichangyectasia: a decreased blood supply of endometrium with concomitant hypoxia and the disturbance of metabolism. dystrophic and necrotic areas occures. Due to this persistent thisuneven rejections of endometrium causing the bleeding and anemia take place.

The JDUB leads to significant disorders in preadolescent girls state: in the majority of them the secondary anemia develops: the functions of cardiovascular and respiratory systems are changed: oxygen consumption is reduced; oxygen regimen of the body are altered [9, 10, 11].

Unfortunately, the efficiency of the methods and drugs used thus far to cure the JDUB patients have proved to be inadequate. The role of this pathology in woman life and her future's off springs make the physicians search for new methods of JDUB treatment.

Hypoxic training was shown to be one of the effective methods of anemic states treatment [7/ 10. 11]. In 1971 Krupko-Bolshova Yu.A., Koltchinskaya A.Z. used mountain training of 30 JDUB patients. A month staying in Terskol - the settlement placed at the foot of Elbrus at the altitude of 2000 m above the sea level, had a favorable effect on the girls with JDUB. In 28 of the tested girls bleedings stopped, normal menstrual cycles reappeared, blood hemoglobin level increased significantly, oxygen regimen of the body became normal. However, the expensiveness of the method and difficulties in the organization of the treatment under these conditions made us to continue the search of a more simple and available method

simulating the effect of mountain climate. Interval hypoxic training (IHT) during which the adaptation to hypoxia takes place and which according to the data of E.N.Tkachouk et al. [16, 17] has a therapeutic effect on some diseases was proposed as such method.

The aim of this work is to describe the effect of applying IHT for the treatment of JDUB patients.

Methods

The IHT course according to the procedure suggested by E.N. Tkachouk and A.Z.Kolchinskaya [9, 11, 16] was used in the Department of Physiology and Pathology of Puberty of the Research Institute of Pediatrics, Obstetrics and Gynecology in the Kiev 14th Children Hospital.

35 girls aged 12-15 years suffering from the JDUB received the course of IHT. Their body mass and height were 48±2 kg and 162±4 cm, respectively. The duration of the disease ranged from 1 to 3 years. The auxiliary diagnostics tests (measurement of basal temperature, analysis of the vaginal smears for determining the estrogen saturation, etc.) revealed anovular cycles.

Before and at the end of the IHT course the functional state of the cardiovascular and respiratory systems at the conditions of basal metabolism and relative rest as well as body responses of the JDUB girls to breathing in hypoxic mixtures (HM - 13) were studied.

Under the conditions of basal metabolism and relative rest the measurements of respiratory minute volume (VE), frequency of breathing (f), O_2 and CO_2 concentrations in the expired air (with the use of gas analyzer, GA-O-4), heart rate (HR), arterial oxygen saturation (SaO_2) (using the "Oxyshuttle" device) were performed. The same values were recorded during the hypoxic test at the 3rd and 8th minutes of HM-13 inhalation. HR and SaO_2 were recorded continuously.

To determine the general working capacity of the patients prior to and following the IHT course the Master test was conducted. During 5-min period the girls ascended to and descended from the 0,35 m-high platform at the rate of 15 movements per minute. HR was measured at the first 10 s. of the recovery after exercise. The maximal oxygen consumption was calculated (using the Dobeln formula, 1968).

Three girls from the basic group (13,6%) displayed infantilism and 4 (18,1%) girls had a low body weight with normal or high height. The overwhelming majority of girls had neurocirculatory dystonia of hypotensive type. All patients complained of headache, weakness and dizziness.

The inpatient complex drug treatment was aimed at termination of bleeding, elimination of secondary anemia, and normalization of subsequent menstrual cycles (MC). Besides symptomatic treatment (uterotonic means: oxytocin, smartweed extract, dicynon) the complex of drug therapy included vitamins. In addition each patient received 5 drop infusions [3, 4] (400 ml of 5% or 10% glucose solution, 4 units of insulin, S units of oxytocin, 50 g of cocarboxylase, and 1 ml of 5% vitamin C solution mixed ex temporae). To normalize function of the hypothalamo-pituitary system choreogonin, profasin, etc. were administered. For fixation and normalization of the cycle patients received for 3-4 months folic acid in the first MC phase (0.001 x 3 times a day), ascorbic acid in second phase (0.1-0.2 x 3 times a day) and aevit capsule once a day for 14 days. The IHT course consisted of 12-14 séances of breathing a hypoxic gas mixture containing 12 % of O_2 (GM-12). Regimes of breathing and O_2 content in hypoxic mixtures were chosen strictly individually general development of the girls since their birth until based on results of the hypoxic test. The IHT was produced using a "Hypoxicator" of the firm “Hypoxia Medical”.

THE CLINICAL EFFECT OF IHT COURSE

After 14-17 days of inpatient therapy uterine bleeding stopped in patients of the control group. Recurrent bleeding was observed in two girls (l5,4 %) from the control group. According to the data of literature patients having undergone the drug treatment display 18 % recidivation.

In patients subjected to - the IHT course in addition to the drug treatment (basic group), the clinical effect was evident as soon as after 5 (6,4 ± l,4) séances of IHT. Bleeding completely stopped in all patients of this group after 8 séances. We continued catamnestic observation of the patients with JDUB treated with conventional means combined with the IHT, about which we have previously reported [4]. None of the patients had recurrent bleeding for months.

The patients subjects to the IHT course displayed a tendency for increasing the basal

temperature in the expected phase of ovulation. Before the treatment the patients had a monophasic curve of basal temperature.

After the IHT course, urine pregnandiol increased by 62,5% (from 8,58-9,73 to 13,94 – 15,81mmol$*l^{-1}$) and the amount of keratosic cells in i vaginal smears increased by 62,7% (from 12,4 - 15.2% to 20,17-24,73%) in patients of the basic group.

The results of clinical and physiological examination.

In patients of the basic-group, Hb increased from 109,7±0,8 $g*I^{-1}$ to 144,5±0,5 $g*I^{-1}$ and RBC increased from 3,401±0.190 10^6*mm^{-3} to 4,116±0,260 10^6*mm^{-3} ($p<0,05$). In patients of the control group, Hb was 107,4±0,9 $g*I^{-1}$ before the treatment and 137,4±0,6 $g*I^{-1}$ after the treatment. Thus the increment of Hb was 34,8 $g*I^{-1}$ in the IHT group and it was significantly smaller in the control group – 22,0 $g*I^{-1}$ ($p<0,05$). The increment of RBC was as significantly greater in patients after the IHT course.

In their physical development, patients with JDUB fell behind healthy girls of the same age. Clinical and physiological investigations have confirmed the previous conclusion [1] that the respiratory system of . girls with JDUB fell behind the age-related norm and that the patients had a reduced rate of step-by-step oxygen delivery and oxygen consumption. The JDUB patients of basic and control groups had the chest volume and the total lung capacity (TLC) at the lowest normal range. The TLC and VC were significantly less by 750±96 and 600±80 ml respectively and the maximal lung ventilation and the respiratory reserve were less than normal by l0-12 $l*min^{-1}$ ($p<0.05$).

Breathing of patients with JDUB was more frequent and shallow. The tidal volume (V_T) was 250±I3 ml and the minute volume of breathing (V_E) was 4,900±0,380 $l*min^{-1}$ while in the norm, the VT comprises 3I5±22 ml and the VB – 5,650±0,I96 $l*min^{-1}$. In patients with JUUB of control and basic groups, the cardiac output (Q) was higher than the age-related norm (4.434±14,5 $l*min^{-1}$). Such volumes rate of blood flow was due to the higher heart rate (75,2±1,99 beats$*min^{-1}$) and at blood with Hb<70 $g*l^{-1}$ 85,0±3,2 beats$*min^{-1}$.

In patients with JDUB, the lowered Hb content and oxygen blood capacity were the cause of low efficient oxygen supply to tissues by the blood flow; on admission the oxygen blood capacity was I46±4.8 $ml*l^{-1}$.

Thus the BOR of patients with JDUB is characterized diminished oxygen transport

rate into the airways and alveoli (740±66 $ml*min^{-1}$) than in norm (1l00±66 $ml*min^{-1}$). Despite the high velocity of blood flow arterial blood of patients delivers less oxygen (480±48 $ml*min^{-1}$ vs. 605±59 $ml*min^{-1}$ in norm) to tissues. Possibly, the reduced oxygen transport. by arterial blood is responsible for the decreased oxygen consumption, i.e., for tissue hypoxia in patients even at rest. In anemia, tissue hypoxia seems to be the major cause for secondary functional disorders of the hypothalamo-hyphophysis-ovarian system [10, 11, 12, 15, 16, 17] .

The IHT course exerted a considerable effect on the functional condition of patients with JDUB. The examinations carried out before and immediately after the course showed that patients subjected to the IHT course displayed improvements in the state of respiration, circulation and in the blood respiratory function. Breathing became more deep and less frequen1; the share of alveolar ventilation in the VE increased; and breathing became more economical. The blood flow became more economical in respect of oxygen supply to tissues; the HR decreased in the conditions of relative rest; and the Q reduced. The increases in Hb and in the blood capacity increased the arterial blood oxygen content and normalized the rate of oxygen delivery to tissues (at lower blood flow). Combined with higher oxygen tension in the blood, this created more beneficial conditions for oxygen utilization in tissues. The oxygen uptake significantly increased from 143±5 to 184±4 $ml*min^{-1}$ ($p<0,05$). The hypoxic test performed before and after the IHT course demonstrated that the organism of patients with JDUB became adapted to hypoxia as a result of the IHT course from subcompensated before IHT was transformed into compensated hypoxia after IHT, the signs of tissue hypoxia disappearing.

The course of IHT enhanced the working capacity of patients: a standard physical load was better tolerated and was performed at a lesser increase in HR.

Discussion

In analyzing the data obtained, a natural question arises on the mechanisms that ensure the beneficial effect of IHT on J DUB patients. A partial answer is given by many-year studies of the effect of reduced partial oxygen pressure in inhaled air (pO_2) on the organism and by available data of the literature on cyclic function of the hypothalamo-hyphophysis-ovarian system [1-6, 10, 12-15]. One can suggest that the therapeutic effect of IHT on patients with JDUB depends both on the generalized effect of low p_I0_2 and on its

specific action on the hypothalamo-hyphophysis-ovarian system [6]. The generalized organismic response to low p_I0_2 ensures the increased rate of oxygen step-by-step delivery and oxygen utilization in tissues [7, 8]. It is due to excitation of higher divisions of the brain, of chemoceptors of carotid and aortic zones, of respiratory and cardiovascular centers of the medulla, which enhance respiration and circulation.

An acute hypoxic exposure induces red cell release from depots and increases the Hb concentration in blood and the oxygen blood capacity [7, 8, 9, 11, 16 and many others]. Breathing air with low pO_2 leads to excitation of vegetative centers, activation of adrenal cortex function, and increased catecholamine concentration in the blood, which, in turn, affects vegetative functions and metabolic processes with mixed venous blood. More protracted hypoxic exposure leads to increased amount of respiratory enzymes and respiratory ensembles in mitochondria, to increased surface of the internal membranes, cristas and total amount of mitochondria, which decreases the critical pO_2 level in tissues [7, 8].

Multiple observations and experimental studies [18, 12, 15] leave no doubt that oxygen deficiency exerts a pronounced effect on sexual function. Chronic infections, intoxication, improper feeding, influence of radiation and other factors on infantile and adolescent organism exerts a negative effect on the function of hypothaiamo-hyphophysis-ovarian system which determines the course of biological cycles in women [3-6, 10, 12-17]. It induces pronounced changes in electrical activity of the hypothalamus [2] in secretion of corticotropic pituitary hormones. Hypoxia induces also changes in ovarian parenchyma. Investigations of A.A. Nazarenko carried out in our laboratory [8] evidence that ovarian tissue is very sensitive to low $p0_2$: the intensity of oxidative processes in ovarian tissue significantly declines in hypoxic environment.

In puberty which is especially sensitive to hypoxia, hypothalamic-pituitary insufficiency entails disorders of the normal process of sexual maturation an'd provokes acyclic bleeding which requires special treatment [5, 10, 13]. A deficiency of sex hormones causes changes in the brain cortex and hypothalamus, which may result in vegetative neuroses, in disorder of to respiration and circulation and BOR control, and worsen the quality of ORO regulation.

The results of the studies carried out allow to conclude that inclusion of the IHT into the complex of therapeutic measures is efficient in JDUB.

References

1. Austin G.R., Short R.V. Hormonal control of reproduction // Cambridge Univers. Press. - 1997. - P.145-195.

2. Casey M.L., Winkel C.A., Porter J.C. et al. Endocrine regulation in women. Clinical perinatal. – 1993 - N 10, P.7.

3. Channing C.P., Gordon W.L., Liu W.K; et al. // Physiology and Biochemistry of ovarial inhibition. Pros.Sos.Exp.Biol.Med. - 2005. - 178. - P.339.

4. Edwards R G. Conception of the human female // London, 2000. - 301 p.

5. Grambach M .M. Control of the inset of puberty // Exerta Med. ICS. - 2003. - N 3. - P.598.

6. Kolchynskaya A.Z. Kislorodnyje rezhymy organizma rebenka i podrostka. [Oxygen Body's Regimen by Child and Adolescent]. Kyiv:--1973. - 319 ss. (In Russian)

7. Kolchynskaya A.Z. Kislorod. Fizicheskoye sostojanie, rabotosposobnost. [Oxygen. Physical Condition. Physical Capasity]. Kyiv. - 1991. - *205* ss. (in Russian)

8. Ko1chinskaya A.Z. Generalized, organ-specific and molecular mechanisms to hypoxia, their role in the interval hypoxic training effect // Hyp. Med J. - 1994. - N 2. - P.6.

9. Kondrykinskaya I.I., Kasatkin V.N., Chechelnitskaya S.M., Tkachuk E.N., Glazachev OS, Kuznetsova I.V. Interval'naya gipoksicheskaya trenirovka v lechenii astenicheskogo sindroma u detey [Interval hypoxic training in the treatment of asthenic syndrome in children] // Hypoxia Medical J. - 1993. - N 3. - P.26-27. (in Russian)

10. Krupko-Bolshova Yu.A.. Patologia podrostkovogo razvitiya devushek

[Pathology of adolescent development of girls and girls]. Киев. - 1990. - 229 c. (in Russian)

11. Krupko-Bolshova, Yu.A., Zakusilo, MP Tkachuk E.N., Kolchinskaya A.Z. O vozmozhnosti primeneniya interval'noy gipoksicheskoy trenirovki dlya lecheniya yuvenil'nykh disfunktsional'nykh matochnykh krovotecheniy [On the possibility of using interval hypoxic training for the treatment of juvenile dysfunctional uterine bleeding] //Hypoxia Medical J. - 1993. - N 3. - P. 16-22. (in Russian)

12. McNattly K.P., Lun S., Fannin L. et al. The recruitment of an ovarian follicle for ovulation // Exerta Med. ICS. - 2003. - N 598. - P.73.

13. Ross G.T., Leipselt M.B. (eds). Clinic in endocrinology and metabolism. Ed. Philadelphia. - P.577-600.

14. Speroff L., Van de Wiele R.Z. Regulation of the human menstrual cycle // Amer. J. Obstetr. Gynecol. - 1991. - P.234.

15. Tepperman G., Tepperman H. Metabolic and endocrine physiology. An introductory Text, fith. ed. - Chicago-London. - 1997. - 656 p.

16. Tkachuk Ye.N. Effektivnost' interval'noy gipoksicheskoy trenirovki v khirurgii: profilaktika oslozhneniy posle operatsii po povodu miomy matki [The effectiveness of interval hypoxic training in surgery: the prevention of complications after surgery for uterine fibroids] //Hypoxia Medical J. - 1993. - N 3. - P.17-21. . (in Russian)

17. Tkachuk Ye.N., Makatsariya A.D. Profilaktika khirurgicheskogo stressa i posleoperatsionnykh oslozhneniy u ginekologicheskikh bol'nykh metodom interval'noy gipoksicheskoy trenirovki v pred- i posleoperatsionnyye periody [Prevention of surgical stress and postoperative complications in gynecological patients by the method of interval hypoxic training in the pre- and postoperative periods]/ /Hypoxia Medical J. - 1993. - N 1. - P.21-24. (in Russian)