GENERAL PATHOLOGY AND PATHOLOGICAL PHYSIOLOGY

Arguments for Revision of Classification of Hypoxic States

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 127, No. 2, pp. 146-151, February, 1999
Original article submitted June 2, 1998

Hypoxia always leads to dysfunction of organs and culminates in the fatal outcome. The principles of classification of the hypoxic states were formulated in 1930-s. The first successful cardiac transplantation posed the problem of dividing of circulatory cardiovascular hypoxia into two subdivisions: hypoxia associated with impaired cardiac contractility (cardiac insufficiency) and hypoxia resulting from vascular smooth muscle cell. Here we attempted to improve classification of hypoxic states on the basis of new medical achievements. The proposed classification considers the following hypoxic states: 1) exogenous hypoxia; 2) respiratory hypoxia; 3) hypoxia resulting from cardiac insufficiency; 4) hypoxia provoked by vascular smooth muscle dysfunction; 5) hemic hypoxia; 6) tissue hypoxia; and 7) combined hypoxia. There are specific and pathogenically substantiated methods for correction of all elements of the "hypoxic chain" that regulate tissue metabolism at the cellular and subcellular level both in the whole organism and in individual organs. These methods open new vistas in biology and medicine, in particular, in transplantology.

Key Words: *hypoxia; classification; smooth muscle insufficiency; smooth muscle dysfunction; serotonin; serotonin deficiency*

One of the most important and difficult problems in medicine is synthesis of scientific data and the search on that basis for new general relationships [12]. Based on our findings that free (not bound to haptoglobin or other proteins) hemoglobin and myoglobin induce spasm of smooth muscles (SM) and accelerate platelet disintegration and our description of endogenous vasomotion (EVM) and serotonin insufficiency syndrome, we propose a new approach to the genesis and classification of hypoxic states [14-18].

Acute and chronic hypoxia always leads to dysfunction of the most important organs and terminate in fatal outcome. The role of hypoxia in thanatogenesis is clearly seen in the next series of events: myocardial hypoxia → myocardial dystrophy → myocardial infarction → cardiogenic shock (single organ failure) → disseminated intravascular coagulation (multiple organ failure) → death. Therefore, the understanding of the genesis of various hypoxic states and the development of pathogenically substantiated methods for their treatment and prevention are fundamental problems in modern medicine and biology.

Classification of the hypoxic states was first formulated in 1930-s. Depending on the causes and mechanisms of hypoxia, it is subdivided into those caused by oxygen deficiency in the inspired air, insufficient diffusion, insufficient oxygen transport to tissues and cells, and disturbed oxygen utilization in mitochondria. Correspondingly, there are the following types of hypoxia: 1) exogenous (low oxygen content in the inspired air); 2) respiratory; 3) circulatory (cardiovascular); 4) hemic (blood-related); 5) tissue; 6) overload (load hypoxia); and 7) combined hypoxia. Hypoxia is also classified by its localization (local or general), the rate of development (fulminant, acute, and chronic), and severity (mild, moderate, and critical or fatal) [5,6,8, 10,23,24,26].

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0007-4888/99/0002-0132$22.00

The first successful transplantation of the heart advanced the necessity of dividing the circulatory hypoxia into two subdivisions: hypoxia resulting from impaired in cardiac contractility (cardiac insufficiency) and hypoxia caused by vascular SM functional impairment (SM-insufficiency). This division is substantiated by pathophysiological evidence and requires adequate diagnostic and therapeutic approaches.

Hypoxia appeared only in a single element of the "hypoxic chain" (exogenous, respiratory, circulatory, or hemic) results in tissue hypoxia, homeostatic disturbance and death. Efficient pathogenic methods were developed and applied for correction of endogenous, respiratory, and hemic hypoxia. The therapeutic and surgical methods used for cardiovascular (circulatory) element of the hypoxic chain are aimed at alleviation of cardiac insufficiency. However, there are no effective pathogenic methods for correction of the second subtype of circulatory hypoxia caused by impaired vascular SM contractility. Tissue hypoxia in the organism or individual organs can not be objectively studied without developing methods correcting vascular SM function.

Blood pressure is determined by cardiac output and peripheral resistance. At a constant cardiac output blood pressure is proportional to peripheral resistance, i.e. depends on the contractility of cardiomyocytes and vascular SM cells [7,22].

It was established that "the state of microcirculation depends on the nature of work and the sensitivity of vascular SM determining their dilation and constrictor capacity" [11]. When discussing the predominance of the nervous or humoral components in the integral neurohumoral regulation of the vascular SM system, some authors emphasize that this problem remains to be solved [1-3,8-11,19-22,25].

This is clearly noted in a fundamental handbook on human physiology [21]: "the role of tonic activity of vasoconstrictor nerves (resting tone) for the circulation is evidently manifested under conditions of spinal cord anesthesia or ganglioblocker treatment abolishing this activity. Vascular dilation decreases arterial pressure to 40-60 mm Hg, which can not provide adequate blood supply of the organs (this paralytic drop of arterial pressure develops also in spinal shock). Sympathectomy also produced vascular dilation in the denervated areas. Under these conditions diameter of blood vessels is entirely determined by the basal tone. Several days after sympathectomy the initially low tone increases and almost returns to the initial level after some weeks. Nervous fibers do not regenerate in this period, therefore this increase in the basal tone is presumably due to increased sensitivity of denervated vessels to catecholamines and other constrictors".

In other words, "basal tone" (the minimal function of SM) is maintained by a humoral agent, while the second component (responsible for the normal function of SM) is produced by neurotransmitters of the autonomic nervous system. We conclude that maintenance of the basal tone and its elevation in response to impaired innervation are caused by "another vasoconstrictor agent", i.e., by serotonin. Some authors noted specificity of the pharmacological effect of serotonin on SM: "Serotonin increases capillary permeability, it induces rapid contraction of SM and vasoconstriction similar to that produced by norepinephrine and vasodilation similar to the reaction to histamine [2].

Therefore, two questions arose: 1) whether serotonin can restore SM function in patients with disturbed humoral regulation and preserved function of the autonomic nervous system, and 2) whether serotonin can improve SM function in patients with disturbed autonomic regulation.

To answer these questions, the following experiments were carried out. Isolated segment of the rabbit ileum placed in nutrient medium contracted spontaneously due to automatism and contractile activity of ileac SM. Serotonin antagonists (gentamicin, papaverine, dimedrol, *etc.*) added to the nutritient medium caused SM dysfunction until complete paralysis. Serotonin antagonists also impaired SM function, despite the presence of oxygen, calcium, potassium, and glucose in the medium, while the addition of serotonin (serotonin adipinate, SA) restored automatism and contractile activity (peristalsis) of SM. This suggests that the agents inhibiting serotonin — serotonin receptors (SR) interaction in SM disturb the spatial and temporal coupling of physicochemical processes underlying transformation of biochemical energy into mechanical one, whereas addition of SA restores the disturbed physiological processes [14-18].

The total peripheral vascular resistance is determined by activity of vascular SM, which similarly to the myocardium undergoes permanent contraction-relaxation cycles referred to as EVM, myogenic microvessel regulation, or vascular peristalsis. Deciphering of the EVM mechanism is a prerequisite for understanding of SM-insufficiency and for a directed search for medical preparations normalizing SM activity similarly to cardiac glycosides restoring cardiac function in patients with cardiac insufficiency.

Our experimental and clinical studies have demonstrated that EVM is controlled by serotonin derived from enterochromaffin cells of the gastrointestinal tract and transferred to microvessel muscle fibers by platelets. Serotonin interacts with SR in SM and induces contraction of microvascular SM with contraction-relaxation-contraction cycles typical for EVM [17].

Vasodilation induced by serotonin antagonists is accompanied by sludge and destruction of erythrocytes. Free hemoglobin interacts with SR in SM and induces or potentiates pathological contraction (spasm). Apart from hemoglobin and myoglobin, other partial serotonin agonists are present in the circulation. Serotonin antagonists induce SM relaxation, while partial serotonin agonists interact with SR in SM and induce pathological contraction that differs by the amplitude and duration from the serotonin-induced contraction [13-18].

Independent of their genesis, antagonists and partial serotonin agonists disturb the interaction of serotonin with SR causing SM dysfunction. These disturbances are reversible, therefore SA infused to the nutritient medium or vascular bed normalizes SM contraction. Cardiac insufficiency is treated with cardiac glycosides, so SA is indicated in SM insufficiency clinically manifested by vascular insufficiency and/or functional intestinal obstruction.

For instance, in our previous studies poisoning with psychotropic preparations in 89 patients was accompanied by considerable SM insufficiency. Intravenous infusion of SA restored SM function, normalized hemodynamics, and corrected tissue hypoxia caused by dysfunction of SM in the microvascular bed. For normalization of the SM function in vascular insufficiency we used SA instead of vasopressors. High efficiency of SA can be attributed to normalization of automatism and contractile activity of SM. This, in turn, restores physiological mechanism of EVM, eliminates tissue hypoxia, and preserves function of vital organs. In comparison with the effect of SA on SM function, the effects of other vasoactive preparations is not so physiological, because vasopressors induced only contraction and spasm of SM, while vasodilators induce only relaxation (atony). In our experiments SA was infused under conditions of artificial ventilation and cardiac glycoside medication, i.e. when other elements of the "hypoxic chain" were eliminated. This reduced the lethality more than 2-fold in comparison with control groups [14-18].

Our previous findings and published data suggest that the aging-related tissue hypoxia results from microcirculatory disturbances, while other elements of the hypoxic chain remain relatively preserved. Under normal conditions blood plasma contains low concentrations of free hemoglobin (10-40 mg/liter). The presence of only this natural metabolite can cause pathological changes in SR of SM and in the entire vascular system. Published data suggest that blood serotonin concentration varies from 20 to 200 μg/liter and does not increase with age to concentrations sufficient to replace hemoglobin from the pathological hemoglobin-SR complex [14,17]. Presumably, hemoglobin interacts with SR in all vessels inducing their degradation and dystrophic alternations in the vascularized tissues, including serotonin-producing cells.

Endogenous serotonin antagonists and/or partial agonists (free hemoglobin and other metabolites) are always present in the circulation and disturb serotonin-SR interaction in SM, inducing initially reversible and then irreversible degradation of SR in SM accompanied by pathological changes in microvascular SM. In young organisms blood concentration of serotonin is sufficient to maintain normal EVM, while with age chronic serotonin insufficiency develops due to permanent presence of endogenous substances in the blood disturbing normal serotonin-SR interaction in SM. These processes are accompanied by pathological changes in the muscular layer of the vascular wall characteristic of aging: reduced elasticity, decreased dilation and constriction potential, *etc.*

Changes in blood vessels in diabetes mellitus are considered as the model of their accelerated aging. We assumed that infusion of SA to patients with pronounced diabetic and age-related angiopathy, i.e., with disturbed SM contractile activity, will correct chronic serotonin insufficiency and normalize (at least partially) SM function, thus intensifying EVM and alleviating tissue hypoxia.

Patients (n=54) with diabetic and age-related angiopathy complicated with microcirculatory disturbances and necrosis of the toes and/or foot caused by local hypoxia, were treated by intravenous injections of SA. Before and during injection, tissue oxygen content was measured transcutaneously near the necrotic area. Infusion of SA at a rate of 5-10 mg/h improved SM function and simultaneously decreased the severity of tissue hypoxia: tissue oxygen increased by more than 50% on average and sometimes returned to normal. This suggests that even in the patients with pronounced angiopathy pathological processes are partially reversible. Since these patients had no respiratory or cardiac insufficiency, anemia, protein or water-electrolyte imbalance, tissue hypoxia was caused entirely by SM dysfunction resulted from more intense degradation of SR in SM of foot microvessels in comparison with the blood vessels in other tissues. The fact that monotherapy with SA successfully corrected tissue hypoxia attests to the necessity of its application for preventing and treating diabetic and/or age-related angiopathy, and confirms our hypothesis on the pathogenesis of tissue hypoxia [15].

Dysfunction of the autonomic nervous system leads to disturbances in the neural component of SM neurohumoral control and development of SM-insufficiency manifested in decreased gastrointestinal motility (characterized by microcirculatory disturbances with and without hypotony) and culminated in func-

tional intestinal obstruction and/or vascular insufficiency. Taking into consideration that serotonin plays a key role in the maintenance of the basal tone and EVM, we concluded that infusion of SA can compensate (replace) the disturbed neural component in the neurohumoral regulation of SM, thereby correcting SM-insufficiency.

We used SA to prevent and treat SM-insufficiency of different degree in patients with traumatic rupture of the spinal cord (n=26), vagotomy (n=42), and pharmacological parasympathetic denervation (intoxication with organophosphorus agents, n=16), i.e. with autonomic nervous system dysfunction. The rate of SA infusion varied from 5-10 mg/h to 2.5 mg/min. The average daily dose was 20-40 mg 1% SA in 20-400 ml physiological saline. The rate of infusion and dose of SA depended on the degree of SM-insufficiency and duration of clinical improvement [4,17]. Infusion of SA normalized SM function, the symptoms of SM-insufficiency disappeared. SA improved microcirculation, normalized hypotension (in normotensive patients blood pressure increased by 10-20 mm Hg), and normalized or accelerated gastrointestinal motility.

The next step after description of the pathogenesis of SM dysfunction is revision of the present classification of the main hypoxic states. The hypoxic chain seems to consist of the following elements: exogenous hypoxia, respiratory hypoxia, hypoxia caused by myocardial dysfunction, hypoxia caused by dysfunction of vascular SM, hemic hypoxia, tissue hypoxia, and combined hypoxia. The arguments in favor of this revision are as follows:

1. Successful cardiac transplantations demonstrate the possibility of correcting hypoxia caused by cardiac dysfunction.
2. Untangling the EVM mechanism (SM pump) explained the genesis of SM insufficiency (SM dysfunction) and its particular individual role in the pathogenesis of tissue hypoxia.
3. Degradation of SR in SM results in SM insufficiency in the microcirculatory bed and tissue hypoxia. Serotonin normalizes SM function and contributes to correction of tissue hypoxia.
4. The development of SM insufficiency and tissue hypoxia in diabetic and aging-related angiopathy as well as intoxication with psychotropic agents, are mediated by humoral agents (antagonists and/or partial agonist of serotonin) and can be reversed with serotonin.
5. SM insufficiency and tissue hypoxia caused by dysfunction of the autonomic nervous system, can be removed by infusion of the endogenous humoral agent serotonin.
6. The use of SA for normalization of the SM function in tissue hypoxia is substantiated pathogenically. The effect of SA on inhibited SM function is analogous to the effect of cardiac glycosides on impaired function of the myocardium.
7. Subdivision of circulatory (cardiovascular) hypoxia into two individual types: hypoxia resulting from cardiac dysfunction and hypoxia provoked by SM dysfunction in the vascular bed is substantiated pathogenically.
8. There are specific methods for correcting all elements of the refined "hypoxic chain".

Therefore, the use of pathogenically substantiated method for the treatment of tissue hypoxia provoked by SM dysfunction in the vascular bed, together with current methods for improvement of other elements of the hypoxic chain, opens the way to regulation of tissue metabolism at the cellular and subcellular levels in the whole body and in specific organs, which is of great scientific and practical value for various biological and medical disciplines including transplantology.

REFERENCES

1. V. F. Ananin, *Human Bioregulation. Bioregulation of the Vasomotor System* [in Russian], Vol. 5, Moscow (1996).
2. M. G. Veil' and G. Shubin, *Diagnostics and Treatment of Shock* [in Russian], Moscow (1971).
3. S. A. Georgieva, N. E. Babichenko, and D. M. Puchin'yan, *Homeostasis, Traumatic Disease of the Brain and Spinal Cord* [in Russian], Saratov (1993).
4. A. B. Gorpinich, *Prophylaxis and Treatment of Postvagotomic and Postresection Impairment of the Gastrointestinal Motility*, Author's Synopsis. of Doct. Med. Sci. Dissertation [in Russian], Moscow (1997).
5. S. N. Efuni and V. A. Shpektor, *Anest. Reanimatol.*, No. 2, 3-12 (1981).
6. A. P. Zil'ber, *Artificial Ventilation in Acute Respiratory Insufficiency* [in Russian], Moscow (1978).
7. T. S. Vinogradova (Ed.), *Instrumental Methods for the Study of the Cardiovascular System. A Manual* [in Russian], Moscow (1986).
8. V. I. Pokrovskii (Ed.), *Concise Medical Encyclopedia* [in Russian], Moscow (1994).
9. A. D. Nozdrachev, *Physiology of the Autonomic Nervous System* [in Russian], Leningrad (1983).
10. G. A. Ryabov, *Hypoxia in Critical States* [in Russian], Moscow (1988).
11. G. A. Ryabov, *Syndromes of Critical States* [in Russian], Moscow (1994).
12. D. S. Sarkisov, *Essays on the History of General Pathology* [in Russian], Moscow (1993).
13. P. V. Sergeev and N. L. Shimanovskii, *Receptors* [in Russian], Moscow (1987).
14. A. P. Simonenkov, *Functional Intestinal Obstruction, Disseminated Intravascular Coagulation, and Syndrome Caused by Poisoning with Psychotropic Drugs as Clinical Manifestations of Serotonin Deficiency*, Author's Synopsis of Doct. Med. Sci. Dissertation [in Russian], Moscow (1992).

15. A. P. Simonenkov and V. D. Fedorov, *Byull. Eksp. Biol. Med.*, **123**, No. 1, 103-110 (1997).
16. A. P. Simonenkov and V. D. Fedorov, *Ibid.*, No. 6, pp. 604-613.
17. A. P. Simonenkov, V. D. Fedorov, A. V. Fedorov, *et al.*, *Vestn. Ros. Akad. Med. Nauk*, No. 6, 11-15 (1994).
18. A. P. Simonenkov, V. D. Fedorov, A. V. Fedorov, *et al.*, *Ibid.*, No. 12, 45-51 (1995).
19. A. V. Smirnov and B. I. Krivoruchko, *Anest. Reanimatol.*, No. 3, 97-98 (1997).
20. A. M. Chernukh, P. N. Aleksandrov, and O. V. Alekseev, *Microcirculation* [in Russian], Moscow (1984).
21. R. F. Schmidt and G. Thews (Eds.), *Human Physiology*, Berlin, New York (1983).
22. H.-P. Schuster, Kh. Schenborn, and Kh. Lauer, *Shock: Pathogenesis, Symptoms, Diagnostics, Control, and Treatment* [Russian translation], Moscow (1981).
23. J. Barcroft, *Lancet*, **2**, 485-489 (1920).
24. J. Barcroft, *The Respiratory Function of the Blood*, Cambridge (1925).
25. P. C. Johnson, *Peripheral Circulation*, New York, Chichester, Brisbane, Toronto (1978).
26. J. P. Peters and D. D. Van Slyke, *Quantitative Clinical Chemistry*, Baltimore (1932).