Journal of Engineering Physics and Thermophysics, Vol. 69, No. 3, 1996

HORMONAL AND METABOLIC CHANGES IN ONCOLOGY PATIENTS SUBJECTED TO GENERAL HYPERTHERMIA AND WAYS FOR THEIR CORRECTION

V. I. Prohkorova, A. A. Mashevskii,
S. V. Lappo, T. P. Tsyrus', and
M. S. Abramovich

UDC 616-006.04:615.838.91/95

Hormonal-metabolic changes in oncology patients subjected to general hyperthermia (GHT) result in enhancement of free-radical oxidation and accumulation of endotoxins under the conditions of violation of their targeted transport to detoxication. A pathogenesis-matched stress-limiting program is developed that allows optimization of the GHT treatment.

General controllable hyperthermia is a practicable way of increasing the chemi- and radiosensitivity of malignant tumors [1-5]. The clinical experience of its use in complex and combined programs of the treatment of local and generalized forms of some tumors testifies to its high effectiveness [6-10]. However, the GHT regimes recommended for treatment of oncology patients cannot provide a rigorously selective action on a tumor; they are stressogenic and cause a substantial load on the vital organs and systems of a patient [11-13]. This restricts indications for hyperthermia in the therapy of oncology patients with the accompanying paraneoplastic syndromes and limited compensatory abilities, and sometimes forces one to give GHT up despite its obvious antitumor effectiveness. One of the important links limiting the GHT treatment or decreasing the level of temperature regimes, multiplicity and duration of treatment is the condition of the cardiovascular system in the oncology patients subjected to GHT treatment. Recent comprehensive studies have demonstrated that hyperthermia treatment causes essential changes in the bioelectrical activity of heart, cardiac rhythm and conduction disturbances, and metabolic cardiopathy [14-17]. In some cases heavy hypoxic changes in the myocardium [18, 19], myocardial ischemia [20, 21], are diagnosed. Pathophysiological disorders developing in the organism due to hyperthermia are caused by hormonal and metabolic changes being a thermal stress reaction that underlies excitation of the hypothalamo-hypophyseal-adrenocortical zone [22-25].

Thist study is devoted to comprehensive investigation of the extent and character of these changes in oncology patients subjected to hyperthermia treatment, development of a pathogenesis-matched stress-limiting program and determination of individual indications for its application for metabolic correction of the pathobiochemical background of GHT. As a basis, we used the data on determination of biochemical and biophysical characteristics of biological fluids of 286 patients suffering from secondary or metastatic melanoma (132 persons), sarcoma of soft tissues (37 persons), and propagated forms of cancer of the lungs (30 persons) and of the kidneys (87 persons) who were subjected to 588 runs of general hyperthermia under the conditions of artificial glycemia (GHT-AG) following the procedure developed at our Institute [1].

We investigated the following homeostasis indices: adrenocorticotropic hormone (ACTH), somatropic hormone (STH), hydrocortisone, immunoreactive insulin, C-peptide, glucogon, somatostatin, cyclic nucleotides, namely, cyclic adenosin-3', 5'-monophosphate and cyclic guanosine-3', 5'-monophosphate that were determined by a radioimmune method using commercial kits of the firms INC (USA), "Sea-Sorin" (France), and the Institute of the General and Inorganic Chemistry of the Academy of Sciences of Belarus (Minsk, Belarus). The excretion of adrenalin, noradrenalin, concentration of triacylglycerol, free fatty acids (FFA), urea, retinol, tocopherol, glucose,

Scientific Research Institute of Oncology and Medical Radiology of the Ministry of Public Health of Belarus, Minsk, Belarus. Translated from Inzhenerno-Fizicheskii Zhurnal, Vol. 69, No. 3, pp. 443-450, May-June, 1996. Original article submitted March 20, 1996.

 1062-0125/96/6903-0354$15.00

metabolites of carbohydrate metabolism (lactic acid (LA), pyroacemic acid (PA)), the activity of enzymes (alanine aminotransferase (AlAT), aspartate aminotransferase (AsAT), creatine phosphokinase (CPhK), superoxide dismutase (SOD), catalases, peroxidases), the level of mean-weight molecules, products of lipid peroxidation (LP) (dien conjugates, dienketones, malonic dialdehyde, Schiff bases) were determined by spectrofluorometric methods. The double bonds (DB) of lipids of blood serum were investigated on a DBA analyzer manufactured by the Russian-Holland enterprise "AMMO" [26].

The parameter α of the EPR-spectrum of spin-labelled blood serum was determined by the EPR-analyzer we had designed for blood investigations [27].

Selection of informative complexes of tests from the total bulk of indices was accomplished with the aid of step-by-step discrimination analysis [28]. Calculations were performed on an AT 386 personal computer using the Rostan package of programs developed by the Chair of Mathematical Simulation and Data Analysis at Belarusian State University [29].

Results and Discussion. In the course of the general hyperthermia treatment on the background of artificial glycemia in patients, abruptly pronounced hormonal activation of stress response and enhanced urenary excretion of catecholamines, namely, adrenalin up to 978 ± 155% and noradrenalin up to 739 ± 148% of the initial level, were observed. At this moment the concentration of ACTH and STH in blood showed a 6- and 10-fold increase, respectively. The cortisol concentration in blood increased to a lesser extent, i.e., by 50%. Simultaneously enhancement of the urinary excretion of cyclic nucleotides, with the prevailing growth of cyclic AMPh, was observed. The content of the latter exceeded its initial value by a factor of two. During 4–6 h of GHT-AG treatment, the amount of immunoreactive insulin and C-peptide in blood showed a 7.5–11.5- and 4.7–6.3-fold increase, respectively, with a decreased level of glucogon and almost the unchanged somatostatin concentration in blood. The molar index of C-peptide/IRI decreased almost by a factor of 2 as compared to its initial value. 1–2 days later after GHT-AG treatment the level of sympatho-adrenal and hypophyseal-adrenocortical hormones fell almost to the initial values. The content of C-peptide and insulin in blood decreased in the next postprocedure period; however during the first week of this period the C-peptide/IRI ratio remained lower than its initial value.

The glycemia level was kept high (22–30 mmole/liter) during 4–6 h of hyperthermia runs. At the end of each run we observed accumulation of the intermediary metabolites of carbohydrates: LA and PAA concentrations showed a 2- and 4-fold increase, respectively, followed by their decrease in the post-treatment period.

At the stage of the GHT-AG treatment there was observed a 3- and 2-fold decrease in the FFA and triacylglycerol concentrations in blood, respectively; the level of double bonds of the lipid fraction of blood serum decreased by 70%. At the same time the concentration of lipoperoxides in blood increased: dien conjugates and Schiff bases by 50–60%, MDA by a factor of two on the background of the decreased activity of the antioxidation system of an organism, in particular, the retinol concentration in blood decreased by a factor of 10, and the SOD activity – by 50%.

During GHT-AG treatment we observed the growth of hour-by-hour uroexcretion of urea. The drastic increase (2–2.5-fold) of urea ejection was observed already at the beginning of the temperature action followed by a decrease in its concentration in urine only after cessation of GHT-AG treatment. The enhancement of protein catabolism was accompanied by accumulation of peptide endotoxins, such as mean-weight molecules, in blood, whose level increased by a factor of 2.5. Owing to the GHT-AG treatment the activity of membrane-bonded enzymes (AlAT, AsAT, and CPhK) increased. It is pertinent to note that in the majority of patients their indices were not normalized within the first week of the post-treatment period. The parameter α of the EPR-spectrum of spin-labeled blood serum became doubled, thus manifesting a decrease in the functional activity of transport albumins of blood.

The reported data indicate that as a result of the GHT-AG treatment an organism of the oncology patients manifests a drastic increase in synthesis with release of hypophyseal hormones in blood and related enhancement of the ejection of catecholamines and corticosteroids. It should be noted that the stress increase of the STH level is not suppressed by the induced artificial hyperglycemia. Apparently, the appearance of the stable excitation source in higher cerebral centers under GHT conditions disturbs the hypothalamus sensitivity to humoral effects (glucose effect), which determines the paradoxical GHT response on the background of artificial glycemia.

Under the conditions of immediate adaptation to the action of the stress factor the energetic needs of biological processes in an organism abruptly grow. The main energetic substrate mobilized in stress situations is glucose. Hyperglycemia caused by the hyperthermal stress and direct glucose injection is a powerful insulin stimulator whose action is targeted to glucose utilization by tissues. Our studies reflect the extreme stress of the insular system accompanied by the essential insulin ejection in blood during GHT treatment. The functional activity of the pancreas in the course of GHT-AG is confirmed by the unchanged somatostatin concentration in blood, which regulates the secretion of pancreatic hormones. However, a comparison of the IRI recorded in blood during treatment with the level of C-peptide being a measure of the secretion of functionally normal insulin reveals the functional deficiency of the essential IRI part. Probably the IRI secreted in large amounts includes a fraction of inactive insulin-like peptides. As a result of the formation of new endocrinic-metabolic interrelations a situation takes place when with the increased insulin concentration and decreased level of glucogon the high concentrations of the hypophyseal-corticoadrenal hormones represent carbohydrate utilization by organism cells. Though large amounts of glucose circulate in the blood during the GHT-AG treatment, the organism fails to use it for energetic needs because of the developed tissue resistance to carbohydrates.

The data obtained on the increase of cAMPh excretion are indicative of the development of cAMPh-dependent mechanisms of changing the energy metabolism from carbohydrate substrates to the alternative, i.e., lipid and albumin metabolites. A decrease in the level of lipid metabolites in blood and total nonsaturation of fatty acids during GHT treatment point to their intense utilization by separate organs and tissues under the conditions of inhibition due to high temperature and glycemia of the mechanisms of enhancement of lipolysis and mobilization of unsaturated fatty acids in blood flow. Utilization of unsaturated fatty acids by tissues for compensation of energy deficiency in GHT initiates the processes of lipid peroxidation, which is indicated by the lipoperoxide accumulation in blood and decreased activity of antioxidants.

The pronounced loss of nitrogen with urination during GHT-AG treatment reflects the activation of albuminous catabolic processes. The enhanced decay of albumins is accompanied by the accumulation of peptide endotoxins and deteriorated transport function of albumin. As a result of the formation of highly reactive FRO products, underoxidized carbohydrate metabolites and peptide endotoxins their targeted transport to the detoxication organs is disturbed due to a decrease in the functional activity of transported albumins. Such a situation inevitably causes damage to cellular structures and favors the development of membrane pathology. Cytoxic and cytolytic reactions are manifested by the activation of the enzymes circulating in blood, which are the indicators of necrobiotic processes in organs and tissues.

On the background of the indicated discrimination disturbances of metabolism almost half the examined patients subjected to GHT treatment were diagnosed with disorders of various degrees in the cardiovascular activity: diffuse ischemic changes in the myocardium, disturbances of the intraventricular conduction and cardiac rhythm, tachycardia and myocardium hypoxia. This testifies to the necessity of prophylaxis of hormonal-metabolic manifestations of the thermal stress and correction of the pathobiochemical background of GHT with the aid of the stress-limiting therapy.

The starting point of the stress-realizing mechanisms developing in an organism of the oncology patients subjected to the GHT treatment is a change in hormonal interrelations, which results in the functional deficiency of insulin and homeostasis disturbance of glucose. In these conditions the best way is to ensure the high energy metabolism in the most efficient and physiologically optimal glycolytic regime that prevents undesirable triggering of fatty and alumbinous metabolism with the aid of the exogenously incorporated insulin [30-32]. We have developed a pathogenesis-matched system of measures aimed at optimization of the GHT treatment that involves infusion of large doses of insulin with glucose, electrolyte solutions, and the antioxidation complex of vitamins A, E, and C [33]. Successful realization of the new GHT method on the background of such a stress-limiting program promoting intense assimilation of carbohydrates and exerting a stabilizing effect on membrane processes calls for working-out of individual indications for its application.

A comparison of the investigated characteristics of biological fluids of an organism of the examined oncology patients revealed reliable differences in the degree of manifestation of their values depending on the evolution or absence of GHT-caused cardiovascular complications. However traditional evaluation of changes in separate

physicochemical preparations is not very effective for the diagnosis of these complications at the stage preceding cytomorphological and functional disturbances. Selection of the most informative tests reflecting the integral sum of hormonal-metabolic changes in a patient's organism and most correlating with pathology development makes it possible to predict individually the possibility of hyperthermia side-effects at the preclinical stage. Using the step-by-step discrimination analysis, we have chosen the following informative characters: the parameter α of the EPR-spectrum of spin-labeled blood serum, double bonds of the total unsaturation of lipids, cAMPh/cGMPh ratio, and molar index of C-peptide/IRI.

Of the chosen informative tests we have composed two sets of tests characterized by the maximum diagnostic effectiveness: 1) α, double bonds, cAMPh/cGMPh; 2) α, molar index of C-peptide/IRI. Using these complexes and the linear discriminant function, we have constructed decisive rules for predicting the GHT side-effects. According to the first decisive rule, an examined oncology patient sent for combined treatment involving GHT receives a prognostic assignment to the unfavorable class provided

$$Z_1 = 0.5433X\alpha - 0.0217X_{DB} - 0.8147X_{cAMPh/cGNPh} > 2.0511 ,$$

where Z is the discriminant function; X is the physicochemical parameter introduced into the analysis.

The diagnostic effectiveness (accuracy) of the decisive rule totals 78.5% for the initial physicochemical characteristics, 66.0% for those recorded at the end of the GHT treatment, and 97.1% one day after GHT1.

According to the second decisive rule an examined oncology patient receives a prognostic assignment to the unfavorable class provided

$$Z_2 = 0.6354X\alpha - 0.6967X_{C-peptide/IRI} > - 3.2837 .$$

The accuracy of this decisive rule is 80.2%, 88.7%, and 90.5%, respectively.

Use of these decisive rules allows determination of individual indications for preventive therapy.

The targeted and pathogenesis-matched use of the stress-limiting program in oncology patients realizes the increased energy needs by creating conditions for the most energy-bearing and physiologically optimal substrate, i.e., glucose, by reducing the load on the insular mechanism and blocking the LP processes. Such optimization of metabolic processes favors, in the long run, the selective protection of biological membranes of an organism from free-radical failure and decreases the probability of development of membrane complications in the vital organs of oncology patients.

CONCLUSIONS

1. Dissociation of the hormonal response to GHT manifested by the abrupt enhancement of the activity of hypophyseal-adrenocortical hormones and decrease in the functional activity of insulin together with a change in the ratios of cyclic nucleotides, reflecting predominance of cAMPh-dependent processes, in the system is a response of the endocrinic system to the thermal stress in the oncology patients subjected to GHT.

2. The increased activity of the membrane-bonded enzymes on the background of accumulation of underoxidized carbohydrate products, peptide endotoxins and lipoperoxides testifies to passing of the reactions of adaptation to the thermal stress to cytotoxic damage. Such a pathobiochemical background of GHT underlies the occurrence of disorders in the cardiovascular system.

3. A system of measures including infusion of large doses of insulin with glucose and the antioxidation complex, which provides an organism with additional energy through intensification of carbohydrate assimilation and exerts a stabilizing action on the membrane processes, is a pathogenesis-matched program aimed at optimization of the GHT treatment carried out in a group of patients with an unfavorable prognosis.

4. Selection of the physicochemical characteristics of biological fluids in the bodies of oncology patients by the step-by-step discrimination analysis and construction of a decisive rule with use of the linear discrimination function allows cardiovascular side-effects of GHT to be predicted at the preclinical stage of biochemical changes.

5. Determination of individual indications for use of the developed stress-limiting program during GHT treatment makes it possible to extend indications to GHT treatment and use higher temperature-exposure regimes on the background of the decreased probability of development of complications in the hemodynamic system.

NOTATION

ACTH, adrenocorticotropic hormone; AlAT, alanine aminotransferase; AsAT, aspartate aminotransferase; AOS, antioxidation system; DB, double bonds of the lipid fraction of serum; IRI, immunoreactive insulin; AH, artificial hyperglycemia; CPhK, creatine phosphokinase; MDA, malonic dialdehyde; MWM, mean-weight molecules; LA, lactic acid; GHT, general hyperthermia; LP, lipid peroxidation; PAA, pyroacemic acid; FRO, free-radical oxidation; FFA, free fatty acids; STH, somatropic hormone; SOD, superoxide dismutase; cAMPh, cyclic adenosin -3′, 5′-monophosphate; cGMPh, cyclic guanosine -3′, 5′, monophosphate.

REFERENCES

1. N. N. Aleksandrov, N. E. Savchenko, S. Z. Fradkin, and E. A. Zhavrid, Hyperthermia and Hyperglycemia in Treatment of Malignant Tumors [in Russian], Moscow (1980).
2. E. A. Zhavrid, S. P. Osinskii, and S. Z. Fradkin, Hyperthermia and Hyperglycemia in Oncology [in Russian], Kiev (1987).
3. S. P. Yarmonenko, Med. Radiolog., No. 1, 10-18 (1987).
4. J. M. Bull, Front. Radiat. Ther. Oncol., 18 171-176 (1984).
5. I. Chr. Lindegaard and I. Overgaard, Radiotherapy and Oncology, No. 11, 143-151 (1989).
6. I. G. Zhakov, S. Z. Fradkin, E. A. Zhavrid, et al., in: Hyperthermia in Oncology [in Russian], Obninsk (1990), pp. 102-103.
7. O. G. Sukonko, A. S. Mavrichev, and S. A. Krasnyi, in: Book of Abstracts of the VI Scientific-Practical Conference of Oncologists of the Republic of Belarus (1994), pp. 216-217.
8. E. A. Zhavrid and S. Z. Fradkin, in: Urgent Problems in Oncology and Medical Radiology [in Russian], Collected Papers, Minsk (1986), pp. 75-82.
9. G. V. Goldobenko, L. A. Durov, V. I. Knysh, et al., Med. Radiolog., No. 1, 36-38 (1987).
10. J. M. Larkin, Cancer. Res., 39, No. 6, Pt. 2, 2252-2254 (1989).
11. V. I. Prokhorova, E. A. Zhavrid, S. Z. Fradkin, et al., Voprosy Onkol., 37, 11-12, 1050-1054 (1991)
12. V. I. Prokhorova, E. A. Zhavrid, S. Z. Fradkin, et al., Med. Radiolog., No. 8, 10-12 (1991).
13. V. I. Prokhorova, V. Z. Rubanova, N. I. Ermilova, et al., in: Hyperthermia in Oncology [in Russian], Obninsk (1990), PP. 90-91.
14. V.F. Rubin and A. G. Rybka, Physiological and clinical problems of the adaptation of human and animal bodies to hypoxia, hyperthermia, hypodynamia and nonspecific ways of recovery, in: Proc. of the 2nd All-Union Symposium, Moscow (1978), p. 188.
15. V. I. Sobolevskii and V. V. Eliseev, Kardiolog., 24, No. 7, 98-99 (1984).
16. S. E. Nodel'son, M. V. Bronshtein, Z. S. Trusevich, et al., Anesteziol. Reanimatol., No. 2, 21-24 (1989).
17. S. Z. Fradkin, S. E. Nodel'son, and G. V. Semenov, in: Urgent Problems in Oncology and Medical Radiology [in Russian], Collected Papers. Minsk (1975), pp. 285-288.
18. Yu. D. Kovalenko, "The condition of the blood circulation and respiratory systems under hyperthermia conditions," Abstract of Candidate's Dissertation, Minsk (1973).
19. V. E. Kratenok, "Changes in the condition of vital functions of the organism subjected to the controllable general UV-hyperthermia," Abstract of Candidate's Dissertation, Moscow (1983).
20. Z. S. Trusevich, "A choice of the adequate method of general anesthesia under the conditions of artificia hyperthermia and hyperglycemia in complex treatment of oncology patients," Abstract of Candidate's Dissertation (1988).

21. S. Z. Fradkin and S. E. Nodel'son, in: Urgent Problems in Oncology and Medical Radiology [in Russian], Collected papers, Minsk (1974), pp. 321-330.
22. P. D. Gorizontov, O. I. Belousova, and M. I. Fedotova, Stress and Blood System [in Russian], Moscow (1983), pp. 23-25.
23. V. I. Kandor, Usp. Sovrem. Biolog., 96, No. 2(5), 280-296 (1983).
24. T. Koks, Stress [in Russian], Moscow (1981), pp. 56-62.
25. F. Z. Meerson, Adaptation, Stress and Prophylaxis [in Russian], Moscow (1981).
26. D. M. Lisitsyn, T. I. Poznyak, and S. D. Razumovskii, Kinet. Katal., 17, No. 4, 1049-1055 (1979).
27. A. A. Mashevskii, V. N. Linev, V. A. Muravskii, et al., EPS-Analyser for Medical-Biological Investigations, in: Extended Abstracts of the 1st Int. Conf. "Science and Medicine to Chernobyl", Minsk (1993), pp. 56-57.
28. A. Afifi and S. Eizen, Statistical Analysis [in Russian], Moscow (1982), p. 28.
29. Yu. S. Kharin, M. D. Stepanov, and M. S. Abramovich, Mathematical Tool and Software of the Stable Statistical Analysis of Data [in Russian], Moscow (1992), pp. 22-24.
30. V. I. Prokhorova, in: Urgent Problems in Oncology and Medical Radiology [in Russian], Collected papers, Minsk (1990), pp. 97-109.
31. I. A. Kozlov and N. V. Meshcheryakov, Anestez. Reanimatol., No. 5, 70-76 (1985).
32. S. Z. Nodel'son, M. I. Bronshtein, E. B. Belenkova, et al., Anestez. Reanimatol., No. 6, 59-63 (1990).
33. V. N. Sukolinskii, Voprosy Onkol., No. 2, 138-144 (1990).