Metabolic Effects of a Succinic Acid-Based Substrate Antihypoxant

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The paper discusses promises for clinical use of substrate antihypoxants. *Objective:* to investigate the efficacy of succinate-containing substrate antihypoxants on systemic oxygen consumption, blood buffer capacity, and changes in the mixed venous blood level of lactate when they are used in gravely sick patients and victims with marked metabolic posthypoxic disorders. *Subjects and methods*. The trial enrolled 30 patients and victims who had sustained an episode of severe hypoxia of mixed genesis, the severity of which was evaluated by the APACHE II scale and amounted to 23 to 30 scores with a 46 to 70.3% risk of death. The standard infusion program in this group involved the succinate-containing drug 1.5% reamberin solution in a total dose of 800 ml. A comparison group included 15 patients who had undergone emergency extensive surgery for abdominal diseases. 400 ml of 10% glucose solution was used as an infusion medium. Oxygen consumption (VO_2 ml/min) and carbon dioxide production (VCO_2 ml/min) were measured before infusion and monitored for 2 hours. Arterial blood gases and acid-base balance (ABB) parameters and mixed venous blood lactate levels were examined. Measurements were made before and 30 minutes after the infusion of reamberin or glucose solution. *Results*. Infusion of 1.5% reamberin solution was followed by a significant increase in minute oxygen consumption from 281.5±21.2 to 310.4±24.4 ml/min. CO_2 production declined (on average, from 223.3±6.5 to 206.5±7.59 ml/min). During infusion of 10% glucose solution, all the patients of the comparison group showed a rise in oxygen consumption from 303.6±33.86 to 443.13±32.1 ml/min, i.e. about 1.5-fold. VCO_2 changed similarly. The intravenous infusion of 800 ml of 1.5% reamberin solution raised arterial blood buffer capacity, which was reflected by changes in pH, BE, and HCO_3^-. There was a clear trend for lactate values to drop in the mixed venous blood. The intravenous injection of 400 ml of 10% glucose solution caused no significant changes in major ABB indicators, which reinforced the statement that there is a difference in the metabolism of these substrates. *Conclusion*. The succinate-containing drugs are able to compensate for metabolic acidosis. Their use is followed by increased oxygen consumption and activated aerobic oxidation processes. The basis of their antihypoxant properties was thought to be recovered intracellular aerobic metabolic processes due to corrected intracellular metabolic acidosis and increased blood buffer capacity. *Key words:* hypoxia, reperfusion, multiple organ dysfunction, antihypoxants, metabolic acidosis, acid-base balance, lactate, oxygen consumption, succinate, fumarate.

Introduction

Hypoxia, which is of a mixed nature in most cases, is the main pathologic process which determines the condition severity in patients. In spite of evident differences in hypoxia triggering mechanisms, metabolic changes in the conditions of oxygen deficiency in biologic systems are largely stereotypical [1—7].

The severity of functional and, subsequently, structural changes in hypoxia-affected organs is different and depends on the characteristics of compensation mechanisms [8]. The course of diseases and their outcome are determined finally by the characteristics of secondary nonspecific metabolic disorders, degree of cell membrane destabilization, as well as reactivation resources of structural and enzyme proteins under hypoxic conditions [9]. The tissue hypoxia events are most often developed as secondary on the background its other variants accompanied by formation of intracellular acidosis, activation of the process of free radical oxidation of biological structures that results in malfunction of mitochondrial enzyme systems. Under the conditions of hypoxia or anoxia, the absence of oxygen as an acceptor of electron-proton pairs results in blockage of respiratory chain cascade and stoppage of NADH and FADH2 oxidation. The excess of reduced co-enzymes regulating Krebs cycle rate leads to attenuation of the latter. It is important to note that the cycle of anaerobic glycolysis cycle known as Embden-Meyerhof-Parnas cycle is also inhibited subsequently under conditions of persisting hypoxia. When lactate is intensively accumulated, cells do not have time to eliminate this substrate and, as a consequence, the reaction described above is inhibited due to disturbance of the dynamic equilibrium.

The recovery of adequate gas exchange and elimination of tissue hypoxia events are accompanied by development of reperfusion disorders of different severity. The main damaging role is played by free oxygen radicals and their metabolites formed in endothelial cells, leukocytes and parenchymal cellular elements. The antioxidant reserve of the body may even be increased in a compensation manner. However, it is decreasing since the damage progresses. Oxygen radicals induce lipid peroxidation (LP) required for phospholipid synthesis and regulation of cell membrane permeability [10]. LP activation, which is not controlled in critical conditions, is one of the most important consequences of excess formation of oxygen active forms. Loosening of the hydrophobic part of the lipid bilayer occurs that makes protein components accessible for proteases. Addition of the hydrophilic peroxide radical to the hydrophobic part results in conformational structural changes and modification of biophysical properties of membrane complexes [11]. Permeability defects facilitate entry of calcium ions activating phosphorylases that facilitates the change of the mitochondrial external membrane potential, disturbance of ATP synthesis, and further destruction of cell membranes [12].

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Currently, most researchers believe that formation of organ dysfunction or failure is associated with the development of reperfusion disorders [13].

Hypoxia and reperfusion are the main pathologic processes observed in critical care medicine. They associated with development of tissue acidosis, energy transmitter production deficiency, impaired functioning of transmembrane energy-dependent processes (disturbed electric stability of biomembranes), and biomembrane damage with disturbed structural function of the cell and its death. Therefore, theprotection of cells from hypoxia, reperfusion and their consequences is continuing to be unsolved urgent problem.

The drugs currently used for the purpose of cytoprotection include drugs with different mechanisms of action, specifically, those that improve the electron transport in the cytochrome oxidase chain (Ubiquinone, cytochrome C, Olyphen), vitamin and mineral complexes, reduce formation or block the damaging effect of free radicals and their metabolites (tocopherol, Mexidol, alpha-lipoic acid), and different nootropic and adaptogenic drugs [14—16].

The drugs belonging to the group of substrate antihypoxic drugs are the most commonly used in Russia. In clinical practice, drugs based on sodium salts of carboxylic acids, namely, fumaric and succinic acids, are most widely used. These drugs are intended to correct hypoxia-induced metabolic disorders. The mechanism of their action is based on intracellular aerobic oxidation with formation of high-energy compounds within the cycle of di- and tricarboxylic acids. Indications for use of this group of drugs are various and vary from correction of syndromes of intoxication to the relief of hypoxic conditions of various etiologies [15—18].

Carboxylic acids are formed in the mitochondrial matrix in a complex of consecutive reactions of citric acid cycle. The initial reaction is formation of active acetate from the reaction of pyruvate with coenzyme A in the presence of pyruvate dehydrogenase [19]. In particular, the sodium salt of succinic acid (succinate) belonging to the group of salts of weak organic acids is capable to penetrate into the cell and participate in metabolic processes. Moreover, G. Krebs identified the catalytic role of practically all tricarboxylic acid cycle metabolites responsible for a significant increase in pyruvate consumption in response to small amounts of cycle substrates [19, 20]. Therefore, all reactions of the cycle are shifted to the right that leads to faster pyruvate disposal. Obviously, only one molecule of pyruvate can participate in the reaction with coenzyme A during one Krebs cycle turnover. Malate accumulation will impede the metabolic reaction cascade rate. Similarly, substrate decarboxylation will be impeded in the case of lack of pyruvate (in case of reduced activity of pyruvate dehydrogenase) or acetyl coenzyme A that is extremely rarely observed in clinical conditions. Activity of the enzyme complex of citric acid cycle may be significantly reduced under conditions of intracellular acidosis and accumulation of high NADF concentration. It is usually associated with the development of respiratory, hemic or tissue hypoxia (at the level of the oxidative phosphorylation system) [14, 19].

It should be noted that the recovery of effective oxygen transport in such situations is not accompanied by rapid recovery of intracellular enzyme activity due to the fact that intracellular acidosis is difficult to correct.

As for energy capacity of succinate and fumarate, it should be noted that complete oxidation of one molecule of succinic acid can produce 5 ATP molecules in oxidative phosphorylation reactions and one molecule of fumaric acid can produce 3 ATP molecules. Thus, the energy value of succinate exceeds the energy produced by anaerobic glycolysis more than 2 times, and the energy value of fumarate exceeds 1.5-fold. And although this value is significantly lower than the energy produced in the full cycle of aerobic glucose metabolism. This ability seems to be rather important in the case of persisting partially reduced hypoxia or early posthypoxic period [20].

The potential buffer activity of sodium salts of succinic and fumaric acids seems to be interesting in therapeutic terms. The ability of succinate and fumarate to intracellular oxidation with replacement of one hydrogen atom by sodium with formation of bicarbonate might be unique in terms of a possible relief from the intracellular metabolic acidosis, which is one of the most serious consequences of hypoxia of virtually any etiology [15, 16, 21—24]. It is possible that elimination of intracellular acidosis can result in recovery of activity of the Krebs cycle enzyme cascade and oxidative phosphorylation enzyme chain.

This study was conducted in order to clarify some systemic effects caused by the use of energy substrates — reamberine (the main active ingredient is succinate) and glucose widely spread in the clinical practice, and more specifically, their effect on oxygen consumption, blood buffer properties and changes in the blood content of lactate as the main hypoxia marker.

Materials and methods

The study included 30 patients aged 25 to 70 years ($M \pm SD$, 51.6±4.2, 17 females and 13 males). The patients were examined on the first day after extensive emergency abdominal surgery or the first day after transfer to the intensive care department from the shock operating room where they underwent surgical correction and intensive therapy of severe multiorgan injuries.

The severity of patient conditions was assessed by APACHE II scale within the range from 23 to 30 points and at a risk of death from 46 to 70.3%.

At the time of examination artificial pulmonary ventilation was carried out in all patients with the use of 50% FiO_2. The standard infusion regimen for this group included 1.5% Reamberine with the total dose of 800 ml. The intravenous infusion of the drug was carried out for 45—50 min.

The group of comparison (control, n=15) included patients aged 32 to 68 years (46.2 ±3.8), who underwent emergency extensive surgery for abdominal diseases. 7 patients were females and 8 patients were males. The severity of patient conditions was assessed by APACHE within the range from 22 to 30 points and risk of death from 42.4 to 70.3%. There was no significant difference in the severity of the condition between the groups (by X^2 test). 400 ml of a 10% glucose solution was used as an infusion liquid.

The following parameters were measured before the beginning of the infusion and then monitoring during two hours consumption of O_2 (VO_2 ml/min) and elimination of CO_2 (VCO_2 ml/min) with the aid of inducet calorimeter (CCM Express, Medgraphics, USA).

The gas composition, ABB parameters of the arterial blood, lactate content in the mixed venous blood were measured before the beginning of the infusion of Reamberine solution or glucose, and then in 5 and 30 minutes after its completion with the use of a portable clinical analyzer i — STAT 300 (Abbott, USA).

Statistical data processing was performed by paired Student's t test with determining significance of differences At $P<0,05$.

Results and discussion

At the beginning of the study, oxygen consumption in the main group (VO_2) was 281.5±21.2 ml/min. Elimination of CO_2 (VCO_2) was 223.3±6.5 ml/min.

The infusion of 1.5% Reamberine solution was associated with a significant increase in the oxygen consumption up to 310.4±24.4 ml/min. At the same time, the elimination of CO_2 started to decrease (on average to 206.5±7.59 ml/min). Termination of Reamberine administration resulted in a rapid (within 3—7 minutes) return to the initial values of VO_2 and VCO_2 parameters (Figure 1).

Inh a control group, a clear, significant increase in the oxygen consumption from 303.6±33.86 to 443.13±32.1 ml/min, i.e. almost 1.5-fold increase, was observed during the infusion of 10% glucose solution. VCO_2 changed similarly (Table 1).

This effect was also short. Oxygen consumption returned to initial values within 3—4 minutes after glucose infusion. VCO_2 returned to initial values somewhat later, in 7—10 minutes (Fig. 2).

The observed changes were not unexpected. It is well known that infusion of any energy substrate utilized under aerobic conditions is associated with an increase in the oxygen consumption. The maximum oxygen consumption is caused by gluconate utilization and, to a lesser extent, utilization of lactate, succinate and malate. Aerobic glucose oxidation requires the highest amount of oxygen (6 molecules per one glucose molecule). Elimination of carbon dioxide is a parameter depending on the end products of oxidation. It is definitely higher for glucose.

The study of gas composition and ABB of the arterial blood, as well as lactate content in the mixed venous blood showed that all patients had metabolic acidosis before the beginning of administration of 1.5% Reamberine solution. pH values were 7.25±0.02. BE was lowered to — 6.73±0.85 mmol/l (Table 2).

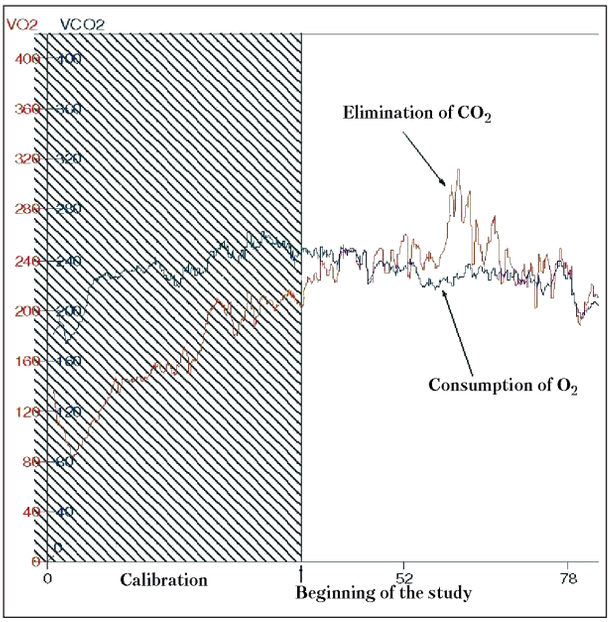

Fig. 1. Dynamics of oxygen consumption (VO_2) in ml/min and elimination of carbon dioxide (VCO_2) in ml/min during the intravenous infusion of 1.5% Reamberine solution

The intravenous infusion of 800 ml of 1.5% Reamberine solution increased the buffer capacity of the blood that was manifested by significant changes in PH, BE and HCO_3^- of the arterial blood. It is noteworthy that the change in the buffer capacity of the blood depended on the dose that gives hope for correction of metabolic acidosis with different decompensation by changing the dose of intravenous succinate. There was a clear trend toward reduction of lactate content in the mixed venous blood that is one of the signs of activation of aerobic metabolism.

Table 1

Dynamics of oxygen consumption per minute (VO_2) and elimination of carbon dioxide (VCO_2) during the intravenous infusion of 1.5% Reamberine solution and 10% glucose solution ($M±m$)

Parameter	Value of indicators on the stages of the research			
	Before infusion of 1.5% Reamberine (n=30)	During infusion of 1.5% Reamberine (n=30)	Before infusion of 10% glucose (n=10)	During infusion of 10% glucose (n=10)
VO_2, ml/min	281,5±21,2	310,4±24,4*	303,6±33,86	443,13±32,1*
VCO_2, ml/min	223,3±6,55	206,5±7,59*	246,8±19,0	410,0±30,0*

Note. Here and table 2, 3: * — $p<0.05$, differences are significant between group.

Table 2

Dynamics of main ABB parameters in the arterial blood and lactate content in the mixed venous blood before and after intravenous infusion of 800 ml of 1.5% Reamberine solution ($M±m$)

Parameter	Value of indicators on the stages of the research	
	Before infusion (n=30)	In 30 min after completing the infusion (n=30)
pH	7,25±0,02	7,31±0,02*
BE ecf, mmol/l	-6,73±0,85	-1,50±1,03*
HCO_3^-, mmol/l	19,14±0,95	21,80±1,0*
Lactate, mmol/l	3,44±0,38	3, 26±0,39

Table 3

Dynamics of main ABB parameters in the arterial blood and lactate content in the mixed venous blood before and after intravenous infusion of 400 ml of 10% glucose solution (*M*±*m*)

Parameter	Value of indicators on the stages of the research	
	Before infusion (*n*=15)	In 30 min after completing the infusion (*n*=15)
pH	7.26±0.03	7.25±0.03
BE ecf, mmol/l	-4.66±1.10	-4.80±1.3
HCO_3^-, mmol/l	17.88±2.21	17.51±2.12
Lactate, mmol/l	4.49±0.63	5.12±0.65*

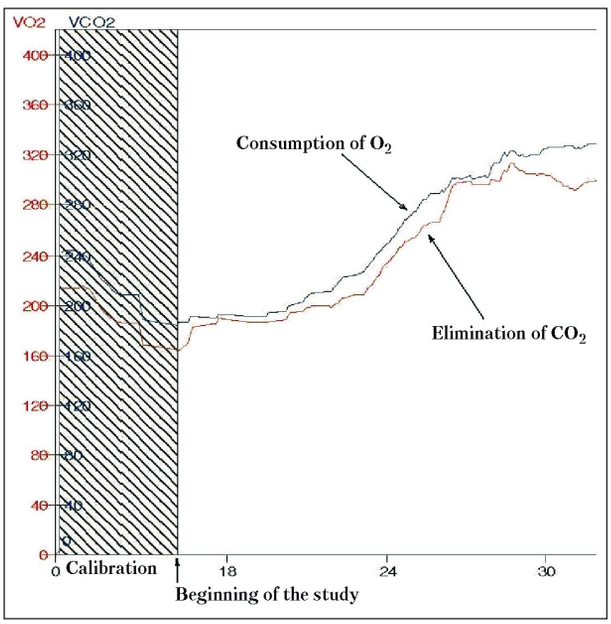

Fig. 2. Dynamics of oxygen consumption (VO_2) in ml/min and elimination of carbon dioxide (VCO_2) in ml/min during the intravenous infusion of 10% glucose solution

There was no any significant change in the main ABB after the intravenous administration of 400 ml of 10% glucose solution that confirmed the assumption on the difference in metabolism of these substrates (Table 3).

A significant increase in the lactate content in the mixed venous blood was typical for this group. It is possible that the latter is associated with an insufficient compensatory increase in the oxygen supply to the tissues and some activation of anaerobic glycolysis processes.

Conclusion

1. Intravenous infusion of 1.5%-solution of succinate-containing drug Reamberine is accompanied with a significant increase in the oxygen consumption per min and some reduction in the elimination of carbon dioxide;

2. Reamberine administered intravenously in the dose of 800 ml of 1.5% solution significantly increases the buffer capacity of the blood allowing to correct metabolic acidosis and contributes to the recovery of aerobic metabolism processes in the posthypoxic period that is manifested by the trend towards normalization of lactate content in the mixed venous blood;

3. The intravenous administration of concentrated glucose solutions causes a significant increase in the oxygen consumption (on average, 1.5-fold increase) and elimination of carbon dioxide (more than 1.5-fold increase), as well as a significant increase in the lactate content in the arterial blood. The possible development of lactic acidosis demands great care in carrying out the infusion of concentrated glucose solutions in patients with limited reserves of oxygen transport function;

4. The comparison of oxygen consumption after intravenous infusion of Reamberine 1.5% succinate-containing solution and 10% glucose solution the most often used in the clinical practice has confirmed that the energy capacity of glucose is considerably higher than the energy capacity of succinate (in concentrations used). However, the lack of buffer properties of glucose solutions and inability to compensate metabolic acidosis (first of all, intracellular one) do not allow to classify this energy substrate as belonging to the group of drugs correcting post-hypoxia disorders. Probably, it is the ability of succinic acid salt solutions that allows classifying it as belonging to the group of substrate anti-hypoxia drugs.

5. Infusion of drugs increasing oxygen consumption at the systemic level in patients with reduced functional resources of the circulatory system should be performed with a caution.

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