Metabolic cardioprotectors in sport: the focus on last changes in WADA Prohibited List (review)

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Summary
At present time, the rational search for a protection of cardiovascular system of athletes and the assessment of such protection efficiency are the very important problems in sports pharmacology and sports cardiology. It is worth noting that athletic training pharmacology, aimed at the stimulation of physical workability in the majority of sports events, can become, together with overloads, the principal reason for a deterioration of health and life’s quality as well as for the sudden death of athletes without a proper cardioprotection. The problem of protection is significantly complicated under modern conditions due to the permanent hardening of anti-doping sanctions (e.g., the recent ban on the use of trimetazidine and meldonium) that essentially limit the possibilities for sports cardiologists. Therefore, the most grounded exit, from the current position, is the use of metabolitotropic medications, in particular, those on the basis of L-carnitine (gamma-butyrobetaine). The wide spectrum of physiologic and biochemical influence of this substance on organism gives possibility to moderately affect the physical and mental workability of athletes even under the conditions of long-term intense physical loads. The complex action of pharmacological agents on the basis of L-carnitine on organism allows one to use it on all stages of the preparation with high efficiency of the cardioprotective and ergogenic effects. Despite the bans of WADA, sports cardiologist possesses a sufficient pool of pharmacological agents that can ensure the protection of myocardium under conditions of training process and competition and can preserve athlete’s health as well as his/her physical workability.

Keywords: cardioprotectors, cardiomyocyte, sport, physical loads, workability, gamma-butyrobetaine.

Introduction
In connection with a permanent growth in the volume and the intensity of training and competitive loads, the urgent task of sports cardiology is the realization of cardiovascular system, as the basic one, protection, which limits the stimulation of physical workability (Smolenskiy, Mihaylova, 2009), since its dysfunction can become the main reason for a deterioration of athletes’ health and life quality under improper conditions of cardioprotection. Therefore, the searches for efficient and safe cardioprotectors, which would have ability to simultaneously execute namely such double function, are not ceased till now. Namely, such are the pharmacological agents with metabolitotropic character of action. According to the modern classifications, they are referred to the group of direct cardioprotectors, immediately affecting the contractile ability of cardiac muscle by means of the decrease in the expression of influence of negative exo- and endogenic factors on cardiomyocytes.
ischemia, and hampers the formation of a metabolic remodelling (change) of myocard” (Bogush et al., 2015).

The analysis of the pharmacological properties of various groups of medicamental agents allowed one to conclude about the obligatory effects of such substances on at least one metabolic way from the above-mentioned ones with the purpose to attain the antianginal, antihypoxic, and/or anti-ischemic effects (Gavrilova et al., 2007). In cardiology and, in particular, in sports cardiology, the metabolic therapy means usually an improvement of the energy metabolism in cardiac muscle by the means of pharmacological control over the processes of release and transfer of the energy on the level of cardiomyocytes without any influence on the coronary circulation and the systemic hemodynamics (Makarova, 2013).

Unfortunately, the use of cardioprotectors in sport occurs till now, in our opinion (Platonov et al., 2010), and, in agreement with the viewpoints of other researchers (Stephens, Greenhaff, 2009), without any system and without regard for the action application points. Moreover, the list of used drugs is rather short and is mainly reduced to the agents, regulating the ionic balance and the tissue trophicity. Therefore, it is quite understandable that the decision of WADA to forbid the application of such most widely used substances of the cardioprotective direction as trimetazidine (Trimetazidine, Preductal MR, Angiozil-retard), meldonium (Metamax, Midolat, Mildroxyn, Mildronate), Pananginum (seu Asparcamum), ATP-LONG, Cratal, etc.

The metabolic effect of synthetic analogues of the natural heterocyclic compounds - trimetazidine and meldonium - is manifested by the conservation of the energetic potential of mitochondria, renewal of the synthesis of ATP and deceleration of its hydrolysis, support of the ionic equilibrium, and shift of pH inside cells. All this protects tissues from free radicals and potentiates the antioxidant effect by modulating the exchange of lipids (Dambrova et al., 2016). By the example of Mildronate, it was experimentally proved that the polytropic pharmacologic action of such drugs is related to the inhibition of the polyphosphoinositidic system of cellular signalization (Frantsuzova et al., 1997) and, hence, to oxidative and energetic biochemical reactions such as, in the first turn, the synthesis and transport of ATP, assimilation of glucose, and transport of fat acids decreases the damaging action of oxidative stress on the tissue level, including the level of myocardocytes.

In particular, one of the drugs, most widely used in sport prior to the entry into force of the ban of WADA in 2015, was Preductal MR, improving the metabolism in myocardium and neurosensory organs under conditions of hypoxia and ischemia. This drug can prevent a decrease in the intracellular concentration of ATP (due to the conservation of the energetic metabolism of cells) and can decelerate the oxidation of fat acids due to the selective inhibition of long-chain 3-ketoacyl-CoA-thiolase, which favours an increase in the oxidation of glucose and determines the protection of myocardium from the damaging effect of negative factors. The drug decreases the expression of intracellular acidosis, magnitude of changes, occurring in a transmembrane ionic flow under conditions of ischemia, as well as the levels of infiltration and migration of polynuclear

Classification of basic cardioprotectors with direct action

At the present time, we know about 2000 molecules, for which the direct protective mechanism of action on heart was experimentally established. However, the essentially less number of drugs with cardioprotective properties are introduced in the real clinical practice (Zhitnikova, 2012). The mechanisms of action of cardioprotectors are diverse and have many aspects. Therefore, we need to form a clear classification, dividing the pharmacological agents of the given category into sorts by their biological properties and other factors (Chekman et al., 2005).

The pharmacological agents that are referred to the regulators of metabolism in myocardium can be partitioned into several basic subgroups:

1. Agents with action mainly on the energetic processes, among which I mention trimetazidine (Trimetazidine, Preductal MR, Angiozil-retard), meldonium (Metamax, Midolat, Mildroxyn, Mildronate), Pananginum (seu Asparcamum), ATP-LONG, Cratal, etc.

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neutrophils in reperfusive and ischemic tissues of heart and favours a decrease in the size of a lesion focus of myocardium. The cytoprotective effect of trimetazidine is determined by increase in the energetic potential and by decrease in myocardium need for oxygen (Chekman et al., 2009). For sports cardiology, the crucial factors are the abilities of PreductalMR and Angiozil-retard to enhance the coronary reserve by favouring a deceleration of the development of tissue hypoxia, caused by intense physical loads, and to increase the contractile ability of myocardium (Yalyimov et al., 2013). This property of pharmacological agents, on the basis of trimetazidine, is of essential importance for athletes, since they undergo regularly the action of psychological and physical stresses during exercises and competitions. The common side effects after the intake of PreductalMR and Mildronate are rare allergic reactions and violations from the side of digestive organs in the form of sickness, vomiting, and gastralgia. Therefore, the agents, on the basis of trimetazidine, are not recommended to use in the presence of diseases of the digestive tract in anamnesis (gastritis with high acidity, gastroduodenitis, etc.). These drugs should not be taken under violations of the functions of liver and kidneys and by young athletes less than 18 years of age.

I additionally note that, in connection with the hardening of the requirements of WADA, the cardioprotective drugs, forbidden by the class S4 “Hormones and metabolic modulators” (in particular, trimetazidine (PreductalMR)), cannot be used since 2015. Since 2016, meldonium (3-[2,2,2-trimethylhydrazinium] propionate), referred to the structural analogues of γ-butyrobetaine (such as Angiocardil, Vazomag, Metamax, Midolat, Mildroxyn, Mildronate, Capicor, Olvazol, etc.) and its derivatives (in particular, meldonium metonat (the Ukrainian drug Vazopro®)), is forbidden as well.  

2. Cardioprotective anabolic agents, including methyluracil, inosine (Riboxin, Adexor, Dibicor, Inosie-F), potassium orotate, etc. Inosine and pharmacologic agent Riboxin on its basis, which is widely spread in sport, are referred by a clinical-pharmacologic group to the medications, able to improve the metabolism in tissues and, in the first turn, in myocardium under conditions of hypoxia and ischemia. Inosine is a derivative nucleoside of purine, which is a predecessor of ATP. This circumstance defines the biochemical mechanism of inclusion of the drug in reactions of the metabolic protection of myocardium. Penetrating into a cell, it can increase the energetic balance of myocardium, render the antiarrhythmic and antihypoxic actions, and improve the coronary circulation. Inosine also favours the activation of xanthine dehydrogenase, stimulates the production of nucleotides, decreases the aggregation of blood corpuscles by lowering its viscosity, and activates the repairment of tissues (in particular, those of mucous membranes of digestive tract and myocardium).

3. Antioxidant metabolitotropic medications are, probably, the most numerous ones in the group of cardioprotective drugs (Essliver, Lipin, Rhythmocor, Thiotriazolin, ascorbic acid, tocopherol acetate, etc.). The expediency and the efficiency of applications of antioxidants of the natural origin (Panza et al., 2008) and a synthetic one (Cordeiro, 2014) as cardioprotectors were demonstrated in sport long ago. The drugs on the basis of essential fatty acids (Essentiale, Essliver, Lipin, etc.) are hepatoprotectors by their primary designation, since they possess the property to normalize the membranes of liver cells by directly incorporating there (Chekman et al., 2005; 2009). Their cardioprotective action is manifested essentially more weakly, and they have no real practical meaning in sports cardiology. In addition, the use of such pharmacological medications as cardioprotectors is not justified economically due to their high cost and large daily dose (3 capsules 2 times per day) (Platonov et al., 2010).

Presently, the synthetic antioxidant Thiotriazolin (morpholini-methyl-triazolyl-thioacetate) is widely used in the clinic practice in the sphere of sports cardiology. This drug was developed in Ukraine in the 1990s and is characterized by a high cytoprotective activity, irrespective of the tissue type of cells, and by the modulatory action under conditions of the norm and the development of a pathology as a result of the universal mechanism of its action (Dunaev et al., 2002). First of all, the drug positively influences the energy exchange under conditions of ischemia. Due to the activation of a malate-aspartate shunt, it ensures the oxidation-based production of the energy by increasing the concentration of ATP, supplying protons to the transport chain, and intensifying the utilization of reducing pyridinenucleotides and the oxidative carbohydrate metabolism. Thiotriazolin decelerates the creation of active forms of oxygen in bioenergetic reactions, decreases the pathologic
L-carnitine is biologically active substance (by chemical nature, it is an amino acid γ-butyrobetaine), which plays an extremely significant role in the exchange of substances and energy in organism. It is worth to note that the D-stereoisomer of carnitine has no biological activity and is toxic (Ferrari et al., 2004). The main physiological role of L-carnitine is the transport of long-term molecules to mitochondria through the internal membrane of those subcellular structure directly in crystals, where the metabolism of fat acids occurs with the energy release (Pistone et al., 2003). The results of a double blind placebo-controlled study, carried out in Italy in 2007, showed that the use of 2 g of L-carnitine on a daily basis for 6 months by athletes intensified their mental and physical activities. The tested persons noticed the ascension of mood and the enhancement of endurance, workability, and total tonus (Basso et al., 2010).

The deficit of L-carnitine, which is considered a vitamin-kind compound, in organism is usually accompanied by muscle weakness, hypotonia, violation of the functioning of the cardiovascular system, liver, and central nervous system in the form of a fast fatigability, sleepiness, or irritability. The deficit of carnitine is frequently formed especially rapidly in athletes under intense physical loads (Brass Eric, 2000). Since L-carnitine favours the \( \beta \)-oxidation of fat acids in skeletal muscles and, hence, participates in aerobic energy release, it improves the provision of cells with oxygen (Efimova et al., 2002) and is an important component of the optimization of the energy balance and an increase in the total durability of athletes’ organisms. In addition of the activation of the anaerobic metabolism in mitochondria, the mechanisms of cardioprotective action of L-carnitine, according to data of the modern scientific literature, causes a decrease in the toxic influence of free fat acids on a cardiomyocyte (due to the suppression of the processes of free-radical oxidation), the stabilization of the membranes of mitochondria, deceleration of apoptosis (programmed death of a cell), and improvement of the endothelium-dependent vasodilatation and microcirculation (Alvarez de Sotomayor et al., 2007).

In the case of the application of exogenic L-carnitine after the liquidation of ischemia, the cardiomyocytes are switched onto a more advantageous oxidation of free fat acids: they are transported back from cytosol in mitochondria by the carnitine shuttle mechanism (Scott et al., 2016).

4. **Stimulators of pyruvate-dehydrogenase** include, in the first turn, L-carnitine (Elcar, Cardonat) and dichloracetate (due to a sufficiently high toxicity, it is not used practically in sport in the last years).
L-carnitine favour the improvement of detoxication function of liver, synthesis of a protein and glycogen, and more intense splitting of lactic and pyroracemic acids (due to the support of the ratio of the coenzymes CoA/acylCoA) (Skagen et al., 2016). Such L-carnitine influence on athletes makes contribution into a decrease in the excess of lactate in blood and skeletal muscles, which is considered as one of the most significant reasons for the development of fatigue and subsequent overstress, including those of cardiovascular system. Respectively, the application of L-carnitine into athletes allows one, from the theoretical positions, to decrease the share of anaerobic lactate-involving energy release and to increase the contribution of the more efficient aerobic energy production by enhancing the activity of respiratory chain in muscles and the workability under intense physical loads (Balykova et al., 2011).

At present, L-carnitine is widely used in sport as an ergogenic medication in the form of biological active additions with mono- and polycomponent compositions (Arnebia L-carnitine, QNT, Carniplus) (Pandareesh, Anand, 2013) and drugs (Elcar, Cardonat) for representatives of various sports as well as the medicamental agents in sports medicine and cardiology. It was shown that the prescription of L-carnitine (in the form of the drug Elcar) to young athletes such as representatives of gaming and complex-coordination kinds of sport in a dose of 50–75 mg/kg\textsuperscript{-1} in one day for four weeks renders a positive influence on the general self-feeling and a state of cardiovascular system and favours a decrease in the laboratory measured manifestations of myocardium dystrophy, caused by stresses and a physical overload (Balykova et al., 2011). While studying the course influence of L-carnitine (as a dietary addition in a daily dose of 2 g for three weeks) on the activity of marker enzymes in myocardioocytes in athletes, who were training mainly for the development of endurance, the reliable decrease in the share of persons (p=0.006) with hyperenzymemia of the cardiac genesis (MB-fraction of creatine phosphokinase) was determined (Gavriloa, Churganov, 2012).

As a result of the decrease in the concentration of endogenic L-carnitine, \(\gamma\)-butyrobetaine, characterized by vasodilatation properties, is intensively synthesized. Under conditions of hypoxia and ischemia of tissues, the structural analogues of \(\gamma\)-butyrobetaine restore the balance between the supply of oxygen, and its consumption by cells (Skagen et al., 2016) prevent the violations of the transport of ATP and simultaneously activate glycolysis, which occurs without additional consumption of oxygen. The modern athletic training pharmacology positions the structural analogues of \(\gamma\)-butyrobetaine as substances improving life quality of athletes. In other words, we say in this case only about the protective action of meldonium-based drugs rather than about the direct increase in workability.

In most clinical situations in sports cardiology, the metabolitotropic medications play an auxiliary role. But if the violations of the metabolism compose the main pathogenous mechanism, which is demonstrated under the overloading of cardiovascular system under intense long-term physical loads, then namely those medications are the basis of therapy (Balykova et al., 2011). Unfortunately, the broadness of the spectrum and the variety of aspects of the metabolic effects give no possibility to clearly systematize the metabolitotropic and metabolic cardioprotectors. The given class of drugs is very diverse by the chemical structure (composition), the mechanisms of action, the pharmokinetics, and pharmodynamics of separate medicamental agents. Therefore, from our viewpoint, it is quite proper to consider the majority of them in correspondence with a dominant directedness of the action on that or other metabolic link.

In a very generalized form, I would like to present the action application points of basic cardioprotective drugs with metabolic directedness (both forbidden and else allowable) that are really now in use in sports cardiology (Fig.). Unfortunately, as it is seen from the data of Fig., WADA is carrying out the certain policy, aimed at the ban of cardioprotectors in sport, and two most speared of them have been already forbidden.

Under such conditions (I do not discuss the ethicality or non-ethicality of such decisions of WADA in the light of the conservation of health and life of an athlete), sport doctors must use the allowable available arsenal of clinical cardiology, which can render a positive action on functional parameters of heart, its metabolic provision, and the pumping function under conditions of permanently increasing physical loads.
Fig. Action application points of basic metabolic cytocardioprotectors with direct action

REFERENCES


15. Gavrilova, E. A., Sherenkov, A. O., Davydiv, V. V. (2007). Modern ideas of adapting the machine to the

**METABOLINIAI KARDIOPROTEKTORIAI SPORTE: PASKUTINIAI POKYČIAI WADA UŽDRAUSTŲ PREPARATŲ SĄRAŠE (APŽVALGA)**

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**SANTRAUKA**

Pastaruoju metu ypač svarbus sporto farmakologijos ir sporto kardiologijos uždavinyms yra sportininkų širdies ir kraujagyslių sistemos efektyvių apsaugos priemonių paieška. Širdies ir kraujagyslių sistema lema daugelio šakų sportininkų fizinio darbingumo didėjimą, o esant nepakankamai kardioprotekcijai gali tapti pagrindine sveikatos ir gyvenimo kokybės blogėjimo ir netgi staigios mirties priežastimi. Šiais metais tokių medžiagų kasinimo procesas leidžia atitinkamai paveikti sportininkų fizinį ir protinį darbingumą. L karnitino pagrindavo pagamintų farmakologinių priemonių kompleksinis poveikis sudaro pagrindinę pagrindinio darbingumo būklės užtikrinimą, nepaisant WADA draudimų, sporto kardiologai disponuoja pakankamai asortimentu farmakologinių priemonių, apsaugančių nuo sunkių treniruočių ir varžybų, padedančių išsaugoti sportininko sveikatą ir jo fizinį darbingumą.

**Raktąžodžiai:** kardioprotektoriai, kardiomiocitas, sportas, fiziniai krūviai, darbingumas, gama butirobetainas.