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Review Article

Clinical Benefits of Metabolic Therapy of Ischemic Heart Disease with L-Arginine Supplementation

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Abstract: Ischemic heart disease (IHD) - one of the major human diseases, which account for a significant portion of all cardiovascular deaths of the world. In spite of recent decrease in cardiovascular mortality, IHD remains the leading cause of death in the developed world. The application of surgical and percutaneous myocardial revascularization promised to be a safe and effective method to control symptoms and to improve prognosis in this disease. However, clinical results do not match these expectations: most revascularized patients remain symptomatic, a large fraction continues to require antianginal medications, and about 10% suffer of either death or myocardial infarction within 2.5 years. In the meanwhile, the clinical variety of IHD is rapidly changing, with a growing prevailing of elderly patients, diabetics, and heart failure patients. Pharmacologic intervention of cardiac energy metabolism, by enhancing the synthesis of nitric oxide (NO) via administration of L-arginine, appears as an innovative and attractive addition to treatment of IHD patients.

Keywords: Angina, cardiac energy metabolism, ischemic heart disease, L-arginine

Introduction

Stable angina pectoris is the initial manifestation of ischemic heart disease in about half of patients. It is difficult to estimate the number of patients with chest pain, but it is measured in millions of patients. For instance, in the United States, the number of patients with stable angina can be estimated as 16.5 million [1]. If we include in this estimate of all industrialized countries, the numbers become incredibly enormous.

Ischemic heart disease is significant, not only due to its prevalence, but also because of its associated morbidity and mortality. Despite the well documented recent decrease in cardiovascular mortality, ischemic heart disease remains the leading single cause of death in the western world. A course of IHD is often associated with a high risk of sudden death, acute myocardial infarction, leading to cardiac remodeling, heart failure and as a result of a sharp decline in the life quality of patients. Modern tendency in pharmacotherapy of CHD mainly involve the use of so-called "hemodynamic" approach, in order to impact on myocardial oxygen demand, the oxygen supply in the ischemic zone, either by exposure to the diameter of the vessel concerned, a vascular wall, or on blood rheology. However, drugs that influence on the hemodynamic parameters are effective mainly when it comes to preventing angina attacks, but do not actually protect myocardial cells from metabolic alterations that form the basis of progression of the disease.

Myocardial revascularization: destroyed hopes

Enormous hopes were inspired by the introduction of surgical and percutaneous myocardial revascularization techniques that promised to be safe and effective alternatives for patients resistant to optimal pharmacological therapy. Abovementioned techniques rapidly gained huge popularity, but, unfortunately, they do not seem to have lived up to initial expectations, in either the short or the long term. About 30% of patients cannot return to work after coronary revascularization and 15-20% of patients rate their own health as fair or poor in spite of revascularization, according to the data from the Bypass Angioplasty Revascularization Investigation [2].

Two more recent studies, one comparing clinical outcomes of patients treated medically with those of patients who underwent revascularization [3], and another comparing percutaneous transluminal coronary angioplasty and coronary artery bypass grafting [4], provided additional data on long-term prognosis, and cast additional doubts on the effective benefits of these procedures in patients with chronic ischemic heart disease. The first of these studies,

although indicating that revascularized patients do better than patients treated medically, revealed that, at follow-up, many revascularized patients complain of angina, that most continue to receive antianginal medication, and that about 10% suffered either death or myocardial infarction within 2.5 years [3]. The second study, which was designed as a comparison between state-of-the-art surgical revascularization and percutaneous revascularization in multivessel coronary disease, proved the two strategies to be equally effective and safe. However, within 1 year, 10% of patients who had undergone revascularization had suffered a major adverse cardiac event, regardless of the procedure received [4].

It can be concluded that, despite increasing pharmacological and mechanical therapy options, IHD continues to be associated with considerable patient mortality and morbidity. Obviously, this also translates in an enormous economic burden. The estimates of the direct and indirect costs associated with chronic stable angina are measured in huge numbers. Given the epidemiologic and economic magnitude of the problem, the need for more effective treatment is self-evident.

The various clinical parameters of ischemic heart disease: treatment implication

According to the current guidelines, the treatment of ischemic heart disease has progressively widened to include risk-factor modification, patient education, and pharmacologic therapy. The pharmacologic agents includes two categories:

(1) Classic antianginal agents such as beta-blockers, calcium antagonists, and nitrates.

(2) Drugs for secondary prevention, such as aspirin, clopidogrel, statins, and angiotensin-converting enzyme inhibitors.

Tailoring therapy to individual needs has become even more challenging because of the marked changes occurring in the clinical profile of patients with chronic ischemic heart disease. As compared with those of the past, today's patients tend to be older, to have undergone revascularization procedures, and to present frequently with associated illnesses, including heart failure and diabetes.

Congestive heart failure is the single most common medical cause for admission to hospital, and is the leading cause of death in industrialized countries. Recent therapeutic advances have improved symptoms and prolonged survival; nevertheless, prognosis remains poor, and rates of re-admission to hospital high. Registry data suggest that the prognosis of patients admitted to hospital with heart failure is even worse than is indicated by clinical trials, with a median survival time of 1.5 years and a mortality rate of 50% within 1 year [5].

Diabetes mellitus is closely associated with coronary heart disease. The prevalence of coronary artery disease increases from the 2-4% found in the general population to a figure as high as 55% among adult patients with diabetes [6].

The prevalence of coronary artery disease also increases rapidly with advancing age, affecting approximately 10% of the population aged over 70 years, with one study reporting an incidence of up to 25% in patients older than 75 years. Elderly patients with ischemic heart disease would appear to be a high-risk subset of patients who may derive substantial benefit from appropriate therapy. Congestive heart failure affects approximately 10% of those over 80 years old and carries a uniformly less good prognosis, regardless of the level of cardiac dysfunction.

The clinical profile of chronic ischemic heart disease is thus characterized by a growing prevalence of elderly patients, diabetic individuals, revascularized patients, and patients with heart failure. These conditions, together with sex, are relevant to patient compliance, drug efficacy, drug safety, and other factors that contribute to the success or otherwise of therapy.

Role of endothelial nitric oxide (NO) in the pathogenesis of myocardial ischemia

There is a strong evidence for involvement of endothelial factors in the development and progression of cardiovascular disease, including atherosclerosis, which is the underlying cause coronary artery disease [7]. Due to intense and diverse research it became apparent that the endothelium is a complex metabolic system and is actively functioning regulator of vascular tone and other physiological processes.. [8] The most important function of the endothelium is considered the regulation of vascular tone. It was found that most vasoregulating substances act on the vascular wall by means of a universal mechanism - synthesis of NO by the endothelium, which is formed by the NO-synthase from L-arginine. It activates guanylate cyclase in smooth muscle cells, stimulating the synthesis of cyclic guanosine monophosphate (c-GMP), which causes vascular relaxation, inhibition of activity of platelet and macrophages.

Vasoprotective function of NO, apart from regulation of vascular tone, is in the release of vasoactive mediators, inhibiting leukocyte adhesion to the vascular wall, which occurs by the inhibition of the expression of molecules' adhesion [9]. Mechanisms of anti-proliferative effect of NO are in its involvement in vascular remodeling by inhibiting mitogenesis and proliferation of smooth muscle cells under endothelium and fibroblasts. In addition, NO inhibits the expression of pro-inflammatory genes of vascular wall. Its participation is also important in the suppression of

activation, adhesion and aggregation of platelets by increasing the c-GMP level in them [9].

Thus, NO has a number of positive effects, the use of which may be useful in the treatment of patients with chronic ischemic heart disease:

• vasodilation;
• reduction of cell proliferation;
• reduced activation and adhesion of leukocyte to the endothelium;
• reducing platelet adhesion and aggregation with prevention of thrombosis;
• suppression of the synthesis of endothelin-1 - a powerful endogenous vasoconstrictor and stimulator of proliferation and migration of vascular myocytes.

Optimization of cardiac energy metabolism: focus on L-arginine

Arginine is one of the 20 amino acids constituting natural proteins, as well as donor and natural carrier of nitrogen, which supplies system of enzymes synthesizing NO. Use of L-arginine, a precursor of NO, justified in the treatment of several cardiovascular diseases. Currently, only the L-arginine, testosterone and estrogen approved by the Food and Drug Administration (FDA) for the treatment of refractory angina [10], which opens up prospects for its use in patients with chronic ischemic heart disease. L-arginine has found application as a mean to treat a variety of diseases with a primary vascular lesion. For example, in the Department of Atherosclerosis and Chronic ischemic heart disease of the National Scientific Centre "Institute of Cardiology named after academician N.D. Strazhesko" of Ukraine during the 8-week patients received L-arginine at a dose of 6.0 g/day orally. This new formulation has been shown to improve anti-anginal efficacy, to enhance anti-ischemic properties in ischemic patients with ventricular dysfunction, to exert a cardioprotective action in patients undergoing coronary artery bypass grafting or percutaneous coronary intervention, and to be of particular value in high-risk subgroups such as the elderly or patients with diabetes [10].

Further researches should be considered with higher dosages, longer supplementing durations, or combined with other supplements.

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