

Clinical benefits of a metabolic approach in the treatment of ischemic heart disease: focus on Vastarel MR

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Abstract

Despite the recent decline in cardiovascular mortality, Ischemic Heart Disease (IHD) remains the leading single cause of death in the western world. Great hopes were provoked by the introduction of surgical and percutaneous myocardial revascularization techniques that promised to be a safe and effective alternative to control symptoms and to improve prognosis in these patients. Unfortunately, clinical results do not correspond to 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 meantime, the clinical profile of chronic ischemic heart disease is rapidly changing, with a growing prevalence of elderly patients, diabetics, and heart failure patients. These associate conditions are relevant to patients compliance, to drug efficacy and safety, and may contribute to the failure of classic therapeutic strategies in so many instances. Pharmacologic manipulation of cardiac energy metabolism, by partial inhibition of free fatty acid oxydation by trimetazidine appears as an innovative and attractive alternative to treat patients with chronic IHD.

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Introduction

Chronic stable angina is the initial manifestation of ischemic heart disease in approximately 50% of patients. It is difficult to estimate the number of patients with chronic chest pain syndromes, but clearly it is measured in the millions. In the USA, the reported annual incidence of angina is 213/100 000 population older than 30 years, and about 50% of patients presenting at hospital with myocardial infarction have preceding angina. Given that, in the USA, there are 1 100 000 patients with myocardial infarction each year, and about 50% of these (550 000) survive until

admission to hospital, it can be estimated that there are 30 patients with stable angina for every patient with infarction who is admitted to hospital. As a result, the number of patients with stable angina in the USA can be estimated as $30 \times 550\,000$, or 16 500 000 [1]. If we include in this estimation all industrialized countries, the figures become incredibly high.

Ischemic heart disease is important, not only because of its prevalence, but also because of its associated morbidity and mortality. Despite the well documented recent decline in cardiovascular mortality, ischemic heart disease remains the leading single cause of death in the western world. The morbidity associated with

this disease is also considerable: each year, millions of patients experience myocardial infarction, or are admitted to hospital for unstable angina. Beyond the need for admission to hospital, many patients with chronic chest pain syndromes are temporarily unable to perform normal activities for hours or days, thereby experiencing a reduced quality of life.

Myocardial revascularization: promise unfulfilled

Great hopes were inspired by the introduction of surgical and percutaneous myocardial revascularization techniques that promised to be safe and effective alternatives for the control of symptoms in patients resistant to optimal medical therapy. These techniques rapidly gained great popularity, but, unfortunately, they do not seem to have lived up to initial expectations, in either the short or the long term. According to the data from the Bypass Angioplasty Revascularization Investigation [2], about 30% of patients never return to work after coronary revascularization, and 15–20% of patients rate their own health as fair or poor despite revascularization.

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 treatment options, ischemic heart disease 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 tens of billions of dollars. Given the epidemiologic and economic magnitude of the problem, the need for more effective therapies is self-evident.

The broad clinical profile of chronic ischemic heart disease: implications for treatment

On the basis of current guidelines, the management of ischemic heart disease has progressively broadened to include risk-factor modification, patient education, and pharmacologic therapy. The pharmacologic agents fall into two categories:

- (1) Classic antianginal agents such as β -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 and race, are relevant to patient compliance, drug efficacy, drug safety, and

other factors that contribute to the success or otherwise of therapy.

Role of cardiac energy metabolism in the pathogenesis of myocardial ischemia

Significant progress has been made in recent years in understanding the role of cardiac energy metabolism in the pathogenesis of myocardial ischemia, and the better understanding of metabolic derangements associated with ischemia and reperfusion is being translated into innovative therapeutic approaches [7].

In normoxic conditions, the healthy heart derives most of its energy from the free fatty acid pathway that accounts for approximately two-thirds of energy (ATP) production, other sources of energy being derived from glucose oxidation and lactate. In hypoxic conditions, myocardial cells respond to mild-to-moderate ischemia by accelerating glucose uptake to generate sufficient ATP to maintain ionic gradients and calcium homeostasis. Severe ischemia rapidly induces an imbalance between the coronary blood supply and the requirement of cardiac tissue for oxygen, producing functional, metabolic, and morphological alterations to the myocardium, including arrhythmia, failure of contractility, and electrophysiological abnormalities. At the cellular level, glucose uptake is decreased and conversion to lactate is increased, lactate uptake by the heart is switched to lactate production, and pyruvate is mostly transformed into lactate, thus increasing cell acidosis. The free fatty acid pathway is slowed down, resulting in reduced production of ATP. These various forms of metabolic damage lead to a disruption of cell homeostasis, alterations in membrane structure, and, ultimately, cell death [7].

Given this pathophysiologic background, and given the failure of classic hemodynamic agents in many patients, it seems logical to consider the pharmacologic manipulation of cardiac energy metabolism as an alternative therapeutic option for patients with myocardial ischemia.

Optimization of cardiac energy metabolism: trimetazidine

Optimization of cardiac energy metabolism is based on promoting cardiac glucose oxidation. This has been proved to enhance the function of the heart and

to protect myocardial tissues against ischemia-reperfusion injury. Stimulation of myocardial glucose oxidation can be achieved either directly or indirectly through inhibition of fatty acid β -oxidation. A new class of metabolic agents, known as the 3-ketoacyl coenzyme A thiolase (3-KAT) inhibitors, is able to elicit an increase in glucose and lactate combustion secondary to partial inhibition of fatty acid oxidation, achieving demonstrable clinical benefits in patients with ischemic heart disease [8].

A modified-release formulation of the first 3-KAT inhibitor, trimetazidine MR, is now available for clinical use. Its optimized pharmacologic profile has made a twice-daily administration regimen possible, and provides round-the-clock cardioprotection. 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 [8]. ■

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