The rationale of metabolic treatment in ischaemic heart disease

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Abstract

Ischaemic heart disease remains the leading cause of death in the western world and jeopardize quality of life in millions people. PTCA plus medical therapy can control symptoms in most patients with stable angina. However, many trials consistently report persistance of angina and/or ischemia in one third of patients. Awareness of the limited benefit from standard treatments is increasing and stimulates the search for innovative approaches. Improved understanding of cardiac energy metabolism offers promising alternatives and new solution to the problem. A partial shift from free fatty acid to glucose oxidations has been shown to improve cardiac efficiency and to increase tolerance to ischaemia. Large clinical trias based on metabolic agents are warranted.

Key words: ischaemic heart disease, PTCA, stable angina.

Introduction

Chronic stable angina is the initial manifestation of ischaemic heart disease in approximately one half of patients. It is difficult to estimate the number of patients worldwide with chronic chest pain syndromes, but clearly it is in the millions.

In Europe stable angina affects 2-5% of middle-aged men and 11-20% of elderly men. In more than half the cases, anginal symptoms limit daily activities, impair quality of life and may lead to premature retirement from work. A decline in the incidence of coronary artery disease has been seen in most industrialized countries, which has been associated with improved prognosis and increased survival of acute episodes. This, together with the aging of the population, results in an increased prevalence of angina pectoris, as confirmed by nationwide surveys.

In the United States, the reported annual incidence of angina is 213 per 100 000 of the population over 30 years old, and about one half of patients presenting at hospital with myocardial infarction (MI) have preceding angina. Given that in the United States there are 1 100 000 patients with MI each year and about half of these (550 000) survive until hospitalization, it can be estimated that there are 30 patients with stable angina for every patient with infarction who is hospitalized [1]. If we extend this estimation to all industrialized countries, the figures become incredibly high.

Despite the recent decline in cardiovascular mortality, ischaemic 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 have an MI, or are hospitalized for unstable angina. Beyond the need for hospitalization, 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.

Based on current guidelines, the management of ischaemic heart disease has progressively broadened to include risk factor modification, patient education, and pharmacological therapy [2]. The latter includes (i) classic antianginal agents such as β-blockers, calcium antagonists, and nitrates, and (ii) drugs for secondary prevention, such as aspirin, clopidogrel, statins, and angiotensin-converting enzyme inhibitors. Tailoring therapy to individual needs has become progressively more challenging because of the marked changes in the clinical profile of patients with chronic ischaemic heart disease. Compared with the past, today's patients tend to be older, to have undergone revascularization procedures, and to frequently have associated illnesses, including heart failure and diabetes.

Therapy of chronic ischaemic syndromes: a settled question?

In recent years, scientific institutions and the pharmaceutical industry have mostly focused on acute coronary syndromes. Thanks to their combined efforts, substantial progress has been made in understanding the mechanisms precipitating acute coronary events. Treatment strategies have been designed that take into consideration both the risk profile of the patient and the resources available in the receiving institution. As a result of these efforts a reduction in mortality and morbidity for ACS has been reported in recent reviews.

Less attention has been paid to chronic ischaemic syndromes, possibly because these conditions are perceived by most cardiologists as a settled problem. However, though several drugs including β-blockers, Ca-channel blockers, and nitrates are effective in controlling anginal symptoms, there is no conclusive evidence that these agents reduce morbidity and mortality.

As stated by C. Pepine, *...from a cohort of patients with chronic stable angina, 64% take more than 1 cardiovascular drug. Despite that, effort angina is present in more than 90% of patients.* [3]. A possible reason why the therapeutic challenge of chronic angina is somehow underestimated by cardiologists is that most patients with angina that are refractory to medical treatment are eventually referred for myocardial revascularization. Revascularization procedures are expected to improve symptoms and prevent death and myocardial infarction. Unfortunately, available data do not support this common belief.

PTCA and medical treatment for non-acute coronary artery disease

Surgical and percutaneous revascularization procedures are performed in thousands of patients every year, based on the implicit judgement that the benefit of the procedure in terms of survival or decreased morbidity outweigh the risks.

Unfortunately, an objective evaluation of available evidence does not provide strong support for this popular opinion.

According to the data from the Bypass Angioplasty Revascularization Investigation, about 30% of patients never return to work following coronary revascularization, and 15 to 20% of patients rated their own health fair or poor despite revascularization [4].

The long-term effects of percutaneous coronary intervention in comparison with an alternative policy of continued medical treatment have been recently reported (RITA-2). After a median seven-year follow-up, death or myocardial infarction occurred in 14.5% of PTCA patients and 12.3% of medical patients. An initial policy of PTCA was associated with a significant improvement of anginal symptoms and exercise tolerance. However, prevalence of angina remained elevated in both groups, with 70 and 83% of PTCA and medical patients, respectively, receiving at least one anti-anginal drug at five years. Treatment differences narrowed over time [5].

A meta-analysis of randomized controlled trials comparing PTCA with medical treatment for non-acute coronary heart disease confirms that PTCA may lead to a reduction of angina in some patients, though the magnitude of the effects varies considerably, and may lead to an increase in coronary bypass grafting, and is unlikely to reduce non-fatal myocardial infarction, death, or the need for further angioplasty [6].

The clinical relevance of these conclusions may be limited by the recent advances in both medical therapy and revascularizations techniques.

The clinical outcomes of patients treated medically after coronary angiography, and sent for revascularization, have been re-evaluated recently [7]. Medically treated patients reported a higher mortality and a higher prevalence of angina at follow-up than revascularized patients. Benefits of revascularization were found to be directly related to the appropriateness of indications. At 12 months of follow-up, 59% of patients that had been maintained on medical therapy still had angina.

Surprisingly enough, angina was also present in 52% of patients that had undergone PTCA and in 40% of patients that received a CABG [7].

At 2.5 years of follow-up, death from any cause or nonfatal myocardial infarction occurred in 17% of patients maintained on medical therapy. However, also 12% of PTCA patients and 8%

of CABG patients had either died or suffered a non-fatal myocardial infarction at 2.5 years [7].

These data confirm that revascularization procedures, when appropriately performed, improve symptoms and prognosis in ischaemic patients. However, this prospective study clearly demonstrates that a substantial portion of patients does remain symptomatic and at risk for major adverse cardiac events following a revascularization procedure.

This prospective study was conducted in the UK and the results may reflect the practice of cardiology in that country and may not apply to other geographical areas with different regulations and different therapeutic strategies.

However, these rather disappointing conclusions have been fully confirmed by a prospective study that recruited patients in Western Europe, South America, and Australia [8]. The purpose of this study was to compare the relative benefits of bypass surgery and percutaneous intervention in patients with multivessel disease potentially amenable to stent implantation. A total of 1205 patients were randomly assigned to undergo either PTCA and stent implantation or bypass surgery with arterial conduits.

At one year no significant difference was found in the rates of death, stroke, or myocardial infarction between the two groups. The authors concluded that the two strategies are equally safe and effective in multivessel coronary artery disease [8].

However, at 12 months after the revascularization procedure, only 19.1% in the stenting group and 38.4% in the surgery group were free of angina and antianginal medications. Moreover, 10.4% of patients in the stenting group and 9.7% in the surgery group had suffered major adverse cardiac events, including death, stroke, and myocardial infarction [8].

So, the current evidence concerning the use of medical therapy and PTCA in stable CAD allows us to draw the following conclusions [9]:

1. PTCA of flow-limiting stenosis in chronic CAD does not reduce the rate of subsequent MI or mortality.
2. PTCA results in superior symptomatic relief of angina and improved exercise tolerance compared with medical therapy, but the difference narrows with time.
3. Only a minority of patients are free from angina and anti-anginal medications after a revascularization procedure.
4. Following a revascularization procedure for chronic stable angina, most patients complain of "persistent" angina-ischaemia and need anti-anginal medications.

Pathogenic mechanisms of "persistent" angina

Several mechanisms may be considered to explain the persistence of angina/ischaemia after a revascularization procedure, including incomplete revascularization, graft/PTCA failure, and disease progression in native coronary arteries.

Incomplete revascularization may be a planned choice in patients with acute coronary syndromes and multivessel coronary disease. Under these circumstances, most operators limit treatment to the culprit lesion. Incomplete revascularization may be inevitable in chronic patients with obstructions not amenable to dilation, such as lesions in small vessels or in the distal portion of larger vessels.

But it appears unlikely for incomplete revascularization to have contributed to any significant extent to the results of the ART study, where patients were carefully selected for being amenable to multivessel revascularization with either technique.

Graft or PTCA failure is today a rare occurrence, both techniques claiming success rates close to 100%. In the ART study, 99% of the patients in the stenting group and 96% in the surgery group received the assigned treatment.

Disease progression in native coronary arteries has been observed during the time interval between the diagnostic angio and the PTCA procedure as well as following bypass operation. Reported rates of disease progression, however, are too low to explain the prevalence of persistent angina early after the procedure.

So, even considering the additive effects of all possible pathogenic mechanisms, it remains difficult to explain why so many patients suffer from persistent angina after the removal of all significant coronary obstructions, that is after the removal of the putative cause of ischaemia.

The unexpected prevalence of angina after the removal of the obstructions in the major coronary branches strongly suggests that additional mechanisms, unrelated to the atherosclerotic plaque, may contribute to the pathogenesis of ischaemia. Microvascular dysfunction may play a prominent role in this context [10, 11].

Persistent angina: clinical relevance and treatment strategies

Direct data on the prevalence of persistent angina are not available. The follow-up data of large intervention trials in CAD suggest the prevalence of persistent angina to be very high and the clinical relevance of this problem to be of great magnitude. In fact, considering that the early symptomatic benefit achieved with coronary revascularization tends to attenuate with time and that eventually all patients become equally symptomatic again, regardless of the treatment received, the estimates of persistent angina tend to become close to the estimates of chronic angina.

This observation stimulates a number of challenging questions: how to deal with persistent

angina in patients that have already used the PTCA/CABG option? In the era of evidence-based medicine, which are the drugs of choice to treat angina in revascularized patients?

Most available drugs have been developed in order to counteract the haemodynamic effects of a flow-limiting stenosis and their efficacy has been attributed to the capacity to increase coronary blood flow or to decrease myocardial oxygen demand in the presence of reduced coronary flow reserve. None of these agents has been proved to be effective when the flow-limiting stenosis has been removed. Nevertheless, most patients are prescribed the same agents they were given when the coronary obstructions were present.

As soon as the cardiological community fully realizes the clinical relevance of "persistent" angina, the inadequacy of current approaches will be apparent and the search for innovative agents will receive a strong push.

Innovative approaches to manage myocardial ischaemia: the metabolic approach

Significant progress has been made in recent years in understanding the role of cardiac energy metabolism in the pathogenesis of myocardial ischaemia. A better understanding of the metabolic derangements associated with ischaemia and reperfusion is translating into new therapeutic proposals [12].

The healthy heart derives most of its energy under normoxic conditions from the free fatty acid pathway that accounts for approximately two thirds of energy (adenosine triphosphate [ATP]) production, the other source of energy being derived from glucose oxidation and lactate.

In hypoxic conditions, myocardial cells respond to mild to moderate ischaemia by accelerating glucose uptake to generate sufficient ATP in order to maintain ionic gradients and calcium homeostasis. Severe ischaemia rapidly induces an imbalance between the requirement of cardiac tissue for oxygen and coronary blood supply, resulting in functional, metabolic, and morphological alteration of the myocardium, including arrhythmias, contractile failure, 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, thereby increasing cell acidosis. The free fatty acid pathway is slowed down, resulting in less ATP production. These metabolic changes lead to disruption of cell homeostasis, alterations in membrane structure, and ultimately cell death. Given this pathophysiological background and the failure of classic haemodynamic agents in many patients, it seems logical to consider pharmacological manipulation of cardiac energy metabolism as an alternative therapeutic option. Optimization of cardiac energy metabolism is based on promoting cardiac glucose oxidation. This has been proved to enhance cardiac function and protect myocardial tissue against ischaemia-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, producing demonstrated clinical benefits in patients with ischaemic heart disease [13].

The metabolic approach to treating ischaemic heart disease is not new: 90 years ago the observation was made that chest pain could be relieved by administration of sugar to patients with heart disease. In the late 1960s and the 1970s the use of metabolic therapies for treating ischaemic myocardium received a great deal of attention following the observation that an infusion of glucose, insulin and potassium (GIK) reduced ventricular arrhythmias and increased survival following a myocardial infarction. During this period Oliver and co-workers developed the concept that suppression of circulating plasma non-esterified fatty acids, and thus myocardial fatty acid uptake and oxidation, reduced ischaemic damage and ventricular arrhythmias during acute myocardial infarction or exercise-induced angina. This concept was taken further in the 1980s with the demonstration that direct inhibition of fatty acid transport into the mitochondria with oxfenicine increased glucose oxidation and decreased lactate production and resulted in symptom relief in patients with stable angina.

The greatest progress in the use of metabolic therapy has come in the last 15 years with the advent of direct inhibitors of myocardial fatty acid oxidation, specifically trimetazidine and ranolazine, for the treatment of chronic stable angina pectoris [13]. Trimetazidine has been the first and, for many years, the only registered drug in this class, and is available in over 80 countries worldwide. Ranolazine has been recently introduced, and has proved effective in two large-scale Phase III clinical trials. In double-blind placebo-controlled trials, trimetazidine significantly improved symptom-limited exercise performance in stable angina patients when used either as monotherapy or in combination with β-blockers, or Ca^{2+} channel antagonists.

In conclusions at variance with classic "haemodynamic" agents, "metabolic" agents have no direct haemodynamic, inotropic, or chronotropic effect and are expected to directly interfere with cardiac energy metabolism. Given this mechanism of action they appear to be the most promising strategy to treat angina when it is no longer related to the presence of a coronary obstruction.

Large clinical trials testing the efficacy of metabolic agents in persistent angina are urgently needed in order to confirm this promising hypothesis and to include these drugs in the guidelines for the treatment of persistent angina or any form of angina unrelated to epicardial vessel obstruction.

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