

Persistent angina

Mario Marzilli, Marta Focardi, Silvia Affinito, Eugenia Capati and Rossella Urselli
Postgraduate School of Cardiology, University of Siena, Italy

Correspondence: Dr M. Marzilli, Postgraduate School of Cardiology,
University of Siena, Policlinico Le Scotte, Viale Bracci, 53100 Siena, Italy.
Tel: +39 0577 585375, +39 0577 585374; fax: +39 0577 23112; e-mail: marzilli@unisi.it

Abstract

We are witnessing an exponential increase in the use of percutaneous transluminal coronary angioplasty (PTCA) for the treatment of coronary heart disease. Given that available evidence does not support a significant reduction of morbidity or mortality after PTCA, the widespread use of revascularization procedures is based on the assumption of a superior symptomatic relief of angina and on improved exercise tolerance. Unfortunately, randomized controlled trials suggest that symptomatic relief after PTCA may be partial, and limited in time. Several studies have shown that patients may remain symptomatic for angina even after removal of coronary obstructions. This observation challenges the assumption that coronary stenosis is the only cause of angina and calls for innovative therapeutic approaches, independent of the classic agents developed to counteract the adverse effects of flow-limiting coronary obstructions.

■ *Heart Metab.* 2006;31:8–12.

Keywords: Persistent angina, percutaneous transluminal coronary angioplasty, coronary stenosis, randomised intervention treatment of angina trial, arterial revascularization therapy study

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 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. In the USA, the reported annual incidence of angina is 213 per 100 000 of the population older than 30 years, and about 50% of patients presenting at hospital with myocardial infarction have preceding angina. In the USA, it can be estimated that there are 30 patients with stable angina for every patient with infarction who is admitted to hospital [1].

On the basis of current guidelines, the management of ischemic heart disease has progressively broadened to include risk factor modification, patient education,

pharmacological therapy, and revascularization procedures [2].

Tailoring treatment to individual needs has become progressively more challenging because of the marked changes in the clinical profile of patients with chronic ischemic heart disease. Compared with the past, today's patients tend to be older, to have undergone revascularization procedures, and frequently to have associated illnesses, including heart failure and diabetes. Most patients are initially prescribed a combination of drugs, including β -blockers, calcium channel blockers, and nitrates. However, 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].

Patients 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.

Percutaneous transluminal coronary angioplasty and medical treatment for non acute coronary artery disease

Surgical and percutaneous revascularization procedures are performed in thousands of patients every year, on the basis of the implicit judgment that the benefit of the procedure in terms of survival or decreased morbidity outweighs the risks. Unfortunately, an objective evaluation of available evidence does not support this popular opinion.

According to the data from the Bypass Angioplasty Revascularization Investigation, about 30% of patients never return to work after coronary revascularization, and 15–20% 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 recently been reported in the Second Randomised Intervention Treatment of Angina Trial [5]. After a median 7 years of follow-up, death or myocardial infarction occurred in 14.5% of patients who had undergone percutaneous transluminal coronary angioplasty (PTCA) and in 12.3% of medical patients. An initial policy of PTCA was associated with a significant improvement in anginal symptoms and exercise tolerance. However, prevalence of angina remained increased in both groups, with 70% and 83% of PTCA and medical patients, respectively, receiving at least one antianginal drug at 5 years. Outcome differences narrowed over time, as shown in *Figure 1* [5].

A meta-analysis of randomized controlled trials comparing PTCA with medical treatment for non acute coronary heart disease confirmed that PTCA may lead to a reduction in angina, although the

magnitude of the effects varies considerably, 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 treatments and revascularizations techniques.

The clinical outcomes of patients treated medically after coronary angiography and sent for revascularization have been re-evaluated recently [7]. In medically treated patients, a greater mortality and greater prevalence of angina at follow-up were reported compared with those in patients who underwent revascularization. Benefits of revascularization were found to be directly related to the appropriateness of indications. At 12 months of follow-up, 59% of patients who had been maintained on medical therapy still had angina. Surprisingly enough, angina was also present in 52% of patients who had undergone PTCA and in 40% of those who had undergone CABG [7]. At 2.5 years of follow-up, death from any cause or non fatal myocardial infarction occurred in 17% of patients maintained on medical therapy. However, in addition, 12% of patients who underwent PTCA and 8% of those who underwent CABG had either died or suffered a non fatal myocardial infarction at 2.5 years [7]. The findings of this prospective study thus confirm that a substantial proportion of patients do remain symptomatic and at risk for major adverse cardiac events after a revascularization procedure.

Similar observations were reported in a prospective study that recruited patients in Western Europe, South America, and Australia [8]. The purpose of the study was to compare the relative benefits of bypass surgery and percutaneous intervention in

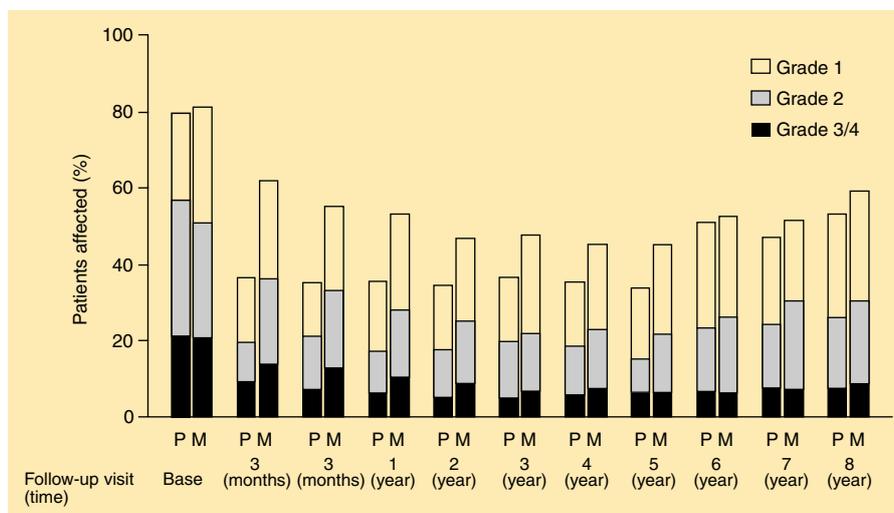


Figure 1. Distribution of grades of angina pectoris in patients undergoing percutaneous transluminal coronary angioplasty (P) or medical treatment (M) for angina pectoris, at baseline before the intervention (Base) and during follow-up. (From Henderson et al [5] with permission.)

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 1 year, no significant difference between the two groups was found in the rates of death, stroke, or myocardial infarction (Figure 2). The authors concluded that the two strategies are equally safe and effective in multivessel coronary artery disease [8]. However, at 12 months, 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].

Current evidence [9] therefore allows us to draw the conclusions that PTCA of flow-limiting stenosis in chronic coronary artery disease does not reduce the rate of subsequent myocardial infarction or mortality, and that PTCA results in superior symptomatic relief of angina and improved exercise tolerance compared with medical therapy, but the difference narrows with time. Only a minority of patients are free from angina and antianginal medications after a revascularization procedure.

Pathogenetic mechanisms of “persistent” angina

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

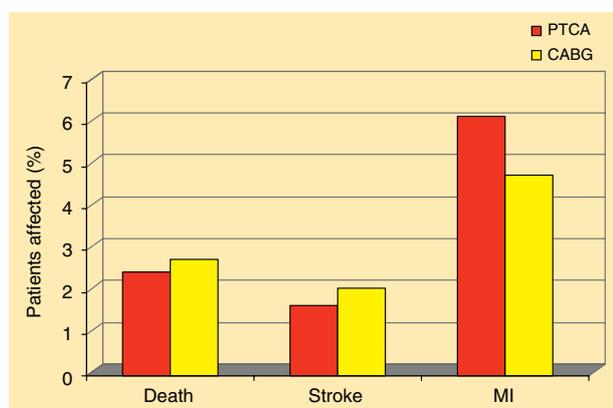


Figure 2. Comparison of the clinical endpoints in patients undergoing percutaneous coronary intervention (percutaneous transluminal coronary angioplasty, PTCA) or coronary artery bypass grafting (CABG) because of multivessel disease. MI, myocardial infarction. (Data from Serruys et al [8].)

Incomplete revascularization may be a planned choice in patients with acute coronary syndromes and multivessel coronary disease. Under several circumstances, operators may find it appropriate to limit treatment to the culprit lesion. Incomplete revascularization may be inevitable in patients with chronic disease and obstructions not amenable to dilatation, such as lesions in small vessels or in the distal portion of larger vessels. However, it appears unlikely that incomplete revascularization has contributed, to any significant extent, to the findings of the Arterial Revascularization Therapy Study (ARTS), in which patients were carefully selected for being amenable to multivessel revascularization with either technique. Graft or PTCA failure is certainly possible, but nowadays is a relatively rare occurrence, both techniques claiming success rates close to 100%. In ARTS, 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 both during the time interval between the diagnostic angiogram and the PTCA procedure, and after bypass operation. Reported rates of disease progression, however, are far too low to explain the prevalence of persistent angina early after the procedure, which can be estimated as being close to 33% of patients who have undergone revascularization.

Thus, even considering the additive effects of several pathogenetic mechanisms, it remains difficult to explain the observation that so many patients suffer from persistent angina after the removal of significant coronary obstructions – that is, after the removal of the putative cause of ischemia. This unexpected prevalence of angina after “successful” revascularization strongly supports the hypothesis that mechanisms unrelated to epicardial coronary artery obstructions contribute to the pathogenesis of ischemia. Microvascular dysfunction may be one of the mechanisms having 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 from large intervention trials in coronary artery disease 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, patients become symptomatic again

regardless of the treatment received, the estimates of persistent angina tend to get close to the estimates of chronic angina.

This observation stimulates some challenging questions. How should one deal with persistent angina in patients in whom the PTCA/CABG options have already tried? In this era of evidence-based medicine, which are the drugs of choice for the treatment of angina in patients who have undergone revascularization?

Most available drugs have been developed in order to counteract the hemodynamic effects of a flow-limiting stenosis and their efficacy has been attributed to their 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 realize the clinical relevance of “persistent” angina, the inadequacy of current approaches will be apparent, and the search for innovative agents will be given strong impetus.

Innovative approaches to the management 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. A better understanding of the metabolic derangements associated with ischemia and reperfusion is translating into new therapeutic proposals [12].

Under normoxic conditions, the healthy heart derives most of its energy from the free fatty acid pathway, which accounts for approximately 67% of energy (ATP) production, the other source of energy being derived from glucose oxidation and lactate. In hypoxic conditions, myocardial cells accelerate glucose uptake to generate sufficient ATP in order to maintain ionic gradients and calcium homeostasis. Severe ischemia 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; uptake of lactate 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 reduced production of ATP. These meta-

bolic changes lead to disruption of cell homeostasis, alterations in membrane structure, and, ultimately, cell death.

Given this pathophysiological background and the failure of classic hemodynamic agents in many patients, it seems logical to consider pharmacological manipulation of cardiac energy metabolism as a promising 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 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 inhibitors, is able to elicit an increase in glucose and lactate utilization secondary to a partial reduction in fatty acid oxidation, producing demonstrated clinical benefits in patients with ischemic heart disease [13].

The metabolic approach to treating ischemic 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 [ref [14]?]. In the late 1960s and the 1970s, the use of metabolic therapies for treating ischemic myocardium received a great deal of attention after the observation that an infusion of glucose, insulin, and potassium (GIK solution) reduced ventricular arrhythmias and increased survival after 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 ischemic damage and ventricular arrhythmias during acute myocardial infarction or exercise-induced angina [ref [15]?].

The greatest progress in the use of metabolic treatment has come in the past 15 years, with the advent of the direct inhibitors of myocardial fatty acid oxidation, specifically trimetazidine and ranolazine, for the treatment of chronic stable angina pectoris [13]. Trimetazidine was the first, and was for many years the only, registered drug in this class, and is available in more than 80 countries worldwide. Ranolazine has recently been introduced, and has proved effective in two large-scale Phase III clinical trials.

At variance with classic “hemodynamic” agents, “metabolic” agents have no direct hemodynamic, inotropic, or chronotropic effect, and are expected to interact directly with cardiac energy metabolism. Given this mechanism of action, they appear to be the most promising strategy for the treatment of angina when it is no longer related to the presence of a coronary obstruction. ■

REFERENCES

1. American Heart Association. *Heart disease and stroke statistics: 2003 Update*. Dallas, TX: American Heart Association; 2002.
2. Gibbons RJ, Chatterjee K, Daly J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol*. 1999;33:2092–2197.
3. Pepine CJ, Abrams J, Marks RG, Morris JJ, Scheidt SS, Handberg E. Characteristics of a contemporary population with angina pectoris. TIDES Investigators. *Am J Cardiol*. 1994;74:226–231.
4. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease: a multicenter randomized trial. *JAMA*. 1997; 277: 715–721.
5. Henderson RA, Pocock SJ, Clayton TC, et al, for the Second Randomized Intervention Treatment of Angina (RITA-2) Trial Participants. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical treatment. *J Am Coll Cardiol*. 2003;42:1161–1170.
6. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ*. 2000;321:73–77.
7. Hemingway H, Crook AM, Feder G, et al. Underuse of revascularization procedures in patients considered appropriate candidates for revascularization. *N Engl J Med*. 2001;344: 645–654.
8. Serruys PW, Unger F, Sousa JE, et al, for the Arterial Revascularization Therapies Study Group. Comparison of coronary artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117–1124.
9. Blumenthal RS, Cohn G, Schulman SP. Medical therapy versus coronary angioplasty in stable coronary artery disease: a critical review of the literature. *J Am Coll Cardiol*. 2000; 36:668–673.
10. Sambuceti G, Marzilli M, Fedele S, Marini C, L'Abbate A. Paradoxical increase in microvascular resistance during tachycardia downstream from a severe stenosis in patients with coronary artery disease. *Circulation*. 2001;103:2352–2360.
11. Marzilli M, Sambuceti G, Testa R, Fedele S. Platelet glycoprotein IIb/IIIa receptor blockade and coronary resistance in unstable angina. *J Am Coll Cardiol*. 2002;40:2102–2109.
12. Stanley WC. Partial inhibition of cardiac fatty acid oxidation for the treatment of chronic stable angina. *Expert Opin Invest Drugs*. 2002;11:1–15.
13. Stanley WC, Marzilli M. Metabolic therapy in the treatment of ischemic heart disease: the pharmacology of trimetazidine. *Fund Clin Pharmacol*. 2003;17:133–145.
14. Goulston A. The beneficial effect of ingestion of cane sugar in certain forms of heart disease. *Brit J Med*. 1911; 1:615.
15. Oliver MF, Rowe MJ, Luxton MR, Miller NE, Neilson JM. Effect of reducing circulating free fatty acids on ventricular arrhythmias during myocardial infarction and on ST-segment depression during exercise-induced ischemia. *Circulation*. 1976;53 (Suppl):210–213.