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Refractory angina or inappropriate antianginal therapy?

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Abstract

Ischemic heart disease (IHD) is a main determinant of global health and mortality. Despite significant advances in therapeutic options, many patients complain with persistent symptoms and/or signs of myocardial ischemia (ie, refractory angina). Main therapeutic strategies used in angina patients aim at either reducing the effects of coronary stenosis on coronary blood flow or at removing the coronary stenosis itself. However, obstructive coronary artery disease is not synonymous with IHD. Indeed, a number of other factors can precipitate myocardial ischemia, including microvascular dysfunction, focal or diffuse spasm, and altered mitochondrial metabolism. It is therefore not surprising that therapeutic strategies that target epicardial coronary stenosis are not effective in all IHD patients. When approaching a patient with angina, the multiple pathophysiology model should be adopted at all levels, including diagnostic and treatment strategies. Angina should be considered refractory once the underlying mechanism has been identified and the targeted treatment has failed to control symptoms. This attitude could help stratify risk and augment treatment strategies, in this way optimizing resource utilization and improving cardiovascular outcome in the individual patient. ■ *Heart Metab*. 2017;72:4-8

Keywords: CAD; guideline-directed medical therapy; persistent angina

Introduction

Cardiovascular disease remains the main determinant of global health and mortality. The incidence of ischemic syndromes, one of the most relevant manifestations, increases with the occurrence of traditional risk factors and with age. For instance, the prevalence of angina pectoris, which constitutes the most frequent clinical presentation, increases progressively among adults aged 40 years and older, ranging from 4% to more than 11%.[1]

Guideline-directed medical therapy (GDMT) and myocardial revascularization represent the cornerstone therapies for ischemic heart disease (IHD) patients.[2] Although significant advances have been registered for both therapeutic strategies, large clinical trials consistently report that many patients complain with persistent symptoms and/or signs of myocardial ischemia.[3-9] In some prospective studies, the proportion of patients with symptom persistence despite GDMT and revascularization may be as high as 25% to 35%.[10,11] Given the burden of the disease and the

Abbreviations

BB: β-blocker; **CAD:** coronary artery disease; **CCB:** calcium-channel blocker; **GDMT:** guideline-directed medical therapy; **IHD:** ischemic heart disease

impact that angina has on quality of life and on prognosis,[12] a better understanding of the "refractory angina/ischemia" phenomenon appears much needed.

Refractory angina

Refractory angina and/or ischemia can be defined as symptoms and/or signs of ischemia that are not adequately controlled with maximally tolerated GDMT and revascularization.[13]

GDMT includes lifestyle interventions (eg, smoking cessation), drugs for risk factor control (eg, antiplatelet therapy, cholesterol-lowering agents) and drugs aiming at controlling symptoms.

In most guidelines, β-blockers (BBs) are the recommended first-line treatment for symptom control. BBs inhibit the action of endogenous catecholamines (epinephrine and norepinephrine in particular) on adrenergic receptors. Their antiangina effects are mediated through a reduction in ventricular inotropy, heart rate, and a decrease in the maximal velocity of myocardial fiber shortening, therefore keeping myocardial oxygen demand below the threshold at which angina occurs.

Calcium-channel blockers (CCBs) can be used either as an alternative to or on top of BBs. CCBs are potent coronary and systemic arterial vasodilators that reduce blood pressure, as well as cardiac contractility. CCBs bind to and inhibit L-type calcium channels and thus reduce calcium influx into cells. Intracellular calcium deprivation relaxes smooth muscle cells, causing vasodilation in the peripheral and coronary beds and increased coronary blood flow. Consequently, CCBs lower the frequency of angina and reduce the need for nitrates.

Nitrates represent another important alternative, particularly for those patients in whom a complete revascularization is not possible or whose symptoms are (at least in part) considered secondary to abnormal coronary vasomotion. Although the predominant effect of nitrates is to reduce preload—with a greater activity in venous than in arterial beds—at higher doses, a direct effect upon arteries also becomes evident and results in a reduction in blood pressure and afterload. These effects translate into reduced myocardial oxygen consumption and a higher threshold level before angina is triggered.

BBs, CCBs, and nitrates constitute the so-called traditional or hemodynamic antiangina agents. As mentioned, hemodynamic agents act by lowering rate-pressure product and/or producing systemic venodilation, thereby lowering left ventricular end-diastolic pressure and volume and reducing myocardial wall tension. Therefore, their main action mechanism is a reduction in oxygen requirements.

Drugs with alternative action mechanisms represent a second-line choice and, as such, have been given a lower class of recommendation.[14] Trimetazidine acts at the mitochondrial level and exerts its action on myocardial ischemia independently from the precipitating mechanism. By preventing the deleterious effects of ischemia, trimetazidine maintains the contractile function of the cardiac cell and reduces anginal symptoms. Ranolazine acts by blocking late sodium channels leading to the lowering of abnormally high cytosolic calcium levels. Ivabradine and nicorandil are two other agents that improve angina symptoms.[15,16] Ivabradine reduces heart rate without affecting contractility and atrioventricular (AV) nodal conduction and without altering hemodynamics. Nicorandil increases potassium ion conductance and induces vasodilation through smooth muscle relaxation.

If symptoms are not adequately controlled by GDMT with hemodynamic agents and with or without alternative agents (*Table I*), revascularization should be pursued in angina patients. However, none of the major international guidelines give clear indications on the time period for a drug therapy or combination to be considered "unsuccessful." On the contrary, revascularization is often pursued without attempting

Hemodynamic agents	Agents with alternative mode of action
β-Blockers (metoprolol, bisoprolol, carvedilol)	Trimetazidine
Calcium-channel blockers (verapamil, diltiazem)	Ranolazine
Nitrates (isosorbide mononitrate)	Ivabradine
	Nicorandil

Table I *Drugs in ischemic heart disease.*

implementation and/or titration of adequate medical therapy, and less than half of patients directed to revascularization receive GDMT before percutaneous coronary intervention.[17] Therefore, the rate of persistent angina despite maximally tolerated GDMT in clinical practice is not properly known.

IHD as a multifactorial disease

As mentioned, the two main therapeutic strategies used in angina patients aim at reducing the effects that a coronary stenosis produces on downstream flow (hemodynamic agents) or at removing the coronary stenosis itself (revascularization). This approach is based on the assumption that narrowing of the coronary artery limits resting and hyperemic coronary blood flow.[18] However, several large-scale studies have shown that many patients with angina do not have obstructive coronary artery disease (CAD). On the other hand, most coronary atherosclerotic obstructions are clinically silent.[12,19,20] Indeed, the effect that a stenosis produces at the level of the downstream coronary flow is not straightforward. Conversely, factors other than atherosclerotic coronary obstructions, including focal or diffuse spasm of normal or plaque-diseased arteries, and microvascular dysfunction due to activated platelets and/or release of constrictive, prothrombotic, and proinflammatory cytokines, can all precipitate myocardial ischemia.[20,21] Moreover, likewise for a combustion engine with a perfect injection mechanism, a cardiomyocyte may still be unable to properly burn the fuel due to cellular dyshomeostasis with altered mitochondrial metabolism, dysfunction of extracellular matrix, barriers to oxygen transport, etc.[21,22]

The concept of IHD as a multifactorial disease has been endorsed by the latest edition of the European Society of Cardiology (ESC) guidelines.[2] However, according to the same documents, the so-called "alternative mechanisms" are considered only after epicardial stenosis has been excluded, as if coronary atherosclerosis were to confer some sort of immunity versus other causes of myocardial ischemia. The frequent observation that symptoms and/or ischemia persist even after stenosis removal strongly challenges this assumption. Indeed, patients with IHD are a heterogeneous group, including those in whom an epicardial stenosis is responsible for angina symptoms, those with vasospastic angina, and those with microvascular dysfunction, epicardial endothelial dysfunction, slow coronary flow, etc.[23] It is therefore not surprising that therapies that target obstructive CAD only cannot control symptoms in all IHD patients.

The choice of the therapeutic strategy for controlling angina symptoms should be based on these new concepts. Indeed, although from a pathophysiological standpoint, the role of alternative factors underlying angina has been fully acknowledged, little or no progress has been made in applying these new concepts to diagnostic and therapeutic protocols.

BBs can be expected to be beneficial in patients with significant epicardial stenosis, whose symptoms are exacerbated by increased workload. Conversely, BBs can be counterproductive in patients with vasospastic angina; in such patients, nondihydropyridinic CCBs and nitrates have been shown to be particularly efficacious.

Hemodynamic agents are probably neutral in other patient subsets. Similarly, overrated use with improper selection of patients that would benefit from revascularization may have contributed to the lack of full-scale beneficial effects of angioplasty.

Patients with angina and suspected IHD should undergo a thorough evaluation irrespective of the coronary angiographic results. In patients displaying obstructive CAD, the effect that the epicardial stenosis exerts on downstream coronary flow should be assessed. Indeed, inadequate microvascular remodeling due to chronic low shear stress distal to the stenosis with decreased nitric oxide activity or a low perfusion pressure distally to a stenosis can negatively influence microvascular remodeling and the capacity of maximal vasodilation.[24] Stenosis removal with coronary revascularization can reverse this effect, with angina patients obtaining symptom control. However, whether coronary microvascular dysfunction is a preexisting condition or is secondary to chronic flow alterations and, as such, potentially reversible cannot be determined with the current state of knowledge. In fact, among revascularized patients with persistent angina, microvascular dysfunction constitutes the most frequent underlying cause. Although a number of drugs have been tested in this setting, none have produced convincing results. Therefore, a patient with microvascular angina should not be labeled as a patient with refractory angina, but rather as a patient to whom we cannot offer appropriate therapy.

The overall unsatisfactory results of angina patients that are treated with the currently available therapeutic regimens have stimulated further research. Nevertheless, the lack of symptom control in all angina patients continues to be attributed to the inaccurate assessment of coronary plaques.[25] As such, imaging modalities that assess anatomical and/or physiological relevance of epicardial coronary plaques are absorbing major resources. This attitude is in line with the diagnostic and therapeutic protocols outlined in contemporary guidelines that aim at identifying and treating coronary obstructions. However, this approach is in conflict with the multiple pathophysiology model for IHD and, again, explains the lack of benefit in all angina patients.

Conclusions

The inability of GDMT and revascularization to control symptoms in all patients with stable angina should not lead to an automatic labeling as "refractory angina." When approaching a patient with angina, the multiple pathophysiology model should be adopted at all levels, including diagnostic and treatment strategies. Angina should be considered refractory once the underlying mechanism has been identified and the targeted treatment has failed to control symptoms (eg, patients with diffuse CAD, not amenable to revascularization). On the contrary, patients with angina despite currently available therapies should be considered as "patients with angina and inappropriate treatment." This attitude could help stratify risk and augment treatment strategies, in this way optimizing resource utilization and improving cardiovascular outcome in the individual patient. ■

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