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The role of optimal medical therapy in patients with refractory angina

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Abstract

The management of patients with refractory angina poses a major clinical challenge. Optimal medical therapy (OMT) is of paramount importance to improving quality of life by reducing (as much as possible) the number of angina attacks with a correspondent increase in exercise tolerance. For that, a judicious use of a combination of all agents currently approved in the management of patients with stable angina should be implemented. Guidelines usually recommend a combination of hemodynamic agents, such as β-blockers, calcium-channel blockers, and/or long-acting nitrates, at maximally tolerated doses, followed by the addition (as needed) of antianginal agents with different modes of action, such as trimetazidine, ivabradine, ranolazine, nicorandil, perhexiline, allopurinol, and/or fasudil (where available). Here, we describe the case of a patient who initially received a diagnosis of refractory angina and in whom OMT greatly helped to improve symptoms. ■ *Heart Metab*. 2017;72:32-36

Keywords: angina; coronary artery disease; treatment

The management of patients with refractory angina poses a major clinical challenge. Because of advanced coronary artery disease (CAD), those patients are deemed to be unsuitable for myocardial revascularization procedures, which makes the role of optimal medical therapy (OMT) of paramount significance.[1] The main goals when treating such patients are directed toward an improvement in quality of life, which can be achieved by a reduction (as possible) in the number of angina attacks with a correspondent increase in exercise tolerance.

Although no medical therapy has been specifically conceived for patients with refractory angina, a judicious use of a combination of all agents currently approved in the management of patients with stable angina should be implemented.[2] The more conventional approach is to initially offer a combination of hemodynamic agents, such as β-blockers, calcium-channel blockers (CCB), and/or long-acting nitrates (LAN), at maximally tolerated doses. A limiting factor to a greater use for the above combination is that it can lead to a significant drop in arterial blood pressure (BP), with hypotension-related symptoms developing afterwards; additionally, other side effects, including headache, flushing (LAN and CCB), fatigue, depression, weakness, insomnia (β-blockers), swollen ankles, constipation, or flushing (CCB) may also occur. In the COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation), for instance, at 3 years of follow-up, roughly 40% of patients were still complaining of angina, regardless of which arm of the trial they were assigned to (OMT

Abbreviations

BEAUTIFUL: morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction; **BP:** blood pressure; **CAD:** coronary artery disease; **CCB:** calcium-channel blocker; **COURAGE:** Clinical Outcomes Utilizing Revascularization and Aggressive druG Evaluation; **HR:** heart rate; **LAN:** long-acting nitrate; **OMT:** optimal medical therapy; **SHIFT:** Systolic Heart failure treatment with I_f inhibitor ivabradine Trial

with or without percutaneous coronary intervention).[3] At the same time point, in patients in the OMT-only group, 86% were taking β-blockers, 50% a CCB, and 61% a LAN.[4] To answer the question of why investigators did not increase the use of those agents to a greater extent if patients were still symptomatic, one must look at the BP: at 123±0.78/70±0.52 mm Hg, BP most likely prevented any further attempt to adjust therapy.[4] Moreover, for patients with stable CAD and hypertension, a systolic BP under 120 mm Hg and diastolic BP under 70 mm Hg have each recently been shown to be associated with adverse cardiovascular outcomes, including mortality.[5] Therefore, if a patient is already being treated with a hemodynamic agent (alone or in combination) and remains symptomatic, one should consider OMT with antianginal agents devoid of a BP-lowering effect. Non–BP-lowering antianginal agents are trimetazidine, ivabradine, ranolazine, nicorandil, perhexiline, allopurinol, and fasudil[2] (*Table I*). However, availability and clinical indications of those agents vary from country to country.

Agent	Mode of action
Trimetazidine	Inhibition of fatty-acid β-oxidation in mitochondria Increased ATP production in mitochondria Improved myocyte tolerance to ischemia
Ivabradine	Inhibition of sinus node I_f pacemaking current Pure heart rate reduction Prolongation of diastole Increased myocardial perfusion and collateral function
Ranolazine	Inhibition of late inward Na^+ current Reduction in Ca^{2+} in ischemic myocytes Improved left ventricular diastolic function
Nicorandil	Release of nitric oxide free radicals Vasodilation of arterial and venous system Activation of ATP-sensitive K^+ channels
Perhexiline	Inhibition of carnitine-palmitoyltransferase 1 and 2 Shifting myocardial metabolism from fatty acids to carbohydrates Enhancement of energy efficiency in ischemic myocytes
Allopurinol	Inhibition of xanthine oxidase Reduction in vascular oxidative stress
Fasudil	Inhibition of rho-kinase Reducing Ca^{2+} sensitization of vascular smooth muscle Maintenance of coronary vasodilation

Table I *Nontraditional antianginal agents and their main mode of action.*
Abbreviations: *ATP, adenosine triphosphate; Ca^{2+}, calcium; K^+, potassium; Na^+, sodium.*

Another important aspect to take into consideration is whether left ventricular systolic dysfunction is present, as some antianginal agents are contraindicated in patients with angina and left ventricular dysfunction—examples include diltiazem and verapamil—or their safety has not been properly assessed in this population.

This article presents a clinical case that highlights the role of OMT in the management of a patient who initially received a diagnosis of refractory angina, and illustrates the rationale for a specific combination of antianginal agents in this scenario.

Clinical case

A 73-year-old man was referred to our outpatient clinical center for persistent angina due to advanced CAD. He had a long history of hypertension and type 2 diabetes mellitus. Stable CAD was diagnosed at the age of 56, and he was managed medically until the age of 63, when he suffered an acute myocardial infarction and, because of severe multivessel disease, he underwent a triple bypass surgery. He did quite well after the procedure and was asymptomatic without any functional limitation until 6 months ago, when angina relapsed and became progressively limiting. He was unable to perform any ordinary activity without pain, for which a short-acting nitrate was frequently taken. When first seen in another health facility, his heart rate (HR) was 80 beats per minute (bpm) and BP, 144/78 mm Hg. Findings on physical examination were unremarkable. He was on metoprolol succinate 50 mg/day, atorvastatin 80 mg/day, aspirin 100 mg/day, and perindopril 8 mg/day. Electrocardiography revealed abnormal Q waves in DII, DIII, and aVF. An echocardiogram showed a mildly enlarged left ventricle (left ventricular end diastolic diameter, 58 mm) with a moderately depressed left ventricular function (left ventricular ejection fraction, 40%). Metoprolol succinate was increased to 100 mg/day. On his next ap-

Heart Metab. (2017) 72:32-36

pointment, he complained of experiencing ten angina attacks per week; he was feeling fatigued but with no shortness of breath. HR dropped to 72 bpm and BP to 136/72 mm Hg. Amlodipine 5 mg daily was added to his treatment regimen. One month later, he did not notice much improvement; angina was still bothering him with an average of eight attacks per week. HR remained unchanged at 74 bpm and BP further decreased to 128/66 mm Hg. Isosorbide-5-mononitrate 20 mg twice daily was added to his treatment regimen. Two weeks later, he was brought to the emergency department after losing consciousness for about 3 minutes. Electrocardiography revealed his heart was in sinus rhythm with a HR of 80 bpm and no acute ischemic abnormalities; troponin levels were normal. BP was low at 96/50 mm Hg. Nitrates were discontinued, and because of persistent angina with a poor response to medical therapy, a coronary angiography was ordered (*Figure 1*). A heart team was consulted; because of the extension and diffuseness of the disease, he was not considered a good candidate for another revascularization procedure and was referred to our center for further evaluation.

At his first appointment in our facility, his disease was still considered to be Canadian Cardiovascular Society (CCS) class III-IV, he was on metoprolol succinate 100 mg/day + amlodipine 5 mg/day, and he had a resting HR of 68 bpm and a BP of 124/60 mm Hg. Trimetazidine 35 mg twice daily was added to his treatment regimen. One month later, angina had improved from eight episodes per week to four, and he could walk briskly in the park without pain. His level of fatigue had improved as well. His vitals showed a HR of 72 bpm and a BP of 126/68 mm Hg. At that point, ivabradine 5 mg twice daily was added to his treatment regimen. At a follow-up visit, at which he had a HR of 68 bpm and no change in BP, ivabradine was uptitrated to 7.5 mg twice daily. When last seen, he could resume most of his daily activities without pain. Occasionally, angina recurred during more strenuous activities, but this was easily relieved by a short-acting nitrate. Another echocardiogram performed 6 months after OMT showed an increase in left ventricular ejection fraction from 40% to 46%. *Figure 2* shows the process of optimization of medical therapy in this patient who initially received a diagnosis of refractory angina.

Discussion

This case illustrates that OMT can improve the quality of life, decrease the number of angina attacks, and increase exercise tolerance in patients who initially receive a diagnosis of refractory angina and have no perspectives for myocardial revascularization procedures, as our group has previously shown.[6]

The decision-making process in this patient followed the more common approach adopted in many international guidelines for the management of patients with stable angina, which state that a combination of β-blocker and CCB should be considered initially.[7,8] If patients remain symptomatic, LAN should be considered along with other non–BP-lowering agents. In this symptomatic patient on metoprolol + amlodipine, severe hypotension developed after the introduction of LAN, and angina could not be adequately controlled. Ranolazine has not been recommended to be used in patients with angina and left ventricular systolic dysfunction because of the lack of

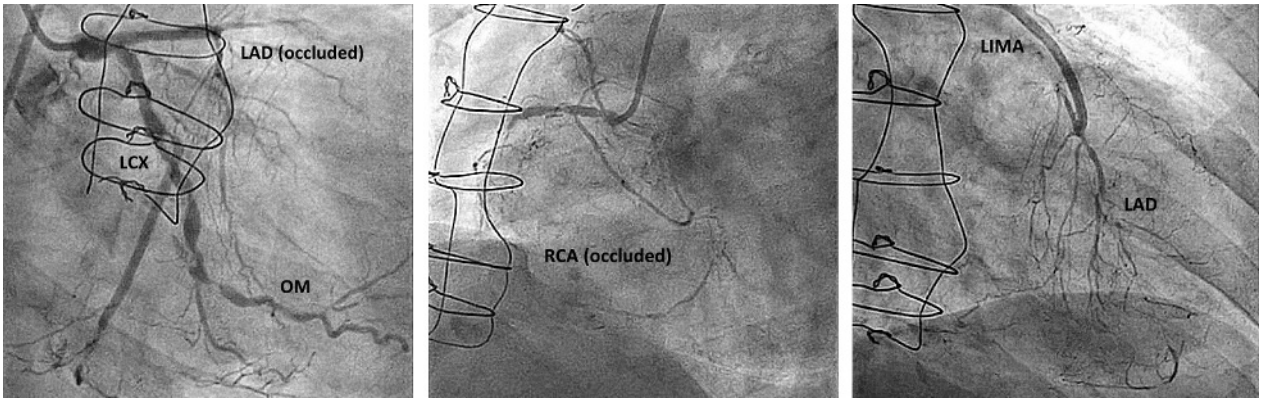

Fig. 1 *Left panel shows the left coronary artery system with left anterior descending (LAD) artery occlusion after the first septal branch and multiple obstructive lesions in the left circumflex (LCX) artery territory. Center panel shows the occluded right coronary artery (RCA). No grafts were visible except for a left internal mammary artery (LIMA)-LAD seen in the right panel. Note the diffuse atherosclerosis from proximal to distal beds, leading to a thread-like appearance with small distal runoff in the LAD.*
Other abbreviation: *OM, obtuse marginal branches.*

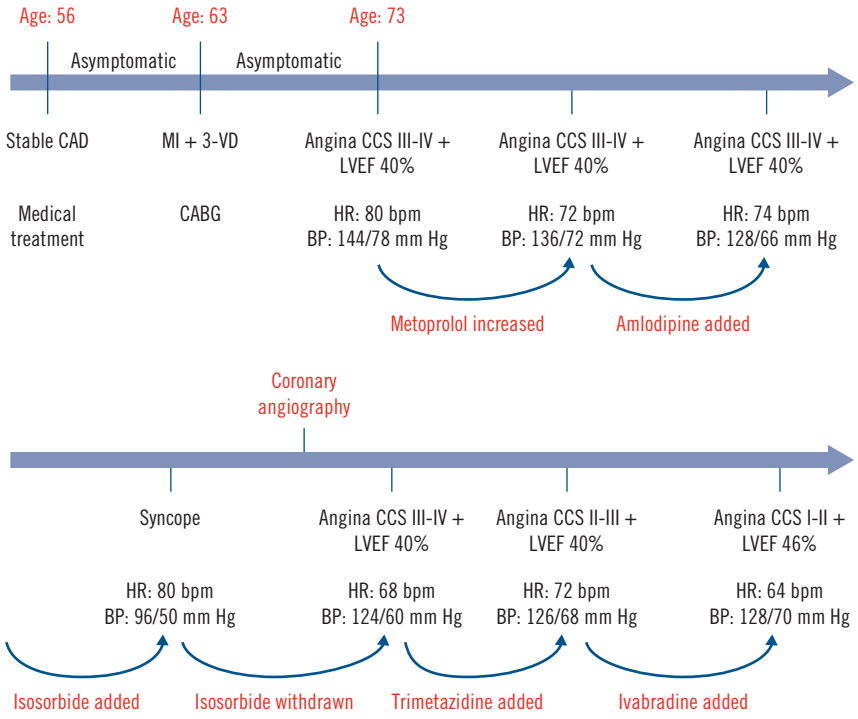

Fig. 2 *Optimal medical therapy in a patient with persistent angina unsuitable for revascularization.*
Abbreviations: *BP, blood pressure; bpm, beats per minute; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society classification; HR, heart rate; LVEF, left ventricular ejection fraction; MI + 3-VD, myocardial infarction + three-vessel disease.*

safety data.[9] Hypotension is an uncommon but potentially disturbing adverse effect associated with the use of nicorandil,[10] available in some countries. Fasudil is a potent rho-kinase inhibitor and vasodilator[11] that has not been approved by the US Food and Drug Administration or by the European Medicines Agency. Perhexiline is an antianginal agent available in few countries; it has a narrow therapeutic index, and because of high inter- and intraindividual pharmacokinetic variability, it requires close monitoring to avoid the risk of hepatotoxicity or peripheral neuropathy.[12] Trimetazidine, owing to its unique mode of action,[13] devoid of any discernible hemodynamic effects and excellent tolerability, was a very good option for this patient, especially in the context of angina and left ventricular systolic dysfunction,[14] in which trimetazidine was shown to increase left ventricle contractility and reduce the risk of death.[15] Because of its synergistic antianginal effect when associated with conventional antianginal agents,[16,17] the Brazilian guidelines on stable angina allowed for the addition of trimetazidine right after the use of β-blockers and before LAN in symptomatic patients.[18] In adopting this strategy, a faster and better tolerated therapeutic strategy may be implemented for better angina control. After the introduction of trimetazidine, the patient experienced a significant improvement in his clinical status, although mild angina was still present. Ivabradine was added because of its proven efficacy in patients with stable CAD and moderate left ventricular dysfunction, not only in terms of symptom control but also for cardiovascular protection, as demonstrated in the trials BEAUTIFUL (morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction)[19] and SHIFT (Systolic Heart failure treatment with I_f inhibitor ivabradine Trial).[20] In fact, after 6 months on OMT, symptoms improved, as well as left ventricular systolic function.

In conclusion, in this nonrevascularizable patient with persistent angina, the combination of conventional antianginal agents (β-blockers and CCBs) with non–BP-lowering agents (trimetazidine and ivabradine) provided an excellent control of angina and increase in exercise tolerance, with good tolerability and no side effects. ■

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