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Angina and left ventricular dysfunction: can we 'reduce' it?

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Despite the evolution in pharmacology and devices, recurrent and persistent angina still represent a frequent issue in clinical practice. A 69-year-old Caucasian female patient has history of surgical aortic valve replacement with a bioprosthesis for severe aortic stenosis with subsequent transcatheter valve-in-valve implantation for bioprosthesis degeneration and single coronary artery bypass graft with left internal mammary artery on left anterior descending (LAD). After transcatheter aortic valve implantation, she started to complain angina [Canadian Cardiovascular Society (CCS) Class III], effectively treated with bisoprolol uptitration and ivabradine 5 b.i.d. addition. After 6 months, she had a non-ST segment elevated myocardial infarction with evidence of left main occlusion and good functioning aortic bioprosthesis. A retrograde drug-eluting balloon percutaneous coronary intervention (PCI) on LAD (in-stent restenosis) was performed. However, the patient continued to complain angina (CCS Class II–III), even after further ivabradine increase to 7.5 mg b.i.d. After 4 months, the patient underwent Reducer implantation. After 2 months, angina started to improve and the patient is currently angina free. In the last decades, PCI materials and stents greatly improved. Medical therapy (such as β-blockers) has been shown not only to improve symptoms but also to add a prognostic benefit in patients with reduced ejection fraction (EF). Ivabradine showed additional benefits in patients with angina and reduced EF. However, still a relevant portion of patients complain refractory angina. The COSIRA trial showed that a coronary sinus Reducer was associated with greater angina relief than the sham procedure and could be a further step in angina treatment.

Introduction

In the last decades, evolution in percutaneous coronary interventions (PCI) materials enabled to 'postpone' the occurrence of 'recurrent and persistent' angina. However, in everyday clinical practice, it often happens to deal with patients without possibility of further percutaneous or surgical revascularization. Medical treatment significantly evolved with new possibilities to reduce angina burden in complex patients (i.e. ivabradine, nicorandil, and ranolazine). In this context, the evolution of an old surgical procedure of coronary sinus reduction invented by Beck[1] led to the development of a new device (Coronary Sinus Reducer, Neovasc) aimed at the reduction of symptoms in refractory invalidating angina.

We present a complex case in which the combination of percutaneous and pharmacological strategies enable to reduce the angina burden in a patient with multiple comorbidities and left ventricular (LV) dysfunction.

Case presentation

A 69-year-old Caucasian female patient has history of chronic kidney disease (ckd), hepatitis C virus-related liver

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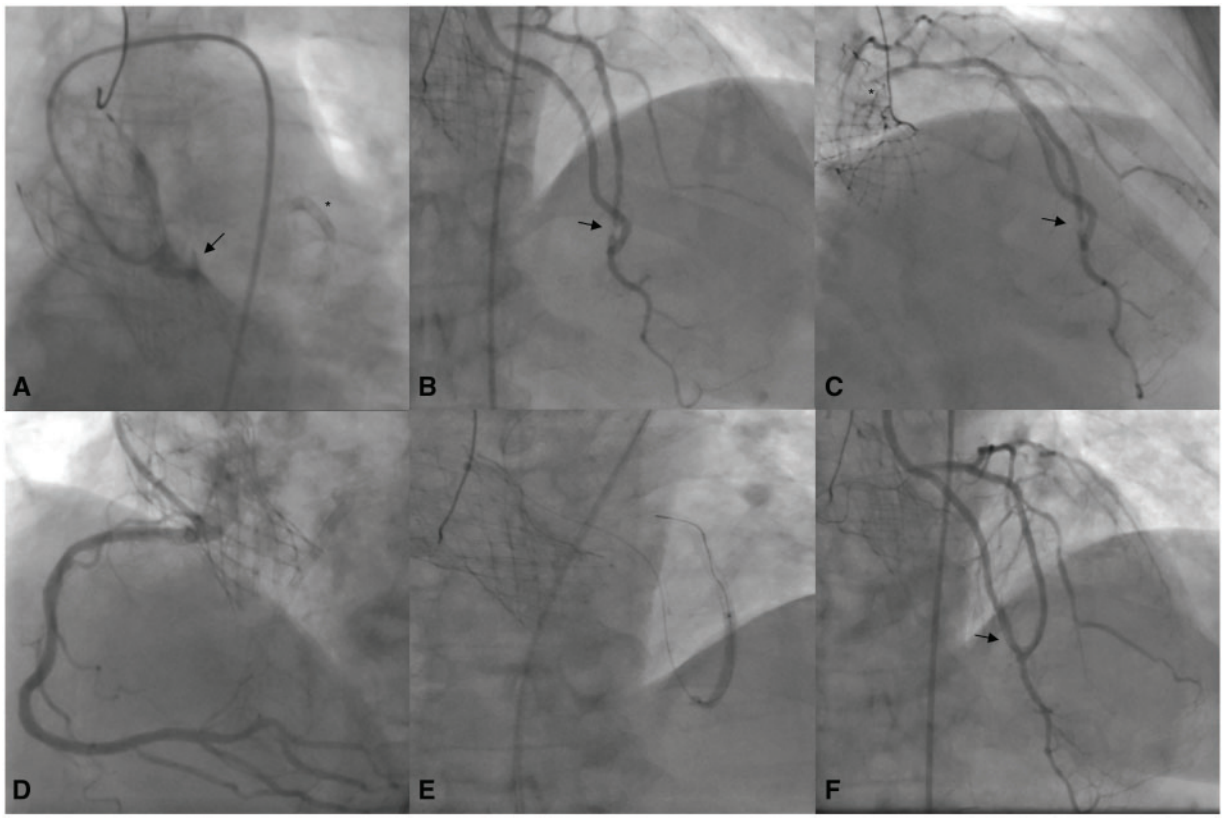

Figure 1 Angiographic images of the percutaneous coronary intervention procedure. (A) Left main occlusion (see arrow) and image of the previous stent implanted on left anterior descending (LAD) (see asterisk). (*B, C*) Critical restenosis on LAD, which lead to coronary artery bypass graft (CABG) (see arrow) and left main occlusion (see asterisk). (*D*) Right coronary artery without critical lesions. (*E*) Drug-eluting balloon (DEB) treatment of in-stent restenosis. (*F*) Final angiographic result (see arrow).

disease, anaemia, and metabolic syndrome (hypertension, dyslipidaemia, and diabetes). She came to our attention in 2017, but in 2002 she received left anterior descending (LAD) artery stenting because of angina. In 2007, she underwent surgical aortic valve replacement with a bioprosthesis for severe aortic stenosis and single coronary artery bypass graft (CABG) with left internal mammary artery (LIMA) due to LAD restenosis. In 2017, the patient was further hospitalized for heart failure (HF) and mild angina [Canadian Cardiovascular Society (CCS) Class I] in another Centre where she was treated with successful transcatheter valve-in-valve implantation (Corevalve Evolute 23, Medtronic) for bioprosthesis degeneration. Before transcatheter aortic valve implantation, coronary computed tomography was performed showing LAD bypass patency and no significant other coronary lesions. At discharge, patient's echocardiography showed moderate left ventricular ejection fraction (LVEF) reduction (40%) with normally functioning aortic bioprosthesis and her therapy was aspirin, statin, nitrates, dihydropyridine Ca^{++}-antagonist, insulin.

In January 2017, the patient was evaluated in our outpatient service for recurrent effort angina (CCS Class III). Echocardiography showed a moderate reduction of the LVEF (38%) and a normally functioning aortic bioprosthesis. Heart rate (HR) was 82 b.p.m.

In view of the previous and current history, therapy was progressively improved with bisoprolol uptitrated to 10 mg—which reduced HR to 75 b.p.m. and blood pressure to 100/70 mmHg—plus ivabradine (5 mg b.i.d.)—which allowed to have a further HR reduction to 62/b.p.m.—with amelioration of the angina.

After 6 months, the patient was hospitalized for a non-ST segment elevated myocardial infarction complicated by HF. Echocardiography was not significantly modified (good functioning aortic bioprosthesis and persistent moderate LV systolic dysfunction with LVEF = 36%). Thus, it was decided to perform coronary artery angiography, which showed left main (LM) occlusion probably due to a bioprosthesis dislocation (*Figure 1A*), normal right coronary artery (RCA) (*Figure 1D*) and in-stent restenosis in the mid portion of LAD, which was the cause of the LIMA graft (*Figure 1 B, C*). However, due to the LM occlusion, a significant portion of the LAD and the circumflex territories were ischaemic. To reduce the burden of ischaemia, a retrograde drug-eluting balloon (DEB) PCI on intra-stent restenosis on LAD was performed (*Figure 1 E, F*). However, despite successful PCI, the patient continued to complain angina (CCS Class II-III), even after further ivabradine increase to 7.5 mg b.i.d. (HR around 60 b.p.m.). After 4 months, the patient underwent a Reducer implantation for refractory angina (*Figure 2 A-C*) and the full medical therapy was maintained. After

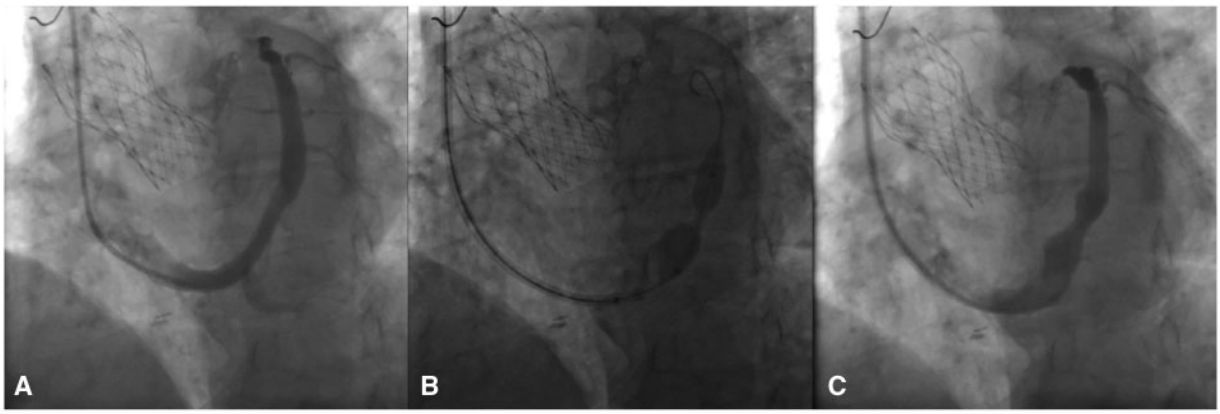

Figure 2 Angiographic images of the Coronary Sinus Reducer. (*A*) Coronary sinus before Reducer implantation. (*B*) Reducer implantation. (*C*) Final angiographic result after Reducer implantation.

2 months, angina started to improve and the patient is currently angina free.

Discussion

The present case reflects the complexity of contemporary patients with ischaemic heart disease and the wide range of possibilities helpful in the challenge to reduce angina and ischaemic burden.

First of all, PCI materials and stents greatly improved allowing operators to perform complex procedures in settings such as the one of this patient. Recently, a paclitaxel-eluting balloon has been tested against second generation sirolimus-eluting stent in in-stent restenosis. Treatment with DEB resulted non-inferior in terms of late lumen loss at 6 month and target lesion failure at 12 and 18 months.[2]

In addition, medical therapy has been shown not only to improve symptoms but also to add a prognostic benefit in patients with reduced EF. In particular, β-blockers showed an improvement in angina associated with a reduction in cardiovascular mortality and sudden death in patients with angina and reduced LVEF (<40%).[3-5] On top of β-blockers treatment, ivabradine showed additional benefits[6] and their synergistic effect suggests that in patients receiving treatment with β-blockers who are still symptomatic, adding ivabradine is more efficient than uptitration of β-blockers.[7]

In patients with angina and reduced EF, ivabradine effect could be not only a symptomatic drug. In fact, a prespecified subgroup analysis of the BEAUTIFUL trial showed that in patients with chronic stable angina at entry, ivabradine reduced the rate of myocardial infarction.[8] It is paramount to note that these results should be interpreted with caution, since they are subanalyses of a negative trial. In addition, ivabradine showed to improve hyperaemic peak coronary flow velocity (CFV) and CFV reserve (CFVR) to a greater extent than bisoprolol in patients with stable CAD, despite a similar decrease in HR.[9]

In the present case, the patient suffered from significant CKD. Otherwise, add-on of trimetazidine could have been another strategy to improve angina symptoms in a patient with HF. In fact, trimetazidine exerts some beneficial effect as on top of β-blockers in patients with HF and angina, while the safety of other antianginal agents in HF with reduced EF, such as ranolazine, is uncertain, while other drugs, specifically diltiazem and verapamil, are thought to be unsafe in patients with HF with reduced EF.[10]

From the symptoms standpoint, a new device seems to be able to reduce the ischaemic burden and, consequently, angina. Coronary sinus Reducer (Neovasc) elevates backward pressure in the coronary venous system and consequently, dilates arterioles with reduction of vascular resistance in the subendocardium. Blood flow redistribution in the ischaemic subendocardial layers translates in contractility improvement, and LV end-diastolic pressure decrease and consequent symptom relief.[11,12] It is noteworthy that Reducer is not able to reduce ischaemia in the territory of the RCA and that its angina reduction starts at least 2 months after the implantation once the device has been endothelialized.

The randomized, double-blind, sham-controlled, multicentre clinical trial (COSIRA)[13] enrolled 104 patients with severe refractory angina (CCS Class III–IV), and objective evidence of myocardial ischaemia. Reducer implantation was associated with a greater angina relief and quality of life than sham procedure.

In conclusion, our case well resumes the complexity of the patients with angina, reduced EF and comorbidities as well as the numerous interventional and pharmacological resources available nowadays to reduce the ischaemic burden and angina in these patients.

Consent statement

The patient consent to report the case has been obtained.

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