European Heart Journal Supplements (2019) **21** (Supplement C), C17–C20
The Heart of the Matter
doi:10.1093/eurheartj/suz042

ESC
European Society
of Cardiology

Angina and chronic obstructive pulmonary disease: facing the perfect storm

Simone Biscaglia[1,*], Rossella Ruggiero[1], Annamaria Di Cesare[1], Matteo Serenelli[1], and Roberto Ferrari[1,2]

[1]*Cardiovascular Centre of Ferrara University, Ferrara, Italy; and*
[2]*Maria Cecilia Hospital, Cotignola, Italy*

KEYWORDS
Angina;
COPD;
Beta-blockers;
Ivabradine

The association of chronic obstructive pulmonary disease (COPD) and ischaemic heart disease (IHD) is challenging both in terms of prognosis and of pharmacological treatment. An 83-year-old Caucasian male patient has chronic kidney disease, COPD, previous myocardial infarction, coronary artery bypass graft with left internal mammary artery (LIMA) on left anterior descending (LAD), saphenous vein graft (SVG) on obtuse marginal (OM)1 and on right coronary artery, and percutaneous coronary intervention (PCI) on LAD (occlusion of LIMA) and on SVG for OM1 (SVG critical stenosis). Recently, the patient complained worsening angina [Canadian Cardiovascular Society (CCS) III] and had residual ischaemia in the anterior wall after an unsuccessful attempt of PCI was performed on LAD for in-stent occlusion due to restenosis. Bisoprolol uptitration failed due to worsening of pulmonary function at spirometry. For this reason, ivabradine 5 mg b.i.d. was added to bisoprolol. Afterwards, the patient referred amelioration of symptoms and he is actually in CCS Class I. The control spirometry showed moderate obstruction comparable to his chronic situation. Patients with IHD and COPD often do not receive β-blockers due to the fear of adverse effects. However, cardioselective β-blockers do not worsen pulmonary function while they reduce mortality in COPD patients. In this setting, ivabradine could be extremely helpful in order to control symptoms since it is effective in patients with asthma and COPD, with no alteration in respiratory function or symptoms and improves exercise capacity and functional class in COPD patients.

Introduction

Chronic obstructive pulmonary disease (COPD) and ischaemic heart disease (IHD) are frequently associated sharing common risk factors. The association translates in a detrimental effect on prognosis. Inhaled noxious particles, hypoxia, systemic inflammation, endothelial dysfunction, heightened platelet reactivity, and arterial stiffness play a role in the development of both the COPD and IHD.[1–4] In most of these patients, death occurs for cardiovascular cause, soon after an acute exacerbation of COPD. Beyond the prognostic disadvantage related to the COPD–IHD comorbidity, pharmacological treatment is also challenging. We present a complex case of IHD/COPD, particularly challenging in terms of decisional and pharmacological management.

Case presentation

An 83-year-old Caucasian man has history of smoking habit, hypertension, dyslipidaemia, COPD with moderate obstructive deficit and chronic kidney disease (CKD) and moderate reduction of glomerular filtration rate (GFR = 45 mL/min).

In 1998, the patient was hospitalized for a non-ST elevated myocardial infarction with documentation of severe

*Corresponding author. Tel: +39(0)532239883, Fax: +39532239532, Email: bscsmn@unife.it

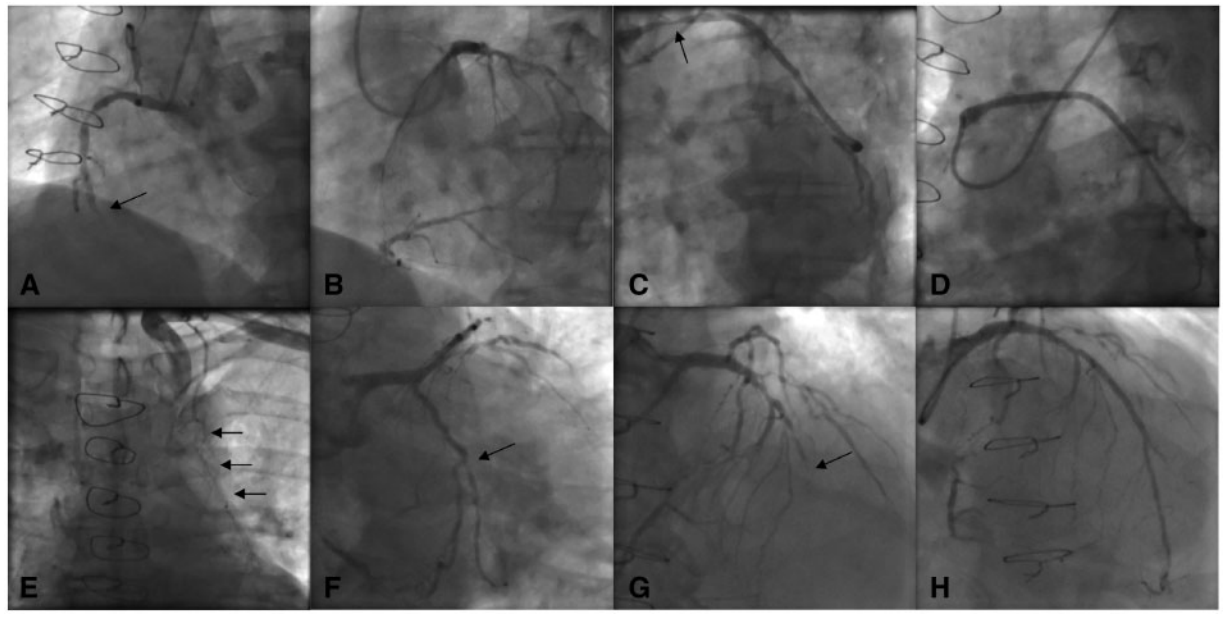

Figure 1 Angiographic images of the first procedure. (*A*) Right coronary artery occlusion (see arrow). (*B*) Collateral circulation coming from left coronary system to right coronary artery. (*C*) Critical lesion of the saphenous vein graft on obtuse marginal 1. (*D*) Saphenous vein graft on obtuse marginal 1 after drug-eluting stent implantation. (*E*) Functional occlusion of left internal mammary artery on left anterior descending artery (see arrows). (*F*) Obtuse marginal 1 occlusion (see arrow). (*G*) left anterior descending artery occlusion (see arrow). (*H*) Angiographic result after drug-eluting stent implantation on left anterior descending artery.

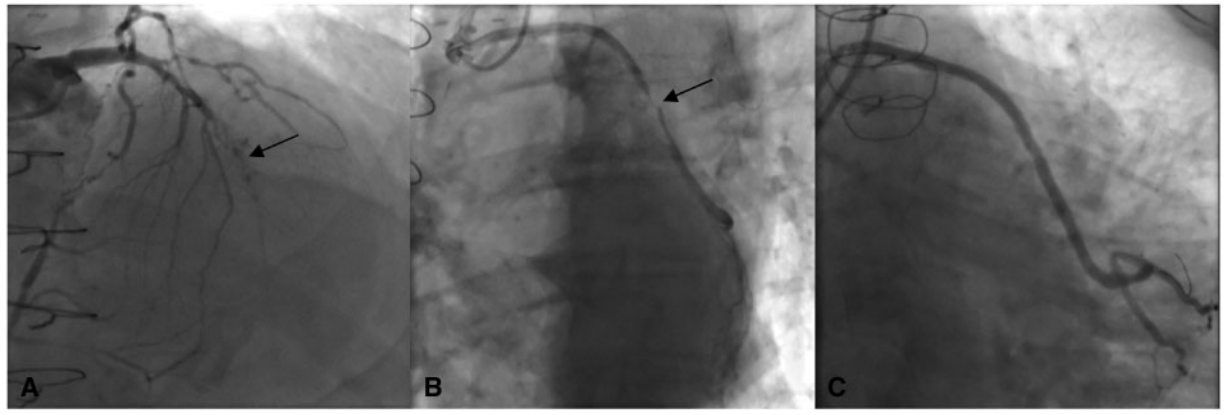

Figure 2 Angiographic images of the second procedure. (*A*) In-stent occlusive restenosis on left anterior descending artery (see arrow). (*B*) Disease progression on the distal portion of then saphenous vein graft for obtuse marginal 1. (*C*) Angiographic result after drug-eluting stent implantation on saphenous vein graft for obtuse marginal 1.

three vessel coronary diseases. Echocardiography showed hypertrophic left ventricle with anterior and lateral hypokinesia and slightly reduced ejection fraction (50%). The patient underwent coronary artery bypass grafts with left internal mammary artery (LIMA) on left anterior descending (LAD), and saphenous vein graft (SVG) on obtuse marginal (OM)1 and on right coronary artery (RCA). Follow-up was uneventful until 2013, when the patient was again hospitalized for unstable angina. On this occasion, he reported classical symptoms of angina [Canadian Cardiovascular Society (CCS) Class III] in the last 6 months and more recently typical chest pain episodes at rest lasting 15 min and responsive to nitrates. Echocardiography was slightly worsened with akinesia of the anterior apex and hypokinesia of the anterolateral wall. Considering the high-risk profile and the symptoms, we decided to perform coronary artery angiography that showed: functional LIMA occlusion, occlusion of the SVG for RCA, and critical stenosis of the SVG for OM1 with LAD, RCA, and OM1 occlusion (*Figure 1 A–C, E–G*). Percutaneous coronary intervention (PCI) on LAD was performed with single drug-eluting stent (DES) implantation and on SVG for OM1 with DES implantation (*Figure 1 D, H*). Patient was discharged on dual antiplatelet therapy (aspirin and clopidogrel), perindopril 5 mg, amlodipine 10 mg, doxazosin 2 mg, and atorvastatin 80 mg. A low dosage of selective β-blocker (bisoprolol

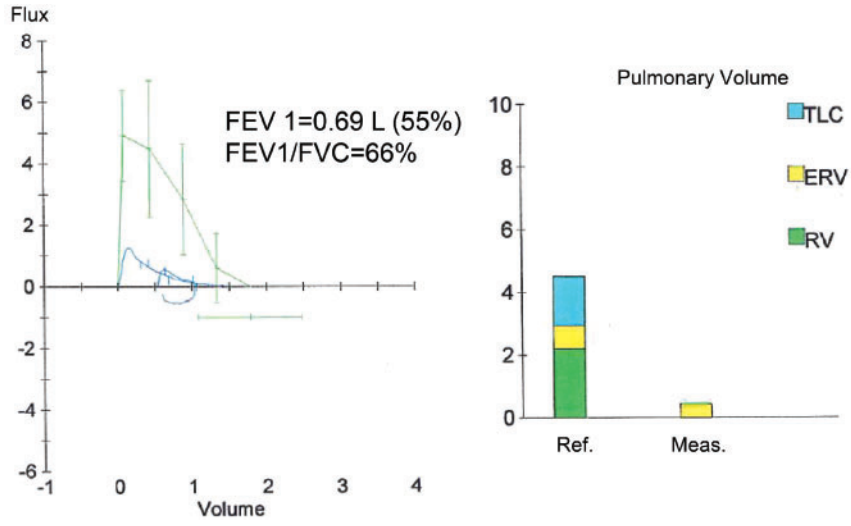

Figure 3 Pulmonary functional evaluation. ERV, expiratory reserve volume; FEV, forced expiratory volume; FVC, forced vital capacity; Meas, measured value; Ref, reference value; RV, residual volume; TLC, total lung capacity.

1.25 mg) was added [blood pressure (BP) 120/80 mmHg, heart rate (HR) 86 b.p.m.]. The patient was already on tiotropium 18 mcg for his COPD. After 5 years, the patient came to our attention for worsening effort angina (CCS III). A myocardial perfusion scintigraphy showed anterior and lateral ischaemia involving 18–20% of the left ventricular mass. In the meanwhile, diabetes mellitus type II was diagnosed and CKD worsened becoming severe (GFR 28 mL/min). Thus, perindopril was withdrawn and doxazosin was uptitrated to 4 mg as well as bisoprolol to 2.5 mg (BP 110/70 mmHg, HR 82 b.p.m.). Coronary artery angiography showed in-stent occlusive restenosis of LAD, critical stenosis of the SVG for OM1 due to distal progression of the disease (*Figure 2 A, B*). Saphenous vein graft for OM1 was treated with another DES (*Figure 2 C*), while an unsuccessful attempt of PCI was performed on LAD. We uptitrated bisoprolol to 5 mg (BP 120/70 mmHg, HR 80 b.p.m.). After 2 months, the patient underwent his scheduled pneumology follow-up that with spirometry that showed worsening of forced expiratory volume (FEV)1 (0.69 L, 55% of the predicted value) and of FEV1/forced vital capacity (66% of the predicted, *Figure 3*) with overall severe obstructive deficit. Salmeterol/Fluticasone 50/500 mcg was added to tiotropium, and a cardiology evaluation was suggested to re-evaluate therapy (in particular the need of β-blocker). The patient referred slight amelioration of symptoms after PCI with residual CCS II angina. Electrocardiogram (ECG) showed sinus rhythm with 78 b.p.m. (*Figure 4*). We decided not to withdraw bisoprolol but to add ivabradine 5 mg b.i.d. in order to control symptoms. The patient is actually in CCS Class I and the control spirometry showed moderate obstruction comparable to his chronic situation.

Discussion

The present case reflects the complexity of the IHD/COPD comorbidity and of the clinical and pharmacological decision-making in these patients. The COPD patients have more complex coronary disease and worse prognosis compared to IHD patients without COPD.[3] The detrimental effect on prognosis is mutual since troponin rise associated with COPD exacerbation is an independent negative prognostic marker and it is more probable in patients with IHD.[4] Moreover, pharmacological treatment in these patients is complex and several studies showed that COPD patients are usually undertreated[1,3,5] due to the fear of adverse effects, especially related to β-blockers. In example, β-blockers are underutilized because of potential respiratory adverse effects. However, cardioselective β-blockers produced no change in FEV1 or respiratory symptoms, as well as they did not affect the FEV1 treatment response to long-acting β2 agonists.[5] In addition, a meta-analysis showed a pooled relative risk reduction in mortality for COPD patients receiving β-blockers (relative risk (RR) 0.69, 95% confidence interval 0.62–0.78).[6] Given its high β1-selectivity, bisoprolol is the β-blocker of choice in COPD patients. For this reason, we used bisoprolol in these patients, although given the worsening of pulmonary function, we were not able to up titrate to the maximal dose. Thus, we decided to add ivabradine in order to reduce the angina symptoms burden. In this setting, ivabradine could have been considered even earlier than we did. In fact, a SHIFT subanalysis showed that ivabradine was similarly effective and safe in chronic HF patients with or without COPD, and can be safely combined with β-blockers in COPD[7] and a randomized trial demonstrated that selective HR reduction with ivabradine was effective in patients with asthma and COPD, with no alteration in respiratory function or symptoms.[8] Interestingly, lowering heart rate with ivabradine can improve exercise capacity and functional class in COPD patients with resting heart rate >90 b.p.m.[9] In addition, several studies showed that addition of ivabradine to β-blocker treatment was associated with a significantly higher benefit on symptoms and quality of life and lower

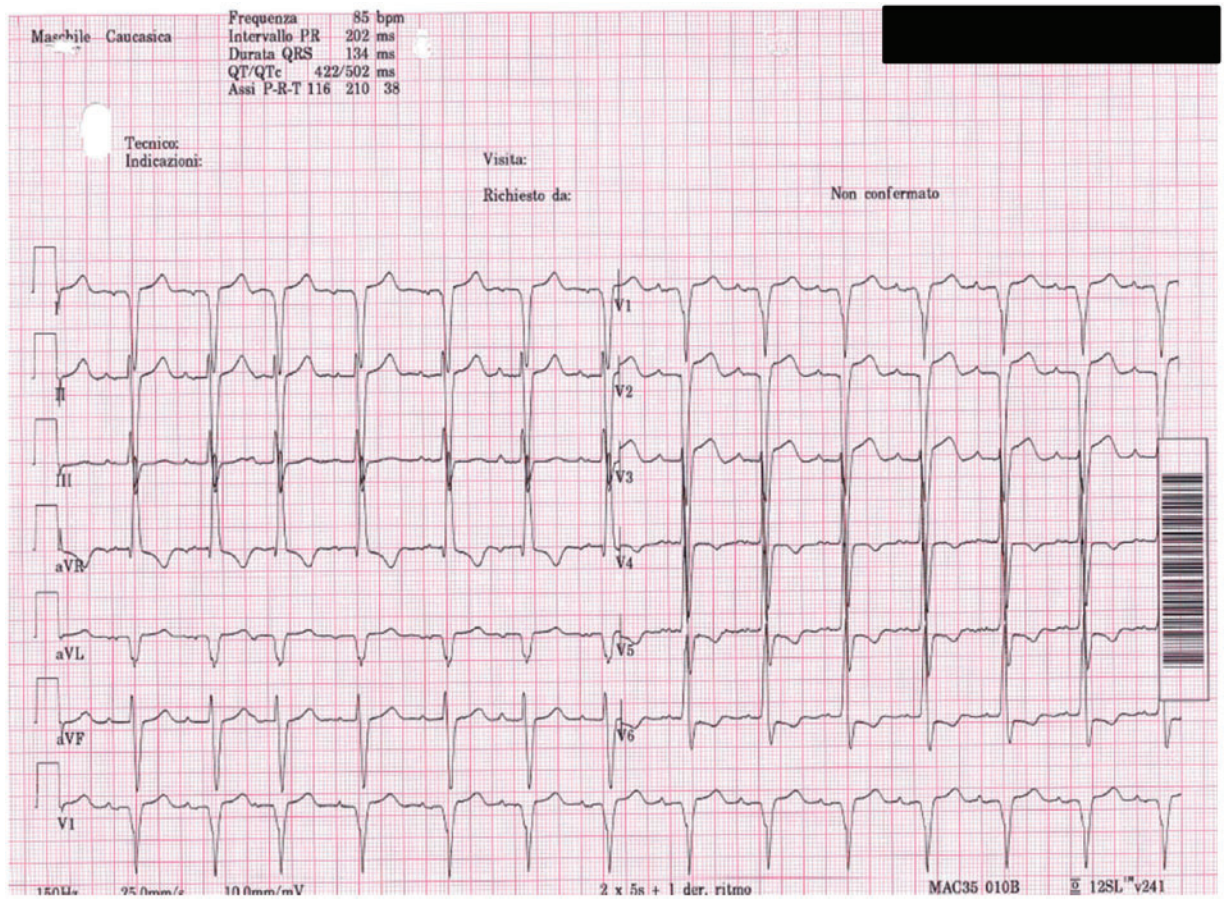

Figure 4 Electrocardiogram at the cardiology evaluation after pulmonary function worsening showing sinus rhythm with 85 b.p.m.

rate of adverse events when compared to β-blocker uptitration.[10,11]

Consent statement

The patient consent to report the case has been obtained.

Conflict of interest: none declared. The authors didn't receive any financial support in terms of honorarium by Servier for the supplement articles.

References

1. Campo G, Pavasini R, Biscaglia S, Contoli M, Ceconi C. Overview of the pharmacological challenges facing physicians in the management of patients with concomitant cardiovascular disease and chronic obstructive pulmonary disease. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:205–211.
2. Pavasini R, Biscaglia S, d'Ascenzo F, Del Franco A, Contoli M, Zaraket F, Guerra F, Ferrari R, Campo G. Antiplatelet treatment reduces all-cause mortality in COPD patients: a systematic review and meta-analysis. *COPD* 2016;**13**:509–514.
3. Campo G, Pavasini R, Malagù M, Mascetti S, Biscaglia S, Ceconi C, Papi A, Contoli M. Chronic obstructive pulmonary disease and ischemic heart disease comorbidity: overview of mechanisms and clinical management. *Cardiovasc Drugs Ther* 2015;**29**:147–157.
4. Pavasini R, d'Ascenzo F, Campo G, Biscaglia S, Ferri A, Contoli M, Papi A, Ceconi C, Ferrari R. Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: systematic review and meta-analysis. *Int J Cardiol* 2015;**191**:187–193.
5. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2005; 4:CD003566.
6. Etminan M, Jafari S, Carleton B, FitzGerald JM. Beta-blocker use and COPD mortality: a systematic review and meta-analysis. *BMC Pulm Med* 2012;**12**:48.
7. Tavazzi L, Swedberg K, Komajda M, Böhm M, Borer JS, Lainscak M, Robertson M, Ford I; SHIFT Investigators. Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: an efficacy and safety analysis of SHIFT study. *Int J Cardiol* 2013;**170**:182–188.
8. Majewski S, Slomka S, Zielinska-Wyderkiewicz E, Ciebiada M, Gorski P. Heart rate-lowering efficacy and respiratory safety of ivabradine in patients with obstructive airway disease: a randomized, double-blind, placebo-controlled, crossover study. *Am J Cardiovasc Drugs* 2012;**12**:179–188.
9. Mahmoud K, Kassem HH, Baligh E, ElGameel U, Akl Y, Kandil H. The effect of ivabradine on functional capacity in patients with chronic obstructive pulmonary disease. *Clin Med (Lond)* 2016;**16**: 419–422.
10. Glezer M, Vasyuk Y, Karpov Y. Efficacy of ivabradine in combination with beta-blockers versus uptitration of beta-blockers in patients with stable angina (CONTROL-2 Study). *Adv Ther* 2018;**35**: 341–352.
11. Amosova E, Andrejev E, Zaderey I, Rudenko U, Ceconi C, Ferrari R. Efficacy of ivabradine in combination with beta-blocker versus uptitration of beta-blocker in patients with stable angina. *Cardiovasc Drugs Ther* 2011;**25**:531–537.