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CASE REPORT
Heart failure

Treatment of refractory vasospastic angina complicated by acute pulmonary oedema with levosimendan: a case report

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Background Vasospastic angina (VA) is an important cause of chest pain and patients often have 3- to 6-month clusters of recurrent attacks, separated by relatively asymptomatic periods. During these episodes the resulting myocardial ischaemia can lead to clinical complications of different severity, including acute myocardial infarction, acute heart failure, and cardiogenic shock. The management of severe and recurrent VA attacks is challenging, and no specific recommendations exist in recent cardiologic guidelines on the pharmacological strategy (inotropic/vasopressor agents) to adopt for this acute clinical setting.

Case summary We present a case of recurrent episodes of VA complicated by acute pulmonary oedema and cardiogenic shock despite maximal tolerated therapy (intravenous calcium antagonist and nitrates) that was successfully treated with levosimendan.

Discussion Levosimendan rapidly reverted cardiogenic shock, acute pulmonary oedema, and mitral regurgitation caused by a refractory coronary spasm, contributing to persistent clinical stabilization. Further evidence and a longer follow-up are needed to support our observation on the efficacy of levosimendan in this specific clinical setting.

Keywords Vasospastic angina • Acute pulmonary oedema • Cardiogenic shock • Mitral regurgitation levosimendan • Case report

Learning points

- The management of severe and refractory vasospastic angina is challenging, and no specific recommendations for this clinical setting exist in recent cardiologic guidelines.
- Levosimendan rapidly reverted cardiogenic shock, acute pulmonary oedema, and mitral regurgitation caused by a refractory coronary spasm, contributing to a persistent clinical stabilization.

Introduction

Vasospastic angina (VA) classically causes rest angina and can contribute to acute coronary syndromes, ventricular arrhythmias, and sudden death. Smoking, Asian ethnicity, and female sex are known risk factors. Its diagnosis is based on the presence of nitrate-responsive angina associated with transient ischaemic electrocardiographic changes due to coronary artery spasm, either spontaneous or induced by acetylcholine, ergonovine, or hyperventilation.[1] Its pathogenesis remains uncertain, with arterial tone ranging from mild

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constriction to completely coronary occlusion. The management usually implicates lifestyle changes (smoking interruption), calcium channel, and nitrates as mainstream pharmacologic therapy. The natural history of patients with VA may be characterized by 3- to 6-month clusters of incoming attacks, in most cases without a defined trigger, poorly responsive to high-dose calcium antagonists and nitrates.[2] The management of severe and refractory VA is challenging, and no specific recommendations for this clinical setting exist in cardiologic guidelines.[3] Several therapeutic approaches have been proposed, including high-dose calcium channel blockers, nitrates, potassium-channel opener (nicorandil), and rho kinase inhibitor (fasudil). Other non-pharmacological strategies are selective coronary stent implantation, coronary artery bypass grafting with cardiac denervation, and left stellate ganglion blockade.[1]

Timeline

Previous 5 months	5 vasospastic angina (VA) episodes complicated by acute pulmonary oedema
ICCU admission	New VA episode complicated by acute pulmonary oedema andcardiogenic shock
2nd day	Coronary angiography
4th day	Refractoriness to maximal tolerated therapy
5-7th day	Levosimendan infusion
15th day	Hospital discharge
3rd month follow up	Asymptomatic patient without further relapses

Case presentation

A 75-year-old woman was admitted to our intensive cardiac care unit (ICCU) because of recurrent VA episodes complicated by acute pulmonary oedema. The diagnosis of VA was firstly made in 2013, when she underwent coronary angiography after experiencing several rest angina episodes, especially at night and in the early morning. The angiogram excluded the presence of obstructive coronary atherosclerosis. After ergonovine administration, left circumflex coronary artery spasm was induced (Timeline table), and it was associated with chest pain and electrocardiographic changes with characteristics similar to those of spontaneous episodes. Since then, the patient continued to experience rare (one/year) and responsive to sublingual nitrates VA episodes while she was on chronic verapamil (240 mg/day) and isosorbide mononitrate (50 mg/day). In the 5 months preceding the index hospitalization, the patient had five more severe VA attacks, associated with acute heart failure, requiring hospitalization. She was then transferred to our ICCU after a new VA episode complicated by acute pulmonary oedema and haemodynamic instability.

After clinical stabilization with intravenous calcium antagonists, nitroglycerine, and diuretics, coronary angiography was repeated and confirmed the absence of any obstructive vessels disease. Spontaneous coronary spasm was not observed due to achieved clinical stability and concomitant vasodilator therapy. In the following days, the patient experienced further abrupt episodes of VA. During them, the electrocardiogram showed new left bundle-branch block (LBBB), with concomitant echocardiographic evidence of posterior and anterolateral wall akinesia, severe mitral regurgitation (MR) secondary to posterior leaflet tethering, with reduction of left ventricular ejection fraction from 65% to 35% and increase in pulmonary systolic arterial pressure from 40 mmHg to 60 mmHg (Supplementary material). Despite maximal tolerated intravenous therapy (verapamil 3 γ/kg/min and nitroglycerine 0.125 γ/kg/min), the patient had once again a severe VA attack characterized by acute pulmonary oedema (O_2 saturation from 98% to 87%) and cardiogenic shock (systolic arterial pressure decreased from 110 mmHg to 65 mmHg, blood lactate levels raised to 5 mmol/L). Non-invasive ventilation was immediately started (pressure support 10 cmH_2O, positive end-expiration pressure 5 cmH_2O, and O_2 inspired fraction 80%) and current intravenous therapy was discontinued because of critical arterial hypotension and lack of coronary vasospasm improvement. Then, an intravenous infusion of levosimendan at a dose of 0.05 γ/kg/min was started without an initial bolus and it was continued at the same infusion rate for 48 h. Few hours after the beginning of levosimendan infusion, a progressive clinical improvement was documented, with a marked reduction of respiratory work and symptoms, restoration of normal arterial pressure and peripheral perfusion. The levosimendan infusion was well tolerated, without symptomatic hypotension requiring vasoconstrictors. In parallel, recovery to baseline electrocardiogram (incomplete LBBB with mild ST-segment depression and negative T-wave in leads D1 and aVL) was observed along with normalization of wall motion abnormalities and return to baseline MR (from severe to mild grade) at echocardiographic evaluation (*Figure 1* and Supplementary material). After 15 days, the patient was discharged with the same initial medical therapy (aspirin 100 mg/day, verapamil 120 mg b.i.d., and mononitrate isosorbide 50 mg/day), and at 3-month follow-up, she was free of recurrences of VA while continuing oral calcium channel blockers and nitrates.

Discussion

Vasospastic angina is a form of angina caused by coronary artery spasm, which consists of a sudden and variable vasoconstriction of a segment of an epicardial artery, potentially resulting in a severe reduction of coronary blood flow. Angina attacks are usually short in duration (2–5 min) and tend to recur, presenting 'hot phases', with frequent recurrence of angina, alternated to 'cold phases', with remission of symptoms for weeks or months.[1] The mainstays of treatment of coronary vasospasm are nitroglycerine and calcium channel antagonists; however, responses to treatment can be variable, as also reflected in the current report. Indeed, in about 10% of cases, coronary artery spasm may be refractory to optimal vasodilator therapy, and may require very high doses of calcium-antagonists/nitrates, in order to manage the vasospastic 'storm'.[1]

According to the extent, location, and duration of the coronary spasm, the resulting myocardial ischaemia can lead to clinical complications of different severity, including acute heart failure, cardiogenic shock, and life-threatening arrhythmias. In our case, recurrent acute pulmonary oedema, and even cardiogenic shock, secondary to significant MR, developed during myocardial ischaemia caused by coronary

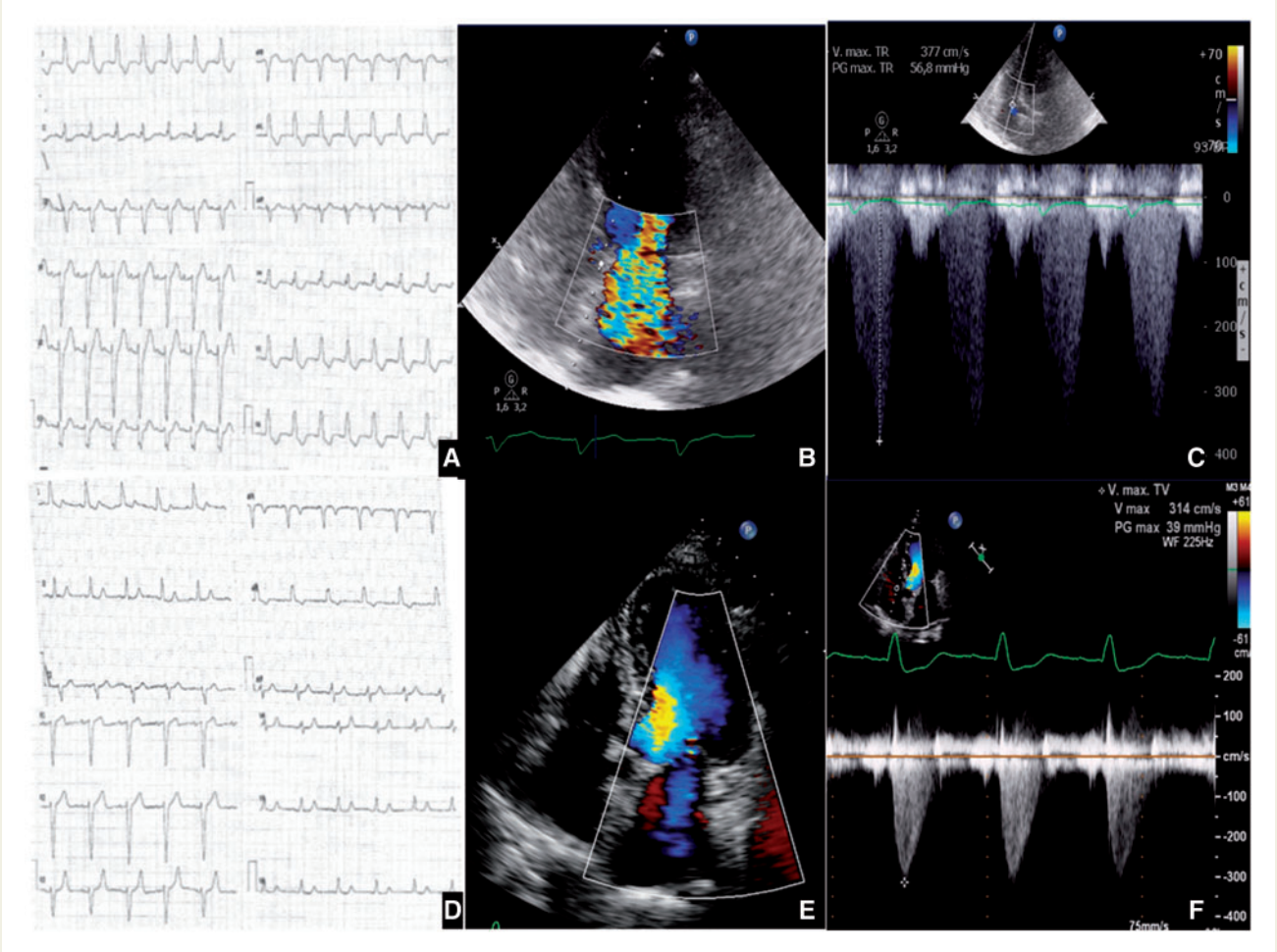

Figure 1 Electrocardiogram and echocardiography during acute pulmonary oedema and after the beginning of levosimendan infusion. Electrocardiogram, echocardiography four-chamber apical view with colour Doppler on mitral valve, and continuous wave Doppler on tricuspid valve during acute pulmonary oedema and chest pain showing an ST-segment depression in anterolateral leads (*A*), significant mitral regurgitation (*B*), and pulmonary hypertension (*C*). After levosimendan infusion was introduced, the patient reported a significant reduction of dyspnoea, normalization of electrocardiogram abnormalities (*D*), and reduction of mitral regurgitation severity (*E*) together with a reduction of pulmonary pressure (*F*).

spasm, despite maximal intravenous vasodilator therapy. A further mechanism that may have contributed to acute ventricular dysfunction includes LBBB development.[4] Moreover, an overlapping takotsubo cardiomyopathy or phaeochromocytoma cannot be excluded although either apical ballooning or hypertensive crisis were observed during VA episodes.[5] The management of these dramatic VA attacks is challenging, and no specific recommendations exist in recent cardiologic guidelines on the pharmacological strategy (inotropic/vasopressor agents) to adopt for this acute clinical setting.[3] Notably, cathecolamines, the most widely inotropic agents use in patients with cardiogenic shock, may exacerbate vasospasm. Moreover, these drugs have chronotropic, pro-arrhythmic, and direct myocyte toxic effects, and may increase myocardial oxygen consumption and induce coronary hypoperfusion, further exacerbating oxygen delivery/consumption mismatch in the setting of VA.

Levosimendan is a calcium sensitizer and ATP-dependent potassium-channel opener that was developed as an inodilating drug for the treatment of acute heart failure. Differently from other inotropic drugs, it has some unique characteristics, in terms of mechanism of action, pharmacodynamics properties, and haemodynamic effects.[6,7] Levosimendan does not raise intracellular calcium but selectively binds to calcium-saturated cardiac troponin C, enhancing the myofilament sensitivity to calcium.[6,7] Therefore, levosimendan-induced improvement in myocardial contraction is not associated with increased oxygen consumption. By opening the ATP-sensitive potassium channels in the vasculature, it also induces vasodilation, and it increases tissue perfusion in all arterial and venous vascular beds, including coronary arteries.[8] Interestingly, dysfunction of these channels has been shown to be involved in VA.[9]

To our knowledge, this is the first case report on the use of levosimendan in this peculiar clinical setting (PubMed search updated to October 2018). In our patient, levosimendan rapidly stabilized the patient, and this clinical benefit was possibly associated with three major haemodynamic effects: (i) positive inotropism without increase in myocardial oxygen consumption; (ii) afterload reduction with improvement of MR; and (iii) direct vasodilation of coronary arteries in

a setting of refractory constriction-induced ischaemia. All these effects may have contributed in our patient to counteract coronary spasm, to improve myocardial perfusion, and to hold back the resulting vicious spiral of haemodynamic deterioration. Notably, the recovery of cardiac performance resulted in systemic arterial pressure increase despite drug-induced vasodilation.

In addition, the peculiar pharmacokinetics of levosimendan might explain the persistent beneficial effect observed during the remaining hospitalization period and after discharge. Indeed, levosimendan is converted to an active metabolite with a prolonged half-life, up to 7–9 days, responsible for its sustained haemodynamic effect.[10]

In conclusion, in our case, levosimendan rapidly reverted cardiogenic shock, acute pulmonary oedema, and MR caused by a refractory coronary spasm, contributing to a persistent clinical stabilization. Further evidence and a longer follow-up are needed to support our observation on the efficacy of levosimendan in this specific clinical setting.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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