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Use of Levosimendan as bridge therapy to surgical correction of post-infarction ventricular septal defect: a case report

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Abstract. – OBJECTIVE: Ventricular septal defect (VSD) is an uncommon but frequently fatal complication following acute myocardial infarction. In medically treated patients, mortality rates exceed 90%, while the surgical repair is associated with better outcomes, even though optimal surgical timing is still under debate.

CASE REPORT: We present the case of a 78-years-old man with no previous remarkable cardiological history admitted to our Emergency Department with the diagnosis of anterior ST-elevation myocardial infarction and significant reduction of left ventricular ejection fraction. The emergency coronary angiography showed sub-occlusion of the left anterior descending coronary artery, treated with stent implantation. The post-procedural echocardiography unveiled the presence of an apical VSD with a large left-to-right shunt, significant right ventricular overload and dysfunction. An intra-aortic balloon pump (IABP) was positioned and, after Heart Team evaluation, a delayed surgical approach was planned. As a bridge to the intervention Levosimendan infusion was administered, on top of IABP support, and a significant improvement in bi-ventricular function and pressure profiles was obtained. Cardiac surgery was successfully performed 9 days after the admission without periprocedural complications.

CONCLUSIONS: This unique case supports the use of Levosimendan as a valid pharmacological strategy for perioperative management of VSD.

Key Words:
Heart failure, Acute myocardial infarction, Ventricular septal defect, Levosimendan, Personalized medicine.

Introduction

Ventricular septal defect (VSD) is a rare but potentially lethal complication of acute myocardial infarction (AMI). Although the incidence of this complication has fallen to 0.17–0.31% after the introduction of early percutaneous revascularization therapy, the survival of post-infarction VSD has remained constantly low, with 43% mortality in case of surgical management and up to 94% for medical treatment[1,2].

Timing of surgical repair is the most important factor affecting patients' survival. Available data show that while early surgery is associated with a high mortality rate and a high risk of recurrent ventricular rupture, delayed intervention allows repair of the scarring tissue but carries the risk of rupture extension, right ventricular failure, and death while waiting for surgery[2]. Therefore, a definite consensus about the optimal timing for surgery is lacking, and the routine use of mechanical or pharmacological support could be a valuable strategy to achieve clinical stabilization.

In this report, we describe the case of a patient affected by post-infarction VSD, in whom Levosimendan was administered as a bridge to reparative surgery.

Case Report

A 78-years-old man with no previous cardiological history was admitted to our emergency department (ED) because of 2 hour-lasting oppressive chest pain and worsening dyspnea.

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Physical examination showed blood pressure of 100/60 mmHg, heart rate of 90 beats per minute, regular heart sounds with a mild systolic murmur, arterial oxygen saturation of 90%, and tachypnea, with bibasilar inspiratory crackles.

The electrocardiogram revealed sinus rhythm with 2 mm ST elevation in anterior leads. High-sensitive Troponin I (HsTnI) levels were significantly increased at first determination. The transthoracic echocardiography showed Left Ventricular Ejection Fraction (LVEF) of 37% and diastolic dysfunction (E/e' 16), apical-septal akinesia, antero-lateral mid ventricular hypokinesia, and moderate functional mitral regurgitation. Mild right ventricular dysfunction [Tricuspid Annular Plane Excursion (TAPSE) 15 mm and Right Ventricle Fractional Area Change (RV-FAC) 35%], moderate tricuspid regurgitation, and mild pulmonary hypertension were also detected.

The diagnosis of anterior ST-segment elevation myocardial infarction (STEMI) was made. Intra-venous acetylsalicylic acid and oral loading-dose Ticagrelor were administered at ED. The patient was transferred to the Cath lab for urgent coronary angiography, which showed sub-occlusion of the left anterior descending (LAD) coronary artery. After successful percutaneous revascularization (PCI) with stent implantation, he was transferred to our intensive cardiac care unit (ICCU) for multiparametric monitoring.

The patient remained asymptomatic and stable until the following day when he experienced acute epigastric pain, hypotension, tachycardia, and mild increase in lactates (3.5 mmol/L). The echocardiography revealed the presence of an apical septal rupture with multiple jets at Color Doppler, determining large left-to-right shunt (Qp/Qs ratio of 2.2), significant right ventricular dysfunction (TAPSE 12 mm, RV-FAC 25%), and severe tricuspid regurgitation (Figure 1 A-B). The patient was rapidly transferred to the Cath Lab for intra-aortic balloon pump (IABP) positioning. For a better morphological characterization, a cardiac computed tomography (CT) scan was also performed and revealed a ragged, large VSD (24 × 22 mm), ruling out the hypothesis of percutaneous repair (Figure 1 C).

The case was discussed at the local Heart Team: in consideration of patient's hemodynamics and in order to increase the probability of surgical success, it was decided to postpone cardiac intervention and adopt a watchful waiting

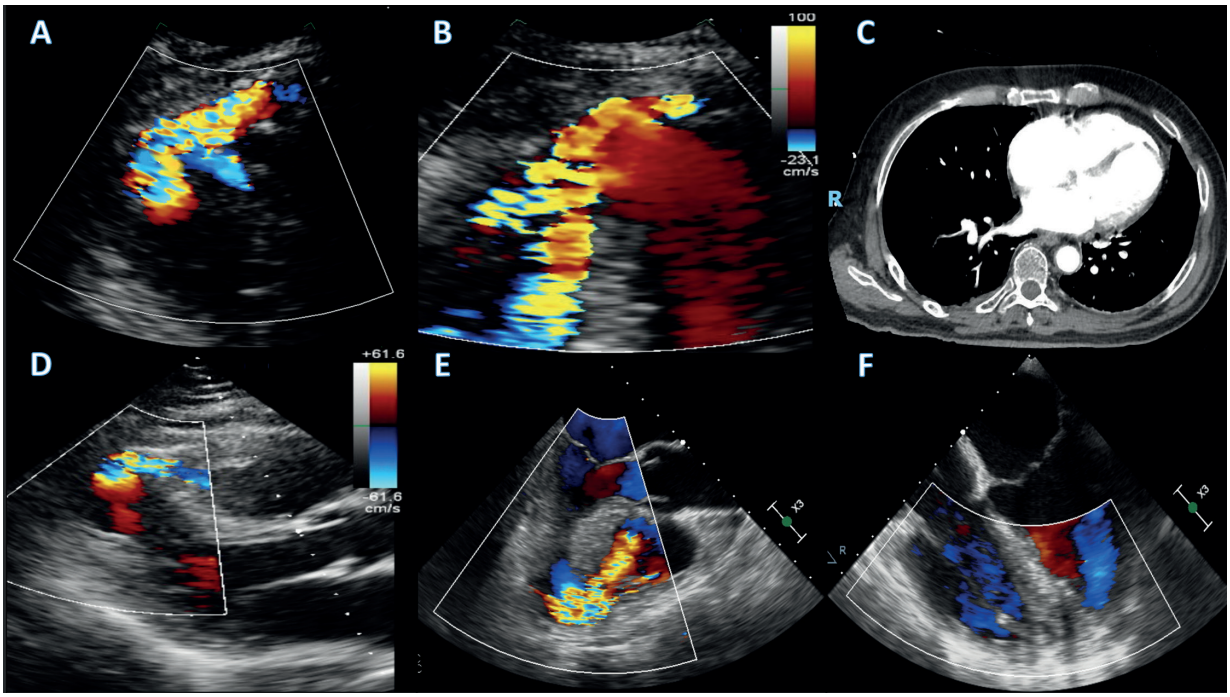

Figure 1. Use of Levosimendan as a bridge therapy to surgical correction of post-infarction VSD. Parasternal long axis **(A)** and apical 4 chamber **(B)** view: apical septal rupture with multiple jets at Color Doppler and a significant left-to-right shunt. Cardiac CT: VSD (24 × 22 mm) with an irregular morphology **(C)**. After Levosimendan infusion, echocardiography revealed an improvement in bi-ventricular function and a reduction in pulmonary pressures **(D)**. Intra-procedural transesophageal echocardiography: apical septal rupture **(E)** and its correction with heterologous pericardial patch and no residual shunt **(F)**.

strategy. Ticagrelor was stopped, and GpIIb/IIIa inhibitors started as bridging therapy.

Considering its effects on pulmonary pressures and on RV function, an intravenous infusion of Levosimendan was started (infusion for 48 h), without hypotension. Levosimendan infusion induced a progressive improvement in bi-ventricular performance, with a reduction of echocardiographic signs of right heart failure (Figure 1 D) and significant clinical improvement with the restoration of normal mean arterial pressure and peripheral perfusion.

On day 9, VSD repair with heterologous pericardial patch and tricuspid annuloplasty with modified De Vega technique were performed under transesophageal echocardiography guide (Figure 1 E-F). No complications occurred after surgery, and IABP was removed on the 3rd post-operative day. Transthoracic echocardiography showed an intact pericardial patch, a moderate reduction in LVEF, mild radial right ventricular dysfunction (RVFAC: 32%), and trivial tricuspid regurgitation. On day 15, the patient was discharged from ICCU and transferred to the cardiac rehabilitation center in good clinical conditions.

Discussion

VSD is a rare but life-threatening complication of myocardial infarction burdened by high perioperative mortality[1,2]. The best surgical window for this condition has not been defined yet, and whether an immediate aggressive approach or a delayed surgery provides better results is still questioned[2]. Retrospective studies demonstrated that operative mortality was significantly lower if the repair was performed more than 7 days from AMI than before (54.1% *vs.* 18.4%)[2]. Guidelines suggest that delayed elective surgical repair may be considered in those patients responsive to an initial aggressive heart failure management[1], while medical approach across this period has never been investigated properly.

IABP implantation is recommended due to its multiple benefits[3-5]: it reduces afterload, increases diastolic perfusion of coronary arteries, and reduces the shunting quote through left ventricle unloading. In this way, it reduces the risk of hemodynamic deterioration and allows to gain time favoring VSD tissue healing[5]. The use of Impella and extracorporeal membrane oxygenation (ECMO) has been supported by few clinical cases[3,5] and formal indications for these devices remain high-risk percutaneous coronary intervention and cardiogenic shock[3].

On the other side, medical therapy is mainly based on inotropes, vasodilators and vasoconstrictors, alone or in combination[5]. Among these drugs, the specific use of Levosimendan has never been described. It is a calcium sensitizer and potassium channel opener, and it has been extensively investigated in clinical studies on overt acute heart failure and cardiogenic shock[6] but its potential use at an earlier stage is not yet defined. In this clinical setting, its administration before planned reparative surgery bridged the patient through the critical phase. Levosimendan has been studied in more than 40 small clinical trials in cardiac surgery[6], showing that it could prevent and effectively treat low cardiac output syndrome. Nevertheless, the results from three recent large, randomized trials were either neutral or inconclusive[6], with mortality benefit limited to patients with low ejection fraction or undergoing coronary artery bypass grafting procedures.

In our clinical scenario, the rationale of using this drug was mainly based on two considerations: on the one hand, in patients with STEMI, Levosimendan hemodynamic effects are similar to those seen with IABP, in terms of increase in cardiac power index and reduction of systemic vascular resistances[6]; on the other hand, by combining pulmonary vascular resistance reduction with increased right ventricular contractility, it improves right ventriculo-arterial coupling and reduces elevated right-sided pressure, which is an important prognostic factor in cardiac surgery. In addition, the pharmacokinetics of Levosimendan might explain the persistent beneficial effect observed during the post-operative phase. Indeed, Levosimendan active metabolites have a prolonged half-life[6]. In this perspective, the use of Levosimendan on top of IABP in the acute management of post-infarction VSD might represent a possible approach as a bridge therapy for candidates to surgical repair.

Conclusions

In our case, Levosimendan contributed to reduce left-to-right shunt with three hemodynamic effects: (1) positive inotropism with an increase in LV stroke volume; (2) afterload decrease with reduction in systemic vascular resistance and left-to-right shunt; (3) improvement in right ventriculo-arterial coupling.

To our knowledge, this is the first case report on the perioperative use of Levosimendan in post-infarction VSD. Even though a larger population of study and long-term follow-up are needed, our experience suggests that the early administration of Levosimendan may be beneficial in selected high-risk patients in reducing mortality and improving surgical outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Consent

The author/s confirm that informed consent has been obtained for submission and publication of this case report including images.

References

1) Birnbaum Y, Fishbein MC, Blanche C, Siegel RJ. Ventricular septal rupture after acute myocardial infarction. N Engl J Med 2002; 347: 1426-1432.
2) Papalexopoulou N, Young CP, Attia RQ. What is the best timing of surgery in patients with post-infarct ventricular septal rupture? Interact Cardiovasc Thorac Surg 2013; 16: 193-196.
3) Russo G, Burzotta F, Aurigemma C, Pedicino D, Romagnoli E, Trani C. Can we have a rationalized selection of intra-aortic balloon pump, Impella, and extracorporeal membrane oxygenation in the catheterization laboratory? Cardiol J 2020 Dec 21. Doi: 10.5603/CJ.a2020.0182. Online ahead of print.
4) Testuz A, Roffi M, Bonvini RF. Left-to-right shunt reduction with intra-aortic balloon pump in postmyocardial infarction ventricular septal defect. Catheter Cardiovasc Interv 2013; 81: 727-731.
5) Pahuja M, Schrage B, Westermann D, Basir MB, Garan AR, Burkhoff D. Hemodynamic effects of mechanical circulatory support devices in ventricular septal defect. Circ Heart Fail 2019; 12: e005981.
6) Cosentino N, Niccoli G, Fracassi F, Rebuzzi A, Agostoni P, Marenzi G. Rationale, experimental data, and emerging clinical evidence on early and preventive use of levosimendan in patients with ventricular dysfunction. Eur Heart J Cardiovasc Pharmacother 2020; 6: 310-316.