Levosimendan in critical aortic stenosis complicated by cardiogenic shock: Case reports and literature review

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INTRODUCTION

Severe aortic stenosis (AS) associated with systolic dysfunction has an ominous prognosis [1]. Aortic valve replacement is the only effective treatment, but procedural risk in this condition is high [2, 3]. In cardiogenic shock (CS), intra-aortic balloon pumps and inotropic drugs may be used in emergency settings. Vasodilators carry risk of hypotension, but afterload reduction may be beneficial. A small prospective study with nitroprusside demonstrated rapid cardiac index (CI) augmentation with stable blood pressure in these patients [4]. Levosimendan (LVS) is a calcium-sensitizer of cardiac troponin with vasodilating properties [5]: its positive effects on heart failure (HF) with low cardiac output have been documented [6]. This article aims to describe our approach to the use of LVS as a stabilizing pharmacologic measure in patients with CS related to critical AS and to provide a review of current evidence in the literature.

CASE REPORTS

Patient 1

An 84-year-old man was admitted to our cardiovascular department for acute HF. His past medical history included moderate aortic stenosis, chronic kidney disease (CKD), and myelodysplasia. Transthoracic echocardiography revealed newly diagnosed impaired systolic function (left ventricular ejection fraction [LVEF] of 20%), low-flow low-gradient AS (mean gradient 28 mm Hg, valve area 0.6 cm^2, indexed stroke volume 20 ml/m^2), and moderate functional mitral regurgitation; right heart function was normal. The patient was treated using intravenous diuretics and initially obtained a clinical improvement. On the seventh day, urinary sepsis precipitated CS with AKI and hypoxic hepatitis. The patient was admitted to the intensive cardiac care unit (ICCU) in a state of profound hypotension, and an infusion of dobutamine and norepinephrine was started. Hemodynamic monitoring with a pulmonary artery catheter (PAC) confirmed a reduced CI (1.4 $l/min/m^2$) and elevated wedge pressure (20 mm Hg). Arterial pressure (AP) was stabilized, but the CI remained low, and the patient's clinical status continued to deteriorate. Emergency balloon aortic valvuloplasty was performed with about a 30% increase in the aortic area. Additionally, we observed a CI improvement allowing for discontinuation of norepinephrine; to verify ventricular response to the afterload reduction, we initiated a nitroprusside infusion and observed an increase in the CI without hypotension, so we proceeded with a 24-hour LVS infusion (0.05 mcg/kg/min titrated to 0.1 mcg/kg/min) with rapid echocardiography and PAC-guided dobutamine withdrawal, gradual reduction in wedge pressure down to 11 mm Hg, and improvement in diuresis. On day 5 after valvuloplasty, the patient underwent successful transcatheter aortic valve replacement (TAVR); he was discharged 7 days later. At 6 months of follow-up, he was

clinically stable; an echocardiogram showed LVEF of 50% and CKD remained in stage 3.

Patient 2

An 85-year-old man with known severe low flow-low low-gradient AS was admitted to our emergency department for acute pulmonary edema. His main comorbidity was stage 4 CKD. Echocardiography showed a severely hypokinetic left ventricle (LVEF 25%), heavily calcified aortic valve (mean transvalvular gradient 34 mm Hg, area 0.5 cm^2), with moderate-severe regurgitation and secondary mitral and tricuspid regurgitation in the absence of right section compromise (tricuspid annular plane systolic excursion 21 mm). The patient was admitted to the ICCU and treated with continuous positive airway pressure and diuretic infusion; nevertheless, he developed cardiogenic shock with acute kidney injury. A PAC catheter was inserted (CI 1.5 l/min/m^2, WP 25 mm Hg) and a dobutamine infusion started, obtaining a CI of 2.0 l/min/m^2 with valid diuresis. Echocardiography showed an increase in the transvalvular mean gradient up to 50 mm Hg and LVEF up to 40%, so we started nitroprusside infusion: the CI grew, and arterial pressure remained stable. Subsequently, a 24-hour LVS infusion at 0.05 mcg/kg/min was possible; dobutamine was gradually discontinued, and WP decreased to 13 mm Hg. Once clinical stability was achieved, organ functions recovered, and a successful TAVR was performed. To prevent contrast-induced nephropathy, continuous veno-venous hemodialysis was started 12 hours before the procedure and discontinued 48 hours later. The patient was discharged 8 days later, with LVEF of 37% and serum creatinine level of 2.4 mg/dl. Four-month follow-up was negative, with LVEF 42% and a stable estimated glomerular filtration rate.

DISCUSSION

CS in patients with severe AS is associated with high mortality; in a US registry, CS before TAVR occurred in 4% of cases and was characterized by 19% 30-day mortality [7]; in a recent observational study, TAVR had a similar outcome at one year in CS and non-CS patients and seemed to be a safe and effective treatment [8]; however, it is not promoted as an emergency approach. Balloon aortic valvuloplasty has been proposed in selected cases, but it is contraindicated in patients with aortic regurgitation, and the mortality rate of patients who do not promptly undergo TAVR remains high [9].

Pharmacological management of these patients is not easy. We used effectively LVS as a bridge to TAVR in the presence of CS, which indicates its capacity to improve ventricle-arterial coupling by reducing after-load mismatch. To address concerns regarding potential hypotension, we first conducted a test on left ventricular afterload sensitivity by co-administering dobutamine and nitroprusside, both with short half-lives. PAC monitoring was necessary to verify the response. To mitigate the risk of metabolite augmentation with excessive vasodilation, we started with a low infusion rate.

The response we observed is in line with other experiences reported in the literature. In the pre-TAVR era, a good clinical response and tolerability in two patients with AHF and AS was reported: a 24-hour LVS infusion sustained the patients till coronary artery bypass and aortic valve replacement, whereupon they were discharged from the hospital without complications [10]. In the same year, a case of a critically ill patient with coronary artery disease, low-gradient AS, and congestive HF was reported: a 16--hour LVS infusion was used as a bridge until surgery [11]. In a randomized clinical trial, 24 patients undergoing surgical aortic valve replacement were matched to receive LVS or placebo for 24 hours after anesthesia induction. In the treatment group, LVEF was lower, but during interventions a drop in cardiac function was noted only in the placebo group, showing that LVS may prevent the worsening of cardiac function; the LVS group needed a higher dose of norepinephrine after surgery but low nitroprusside doses [12].

Caetano et al. [13] reported 3 cases of AS patients undergoing LVS in different scenarios: two underwent successful surgical aortic valve replacemenwhile the third was an 85-year-old man whose hospitalization was complicated by urosepsis. He died one month after discharge [13]. Finally, in an interventional study, 9 patients affected by severe AS and AHF underwent one-day LVS administration with an improvement in the mean CI (patients with severe hypotension or end-stage renal failure were excluded) [14].

Table 1 summarizes currently available evidence in the literature; our experience is the first with LVS as a bridge to TAVR. It confirms that LVS might be a valid option in patients with low cardiac output syndrome requiring clinical stabilization.

CONCLUSIONS

Our small case series may suggest that LVS infusion can stabilize patients with CS precipitated by AS and systolic dysfunction. A dobutamine-nitroprusside testing under PAC monitoring in the ICCU may make this approach safe. Literature data are poor, but they corroborate our observations; further studies are needed to confirm this hypothesis.

Article information

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Table 1. Literature data about levosimendan in aortic stenosis and cardiogenic shock

Study (year)	Number of patients	Design	Therapeutic Regimen	Type of Surgery	Key findings
Prior et al. (2006) [10]	2	Case series	LVS 0.05 mcg/kg/min and 0.01mcg/kg/min, pre-surgery	SAVR + CABG	Negative fluid imbalance, fall inbody weight, and dyspnea improvement; no hypotension
Hoefer et al. (2006) [11]	1	Case report	LVS 0.1 mcg/kg/min without loading-dose, pre-surgery	SAVR + CABG	Improvement in ejection fraction,cardiac index, and mean gradient; no hypotension or arrhythmias
Jarvela et al. (2008) [12]	24	Randomized clinical trials	LVS 0.2 mcg/kg/min after anesthesia induction for SAVR and for 24 hours vs. placebo	SAVR or SAVR + CABG	In the control group, a significant drop in ejection fraction during surgery; after SAVR LVS, the group needed more norepinephrine and less nitroprusside
Caetano et al. (2012) [13]	3	Case series	LVS 0.01 mcg/kg/min for 24 hours	SAVR or medical therapy	Case 1: clinical improvement untildischarge and elective SAVR afterone month Case 2: clinical improvement untildischarge on medical therapy; the patient died after one month Case 3: clinical improvement until SAVR
Garcia-Gonzalez et al. (2015) [14]	9	Interventional non-randomized study	LVS 0.1 mc/kg/min for 24 hours	5 patients SAVR 4 patients medical therapy	Improvement in CI, pulmonary capillary wedge pressure, mPAP,PVR, SVi No hypotension or arrhythmias

Abbreviations: CABG, coronary artery by-pass grafting; CI, cardiac index; LVS, levosimendan; mPAP, mean pulmonary arterypressure; PVR, pulmonary vascular resistance; SAVR, surgical aortic valve replacement; SVi, stroke volume index

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