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Authors: Andrea Farina, Giuseppe Uccello, Gianluca Tiberti, Alfredo Bianchi, Stefano Savonitto

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

Short title: Levosimendan in patients with aortic stenosis and cardiogenic shock

Andrea Farina[1], Giuseppe Uccello[1], Gianluca Tiberti[1], Alfredo Bianchi[1], Stefano Savonitto[2]

[1]Cardiology Unit, Alessandro Manzoni Hospital, Lecco, Italy
[2]Clinica San Martino, Malgrate, Italy

Correspondence to:
Giuseppe Uccello, MD,
Cardiology Unit,
Alessandro Manzoni Hospital,
Via dell'Eremo 9/11,
23900 Lecco, Italy,
e-mail: gi.uccello@asst-lecco.it

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 is elevated in this condition [2, 3]. In cardiogenic shock (CS), intra-aortic balloon pump and inotropic drugs may be part of the emergent setting. 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 for these patients [4]. Levosimendan (LVS) is a calcium-sensitizer of cardiac troponin with vasodilating properties [5]: its positive effects in heart failure (HF) with low cardiac output are documented [6]. The aim of this article is to describe our approach with 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 division for acute HF. His past medical history included moderate aortic stenosis, a chronic kidney disease (CKD) and myelodysplasia.

Transthoracic echocardiography revealed an unknown impaired systolic function (left ventricular ejection fraction [LVEF] 20%), a low-flow low-gradient AS (mean gradient 28 mm Hg, valve area 0.6 cm^2, indexed stroke volume 20 ml/m^2) and a moderate functional mitral regurgitation; right heart function was normal. Patient was treated using intravenous diuretics obtaining an initial clinical improvement. On the seventh day an urinary sepsis precipitated CS with AKI and hypoxic hepatitis. The patient was admitted to intensive cardiac care unit (ICCU) in a state of profound hypotension and an infusion of dobutamine and norepinephrine was started. Hemodynamic monitoring with 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 CI remained low and the clinical status continued to deteriorate. An emergent balloon aortic valvuloplasty was performed with an about 30% increasing in aortic area. Additionally, we observed a CI improvement allowing for discontinuation of norepinephrine; to verify ventricular response to afterload reduction we initiated a nitroprusside infusion observing an increase in CI without hypotension, so we proceeded with a 24-hours LVS infusion (0.05 mcg/kg/min titrated to 0.1 mcg/kg/min) with a rapid echo- and PAC-guided dobutamine withdrawal, a 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 after. At 6 months follow-up, he was clinically stable: an echocardiogram showed a LVEF of 50% and CKD remained in third stage.

Patient 2

An 85-year-old man with known severe low flow-low gradient AS was admitted to our emergency department for acute pulmonary edema. His main comorbidity was a stage 4 CKD. Echocardiography showed a severely hypokinetic left ventricle (LVEF 25%), a heavilycalcified aortic valve (mean transvalvular gradient 34 mm Hg, area 0.5 cm^2), with moderate-severe regurgitation and secondary mitral and tricuspid regurgitation in absence in absence of right section compromising (tricuspid annular plane systolic excursion 21 mm). The patient was admitted to ICCU and treated with c-PAP and diuretic infusion, he nevertheless developed cardiogenic shock with acute kidney injury. A PAC catheter was positioned (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: CI enhanced and arterial pressure remained stable. Subsequently, a 24-hours LVS infusion at 0.05 mcg/kg/min was possible; dobutamine was gradually interrupted and WP decreased to 13 mm Hg.Once clinical stability

was achieved organ functions recovered, a successful TAVR was performed. To prevent contrast-induced nephropathy, CVVHD was started 12 hours before the procedure and discontinued 48 hours later. The patient was discharged 8 days after with a LVEF of 37%, and a serum creatinine of 2.4 mg/dl. Four-month follow up was negative with LVEF 42% and stable estimated glomerular filltration 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 a 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] but is not labelled 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 of patients who are not promptly subjected to TAVR remains high [9].

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

The response we observed is in line with other experiences reported in the literature. Already in a pre-TAVR era, it was firstly documented a good clinical response and tolerability in two patients presented with AHF and AS: a 24-hous LVS infusion brought patients to coronary artery by-pass and aortic valve replacement, being 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 bridge until surgery [11]. In a randomized clinical trial, twenty-four patients undergoing SAVR 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 worsening of cardiac function; the LVS groupneeded a higher dose of norepinephrine after surgery but low nitroprusside doses [12].

Caetano et al. [13] reported 3 cases of AS patients with different scenarios subjected to

LVS: two underwent successful SAVR while the third was an 85-year man with a hospitalization complicated by urosepsis that died one month after discharge [13]. Finally, in an interventional study, nine patients affected by severe AS and AHF underwent one-day LVS administration with an improvement in mean CI, even if patients with severe hypotension or end-stage renal failure were excluded [14].

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

CONCLUSIONS

Our small experience could suggest LVS infusion might be an option to stabilize patients with CS precipitated by AS and systolic dysfunction. Adobutamine-nitroprusside testing under PAC monitoring in the ICCU may make safer this approach. Literature data are poor but are moving in this direction; further studies are needed to confirm this hypothesis.

Article information

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REFERENCES

1. Varadarajan P, Kapoor N, Bansal RC, et al. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. Ann Thorac Surg. 2006; 82(6): 2111–2115, doi: 10.1016/j.athoracsur.2006.07.048, indexed in Pubmed: 17126120.
2. Tribouilloy C, Lévy F, Rusinaru D, et al. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol. 2009; 53(20): 1865–1873, doi: 10.1016/j.jacc.2009.02.026, indexed in Pubmed: 19442886.

3. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. EuroIntervention. 2022; 17(14): e1126–e1196, doi: 10.4244/eij-e-21-00009, indexed in Pubmed: 34931612.
4. Khot UN, Novaro GM, Popović ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. N Engl J Med. 2003; 348(18): 1756–1763, doi: 10.1056/NEJMoa022021, indexed in Pubmed: 12724481.
5. Pathak A, Lebrin M, Vaccaro A, et al. Pharmacology of levosimendan: inotropic, vasodilatory and cardioprotective effects. J Clin Pharm Ther. 2013; 38(5): 341–349, doi: 10.1111/jcpt.12067, indexed in Pubmed: 23594161.
6. Fang M, Cao H, Wang Z. Levosimendan in patients with cardiogenic shock complicating myocardial infarction: A meta-analysis. Med Intensiva (Engl Ed). 2018; 42(7): 409–415, doi: 10.1016/j.medin.2017.08.009, indexed in Pubmed: 29126662.
7. Masha L, Vemulapalli S, Manandhar P, et al. Demographics, procedural characteristics, and clinical outcomes when cardiogenic shock precedes TAVR in the United States. JACC Cardiovasc Interv. 2020; 13(11): 1314–1325, doi: 10.1016/j.jcin.2020.02.033, indexed in Pubmed: 32499022.
8. Debry N, Kone P, Vincent F, et al. Urgent balloon aortic valvuloplasty in patients with cardiogenic shock related to severe aortic stenosis: time matters. EuroIntervention. 2018; 14(5): e519–e525, doi: 10.4244/EIJ-D-18-00029, indexed in Pubmed: 29741481.
9. Goel K, Shah P, Jones BM, et al. Outcomes of transcatheter aortic valve replacement in patients with cardiogenic shock. Eur Heart J. 2023; 44(33): 3181–3195, doi: 10.1093/eurheartj/ehad387, indexed in Pubmed: 37350747.
10. Prior DL, Flaim BD, MacIsaac AI, et al. Pre-operative use of levosimendan in two patients with severe aortic stenosis and left ventricular dysfunction. Heart Lung Circ. 2006; 15(1): 56–58, doi: 10.1016/j.hlc.2005.03.008, indexed in Pubmed: 16473793.
11. Hoefer D, Jonetzko P, Hoermann C, et al. Successful administration of levosimendan in a patient with low-gradient low-output aortic stenosis. Wien Klin Wochenschr. 2006; 118(1-2): 60–62, doi: 10.1007/s00508-005-0508-2, indexed in Pubmed: 16489528.
12. Järvelä K, Maaranen P, Sisto T, et al. Levosimendan in aortic valve surgery: cardiac performance and recovery. J Cardiothorac Vasc Anesth. 2008; 22(5): 693–698, doi: 10.1053/j.jvca.2008.01.024, indexed in Pubmed: 18922425.
13. Caetano F, Mota P, Barra S, et al. Use of levosimendan in critically ill patients with severe aortic stenosis and left ventricular dysfunction. Eur Heart J Acute Cardiovasc

Care. 2012; 1(4): 281–284, doi: 10.1177/2048872612467294, indexed in Pubmed: 24062918.

14. García-González MJ, Jorge-Pérez P, Jiménez-Sosa A, et al. Levosimendan improves hemody-namic status in critically ill patients with severe aortic stenosis and left ventricular dysfunction: An interventional study. Cardiovascular Therapeutics. 2015; 33(4): 193–199, doi: 10.1111/1755-5922.12132, indexed in Pubmed: 25959786.

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 0.01 mcg/kg/min, pre-surgery	SAVR + CABG	Negative fluid imbalance, fall in body 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	Randomised clinical trials	LVS 0.2 mcg/kg/min after anaesthesia induction for SAVR and for 24-hours vs. placebo	SAVR or SAVR + CABG	In control group significant drop in ejection fraction during surgery; after SAVR LVS 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 until discharge and elective SAVR afterone month Case 2: clinical improvement until discharge on medical therapy; he passed after one month Case 3: clinical improvement until SAVR
Garcia-Gonzalez et al. (2015) [14]	9	Interventional nonrandomised 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

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