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

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 Farina¹, Giuseppe Uccello¹, Gianluca Tiberti¹, Alfredo Bianchi¹, Stefano Savonitto²

¹Cardiology Unit, Alessandro Manzoni Hospital, Lecco, Italy
²Clinica 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 cm², indexed stroke volume 20 ml/m²) 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/m²) 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 heavily calcified aortic valve (mean transvalvular gradient 34 mm Hg, area 0.5 cm²), with moderate-severe regurgitation and secondary mitral and tricuspid regurgitation 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/m², WP 25 mm Hg) and a dobutamine infusion started, obtaining a CI of 2.0 l/min/m² 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 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 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-hours 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 group needed 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.

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REFERENCES


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

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of patients</th>
<th>Design</th>
<th>Therapeutic Regimen</th>
<th>Type of Surgery</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior et al. (2006) [10]</td>
<td>2</td>
<td>Case series</td>
<td>LVS 0.05 mcg/kg/min and 0.01 mcg/kg/min, pre-surgery</td>
<td>SAVR + CABG</td>
<td>Negative fluid imbalance, fall in body weight and dyspnea improvement; no hypotension</td>
</tr>
<tr>
<td>Hoefer et al. (2006) [11]</td>
<td>1</td>
<td>Case report</td>
<td>LVS 0.1 mcg/kg/min without loading-dose, pre-surgery</td>
<td>SAVR + CABG</td>
<td>Improvement in ejection fraction, cardiac index and mean gradient; no hypotension or arrhythmias</td>
</tr>
<tr>
<td>Jarvela et al. (2008) [12]</td>
<td>24</td>
<td>Randomised clinical trials</td>
<td>LVS 0.2 mcg/kg/min after anaesthesia induction for SAVR and for 24-hours vs. placebo</td>
<td>SAVR or SAVR + CABG</td>
<td>In control group significant drop in ejection fraction during surgery; after SAVR LVS group needed more norepinephrine and less nitroprusside</td>
</tr>
</tbody>
</table>
| 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 after one 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 mcg/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 artery pressure; PVR, pulmonary vascular resistances; SAVR, surgical aortic valve replacement; SVi, stroke volume index