


CASE REPORT

Addition of levosimendan to overcome acute cardiogenic shock—Paving the way for later heart transplantation—A first case report

Christian Flottmann¹ | Daniel Dumitrescu¹ | Christian Sohns² | Volker Rudolph^{1,3} | Henrik Fox^{3,4} 

¹Clinic for General and Interventional Cardiology/Angiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

²Clinic for Electrophysiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

³Heart Failure Department, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

⁴Clinic for Thoracic and Cardiovascular Surgery, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

Correspondence

Henrik Fox, Clinic for Thoracic and Cardiovascular Surgery, Herz- und Diabeteszentrum Nordrhein-Westfalen, Ruhr-Universität Bochum, Georgstrasse 11, D-32545 Bad Oeynhausen, Germany.
Email: hfox@hdz-nrw.de

Abstract

Treatment of refractory cardiogenic shock has poor outcome. Levosimendan addition may help to achieve hemodynamic stabilization and improve conditions to where further treatment options such as listing for heart transplantation may become possible.

KEY WORDS

cardiogenic shock, hypoperfusion syndrome, levosimendan, low output syndrome, mechanical circulatory support, transplantation

1 | INTRODUCTION

Cardiogenic shock is associated with high mortality. Pharmacologic treatment options are limited, and mechanical circulatory support implies risks. There is need for novel pharmacological approaches. We report a unique case of a 57-year-old in cardiogenic shock with multiorgan failure. Intravenous levosimendan application resulted in hemodynamic stabilization and allowed heart transplantation.

Acute heart failure and cardiogenic shock are challenging diseases in daily clinical practice and remain associated with high mortality rates.¹ There are currently no consistent

treatment strategies for these patients, because individual patient characteristics vary widely.¹ This means that recommendations for the optimal treatment of this patient cohort are scarce.

This is a relevant topic because there are limited pharmacologic treatment options for cardiogenic shock, and the use of mechanical circulatory support is associated with risk of infection, bleeding, and vessel or nerve injury.² Therefore, alternative treatment options and strategies are needed, especially to manage hypoperfusion syndrome, where use of catecholamines is unavoidable but accompanied by well-documented side effects.³ Alternatives to catecholamines are

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preferred, such as the calcium sensitizer levosimendan.¹ Use of levosimendan is the subject of debate, because this agent appears to be a novel and promising approach to treatment, but no large study has yet been able to demonstrate significant advantages with levosimendan treatment.⁴

The goals of therapy in cardiogenic shock are to overcome hypoperfusion syndrome (restoring sufficient tissue perfusion), maintain cellular function, preserve cardiac function, and stabilize hemodynamics.⁵ While there is debate over the beneficial long-term effects of levosimendan, nothing is known about the potential benefits of adding levosimendan to overcome cardiogenic shock, and perhaps stabilize a patient for long enough to allow alternative approaches of treatment (eg heart transplantation).

To provide some information on the use of levosimendan as an add-on therapy to manage cardiogenic shock, we present the case of an adult male patient with worsening of heart failure resulting in therapy-refractory cardiogenic shock whose clinical condition stabilized after the addition of levosimendan, meaning that the patient could be bridged to successful heart transplantation.

2 | CASE HISTORY

The patient was a 57-year-old male with end-stage ischemic heart failure based on a history of extended anterior myocardial infarction resulting in ventricular fibrillation and cardiopulmonary resuscitation 9 years ago. History also included resuscitation after ischemia-related sudden cardiac death and revascularization (urgent coronary artery bypass graft surgery using a left internal mammary artery graft onto the left anterior descending artery and a vein graft onto the ramus posterolateralis sinister artery). Subsequently, a primary-prophylactic implantable cardioverter-defibrillator (ICD) was implanted because echocardiography revealed a left ventricular ejection fraction (LVEF) of 30%. Despite this, the patient continued to experience shortness of breath, with moderate-to-severe mitral and tricuspid valve regurgitation. Medical history was also significant for persistent atrial fibrillation and chronic renal failure.

The patient's clinical condition continued to progressively deteriorate despite optimal guideline-driven medical treatment for heart failure with reduced ejection fraction.¹ Cardiogenic shock developed, necessitating continuous intravenous infusion of inotropes and renal replacement therapy for volume and potassium overload. In this setting of progressive end-stage heart failure including renal failure and systemic hypoperfusion syndrome, the patient was listed for heart transplantation at our center. While waiting for a transplant organ, the patient was hospitalized in the intensive care unit (ICU) and was dependent on continuous intravenous inotropic support with milrinone and dobutamine.

In addition, he developed tachyarrhythmic atrial fibrillation further reducing cardiac output and perpetuating cardiogenic shock (parameters depicted in Table 1). Aggravation of cardiogenic shock resulted in dyspnea at rest (New York Heart Association [NYHA] functional class IV), orthopnea, anuria, pallor, chills and cyanosis. Multiorgan failure occurred, confirmed by increases in liver and kidney marker levels, lactic acidosis and INR perturbation (Table 1). Serum lactate levels continued to rise despite comprehensive ICU treatment, resulting in a diagnosis of therapy-refractory cardiogenic shock. Mixed venous oxygen saturation, measured using a Swan-Ganz pulmonary artery catheter, fell from 78.2% to below 30%, highlighting the fulminant mismatch between oxygen demand and supply (Table 1).

Echocardiography revealed highly impaired systolic left ventricular function (LVEF 15%) and a dilated left ventricle (left ventricular end-diastolic diameter [LVEDD], 62 mm); right heart function was also impaired and the right ventricle was severely enlarged (right ventricular end-diastolic diameter, 68 mm) and tricuspid annular plane systolic excursion (TAPSE) was 14 mm. In this state, the patient could not undergo heart transplantation and he was not eligible for any other procedures. Mechanical circulatory support was considered necessary and was immediately prepared, while weighing the benefit of hemodynamic stabilization against the risks of an invasive procedure, including bleeding, infection and thromboembolism.

Given the life-threatening scenario for the patient, with therapy-refractory cardiogenic shock with biventricular pump failure, add-on treatment with intravenous levosimendan 2.5 mg was started (Tables 1 and 2). This was associated with a slowing of cardiogenic shock progression, then stabilization of lactate levels, blood gas analysis parameters, transaminase levels, and kidney function, plus improvements in right heart catheter hemodynamic parameters and recovery of systemic blood pressure (Table 2). The patient also showed clinical improvement, including warm peripherals and resumption of urinary output. In addition, transthoracic echocardiography showed slightly improved left ventricular systolic function (LVEF now 25%) and unloading of the left ventricle (LVEDD, 62 mm). These improvements meant that invasive mechanical circulatory support and its potential risks could be avoided. In addition, the patient was stable enough to be put back on the list for heart transplantation. Successful heart transplantation was performed after only a few weeks. The patient remains well and has been able to return to regular daily life.

3 | DISCUSSION

We report a clinically impressive and unique case that highlights a potential new treatment strategy for achieving

Laboratory parameters	Addition of levosimendan in this patient ↓				
	Day 1	Night 1	Day 2	Night 2	Day 3
Urea (mg/dL)	46	54	66	75	62
Creatinine (mg/dL)	1.2	1.8	1.8	1.7	1.4
MDRD (mL/min)	62	39	39	42	52
GOT (U/L)	21	101	560	263	150
GPT (U/L)	8	46	275	211	155
GGT (U/L)	105	109	93	92	94
LDH (U/L)	246	471	599	306	406
Bilirubin (mg/dL)	2.23	4.17	3.32	2.47	2.46
pH	7.346	7.418	7.416	7.469	7.462
pCO ₂	30.7	23.3	31.2	29.9	32.1
HCO ₃ (mmol/L)	16.3	14.8	19.7	21.4	22.6
Base excess	-7.9	-8	-3.6	-1.2	-0.3
Lactate (mmol/L)	7.6	10.9	8.4	4.6	2.9
CVPO ₂	47.6	30	43.9	51.8	49.1

Abbreviations: CVPO₂, central venous oxygen saturation; GGT, gamma-glutamyl transpeptidase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transaminase; HCO₃, bicarbonate; LDH, lactate dehydrogenase; MDRD, modification of diet in renal disease; pCO₂, partial pressure of carbon dioxide; pH, pH, decimal logarithm of the reciprocal of the hydrogen ion activity.

clinical stability in a patient with therapy-refractory cardiogenic shock and biventricular pump failure, ultimately allowing heart transplant. Our patient was in a life-threatening situation where there appeared to be no options other than invasive mechanical circulatory support (MCS). However, the addition of levosimendan to other ICU-based therapies was associated with resolution of cardiogenic shock. Although hemodynamic stability might have been achieved using MCS, this invasive approach also carries significant risk (including bleeding, infection and thromboembolic complications),⁶⁻⁸ which were particularly relevant in our patient who had been listed for heart transplantation. Use of MCS might compromise the ability to perform heart transplant surgery, and it may not be possible to continue MCS for the length of time it takes to wait until a heart becomes available for transplantation.^{6,9}

Levosimendan currently is subject of intense discussion, because the novel approach to providing positive inotropic effects is promising, but as of today literature is not consistent on the benefits of using levosimendan. Recent European Society of Cardiology (ESC) guidelines recommend levosimendan (or a phosphodiesterase III inhibitor) for acute heart failure to reverse the effects of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion (evidence class IIb, level C).¹ Furthermore, it is recommended that electrocardiography monitoring and blood pressure monitoring are performed during treatment

TABLE 1 Laboratory parameters in multiorgan failure

with levosimendan because it can cause arrhythmia, myocardial ischemia and hypotension (evidence class I, level C). ESC guidelines also state that levosimendan may be used in combination with another inotrope (usually dobutamine) and a vasopressor for patients with cardiogenic shock.¹

Large randomized controlled trials such as the Levosimendan in High Risk Patients Undergoing Cardiac Surgery (CHEETAH) study investigated the effects of hemodynamic support with levosimendan in 506 high-risk cardiac surgery patients and found no benefit in mortality or clinical endpoints compared with placebo.⁴ Similarly, the Levosimendan in Patients with Left Ventricular Systolic Dysfunction Undergoing Cardiac Surgery Requiring Cardiopulmonary Bypass (LEVO-CTS) trial of 882 patients with left ventricular dysfunction undergoing cardiac surgery found that rates of a composite endpoint of death, renal replacement therapy, perioperative myocardial infarction or use of a mechanical ventricular assist device were similar in subjects randomized to levosimendan or placebo.¹⁰ Furthermore, the addition of levosimendan to standard treatment in adults with sepsis was not associated with less severe organ dysfunction or lower mortality compared with placebo in the Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) trial.¹¹

There have not yet been any randomized controlled clinical trials evaluating the use of levosimendan for the treatment of critical cardiogenic shock in the context of

TABLE 2 Continuous Swan-Ganz right heart catheterization measures in multiorgan failure

Right heart catheter measures	Addition of levosimendan in this patient ↓				
	Night 1		Night 2		Day 3
	Day 1	Day 2	Day 2	Day 3	
CVP (mmHg)	13	29	27	13	11
Cardiac output (L/min)	1.56	1.31	2.1	2.1	2.4
Cardiac index (L/min/m ²)	1.62	1.39	2.39	2.42	2.52
Systolic pulmonary artery pressure (mmHg)	43	49	63	57	55
Diastolic pulmonary artery pressure (mmHg)	32	25	35	32	31
Stroke volume (mL)	30.1	16.5	43.1	33.7	36.5
Vital signs					
Heart rate (beats per minute)	97	102	95	95	95
Systolic blood pressure (mmHg)	95	95	114	105	104
Diastolic blood pressure (mmHg)	73	77	74	69	70

Abbreviation: CVP, central venous pressure; mmHg, millimeter of mercury.

transplantation.⁵ Despite the serious life-threatening condition, our patient achieved clinical stability after treatment with levosimendan addition and was able to progress the course until successful heart transplantation. Additional research is needed to more clearly define the indications for, and benefits of, levosimendan therapy. Studies in patients with cardiogenic shock would provide data on whether other heart failure patients with cardiogenic shock might achieve similar impressive benefits with the addition of levosimendan therapy.

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CONFLICT OF INTEREST

Christian Flottmann has received reimbursements of travel expenses from Orion Pharma. All other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

CF: collecting data, analysis and manuscript draft. DD: critical review of data, literature and manuscript. CS: critical review of data, literature and manuscript. VR: critical

review of data, literature and manuscript. HF: finalizing manuscript, critical review of data, literature and manuscript coordination.

ETHICAL APPROVAL

An exemption of ethical approval has been assigned for reporting this case and this report is in accordance with the Declaration of Helsinki. All persons gave their informed consent prior to inclusion in this report.

DATA AVAILABILITY STATEMENT

All data are incorporated into the article and its material.

ORCID

Henrik Fox  <https://orcid.org/0000-0002-2187-8715>

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