

Original Research

Haemodynamic Effects of Levosimendan for Low Cardiac Output After Cardiac Surgery: A Case Series

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Introduction: Levosimendan is a new inotropic vasodilator for the treatment of decompensated heart failure. Compared to other inotropic agents, it has been shown to improve myocardial contractility without increasing oxygen requirements. However, experience with levosimendan in patients with low cardiac output after cardiopulmonary bypass is limited. In this case series we present the short-term haemodynamic effects of levosimendan added to dobutamine for the management of low cardiac output syndrome after cardiac surgery.

Methods: Twelve patients with low cardiac output during the first 6 hours after completion of cardiopulmonary bypass, who were already receiving dobutamine at a mean dose of 6.7 µg/kg/min, were treated with levosimendan at a loading dose of 6 µg/kg, followed by a 24-hour infusion of 0.2 µg/kg/min. During a 24-hour observation period the following haemodynamic parameters were measured: arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressure, heart rate, cardiac index, stroke volume, systemic and pulmonary vascular resistance, as well as mixed venous oxygen saturation, oxygen delivery and oxygen extraction ratio.

Results: Levosimendan significantly improved cardiac index (from 2.1 ± 0.1 L/min/m² at baseline to 3.2 ± 0.3 L/min/m² at 24 hrs, $p < 0.001$) as well as mixed venous oxygen saturation, oxygen delivery and oxygen extraction ratio ($p < 0.001$) and caused a significant reduction in systemic and pulmonary vascular resistance ($p < 0.001$). At the same time, a significant decrease in central venous, pulmonary arterial and pulmonary capillary wedge pressure was noted ($p < 0.001$). These beneficial haemodynamic effects resulted in significantly decreased catecholamine requirements.

Conclusions: In this group of cardiac surgical patients with postoperative myocardial dysfunction resistant to dobutamine, levosimendan added to dobutamine was effective in reversing low cardiac output syndrome.

Patients undergoing heart surgery involving cardiopulmonary bypass (CPB) experience global myocardial ischaemia with subsequent reperfusion which, despite cardioplegic protection, may result in different degrees of transient ventricular dysfunction – also known as myocardial stunning – in the immediate postoperative period.^{1,2} If severe enough, this dysfunction can cause postoperative low car-

diac output syndrome, a complication with an estimated prevalence of about 10% and a mortality of 17%.³ Pharmacological support, in the form of vasodilator and inotropic therapy, as well as mechanical support, such as intra-aortic balloon counterpulsation and ventricular assist devices, is often necessary to restore adequate tissue perfusion in the immediate postoperative period.² Perioperatively, the most frequently

used inotropes are beta-adrenergics and phosphodiesterase III inhibitors.⁴⁻⁶ Levosimendan (Simdax, Orion, Espoo, Finland) is a recently introduced inodilator. It belongs to a novel group of agents called calcium-sensitizers, which increase the sensitivity of contractile proteins to calcium. The use of this agent in the treatment of decompensated heart failure is based on its dual mechanism of action. It improves myocardial contractility by sensitising troponin C to calcium without increasing myocardial oxygen consumption⁷ and without impairing relaxation and diastolic function.⁸ In addition, it causes opening of ATP-dependent potassium channels on smooth muscle fibres, which induces systemic, pulmonary and coronary vasodilation and may offer cardioprotective effects during myocardial ischaemia.⁹⁻¹¹ Furthermore, growing evidence from *in vitro* and *in vivo* studies indicates that, unlike other inotropes, levosimendan does not affect or even improves diastolic function in failing myocardium.¹²⁻¹⁵

Several studies have shown the effectiveness and safety of levosimendan in both acute and decompensated chronic heart failure.¹⁶⁻²⁰ The recent guidelines of the European Society of Cardiology for the diagnosis and treatment of acute heart failure suggest the use of levosimendan in cases of symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction.²¹ However, evidence concerning the use of levosimendan for the treatment of postoperative myocardial dysfunction is still limited.²²⁻²⁷ The aim of this case series was to report our experience with this agent in the management of post-CPB low cardiac output syndrome.

Methods

All cardiac surgical patients treated at our institution with levosimendan for post-CPB low cardiac output syndrome were included in this study. Patient files were consulted to collect the following patient data: age, weight, height, concomitant diseases, EuroSCORE, predicted death rate, preoperative medication, preoperative left ventricular ejection fraction (LVEF, estimated by cardiac ultrasound), indication for surgery, type of surgical procedure, APACHE II on admission to the intensive care unit (ICU), timing and duration of levosimendan infusion, its side effects and their treatment, concomitant vasoactive medication and duration of postoperative intensive care. EuroSCORE (European system for cardiac operative risk evaluation) was used as the surgical risk scoring system and to calculate the predicted death rate.²⁸ The anaesthetic and

surgical techniques used were similar in all patients. After anaesthetic induction, a Swan-Ganz catheter (CCoMboV, CCO/SvO₂, Edwards, Irvine, CA, USA) was inserted and cardiac output as well as mixed venous oxygen saturation were measured continuously. Surgery was performed with CPB and global myocardial ischaemia induced by aortic clamping and under electromechanical heart arrest, using intermittent cold hyperpotassic cardioplegic solution. After surgery, all patients were taken to a post-surgical ICU. As part of our institution's protocol, weaning from CPB was facilitated by dobutamine infusion at a maximal dose of up to 7.5 µg/kg/min, which was continued for at least 12 hours after ICU admission unless otherwise indicated, while the concomitant administration of other vasoactive medication was left to the discretion of the treating physician.

Post-CPB low cardiac output syndrome was defined as a cardiac index of <2.2 L/min/m² plus a pulmonary capillary wedge pressure of >15 mmHg during the first 6 hours after aortic declamping, despite adequate control of heart rhythm and in the absence of myocardial ischaemia, valve dysfunction or cardiac tamponade. Once low cardiac output syndrome was diagnosed, levosimendan was administered at a loading dose of 6 µg/kg over 10 minutes, followed by continuous infusion of 0.2 µg/kg/min for 24 hours. Arterial, central venous and pulmonary capillary wedge pressure, as well as cardiac output and mixed venous oxygen saturation were monitored continuously in all patients for the first 24 hours after initiation of levosimendan treatment. Heart rate was analysed from a continuous electrocardiographic recording with ST segments monitored. Systemic and pulmonary vascular resistance, stroke volume, left ventricular stroke work index, right ventricular stroke work index, as well as oxygen delivery and oxygen extraction ratio, were calculated according to standard formulae (Vigilance, Edwards, Irvine, CA, USA) immediately before starting levosimendan and at 6, 12 and 24 hours after levosimendan initiation.

SPSS software for Windows v.14 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. A paired sample t-test was used to compare baseline values with the corresponding values obtained at each of the three time points. A p value <0.05 was considered significant.

Results

From February 2005 to November 2006 12 patients

received levosimendan for post-CPB low cardiac output syndrome. Patients' clinical and demographic characteristics are shown in Table 1. Two patients underwent emergency coronary artery bypass graft (CABG) surgery, the remaining cases being elective. Four patients had a preoperative LVEF of less than 50%, the lowest being 20%. Beta-blockers were part of the preoperative medication in seven patients. No patient was on mechanical inotropic support, either pre- or postoperatively.

The haemodynamic effects of levosimendan are shown in Tables 2-4. Levosimendan significantly improved cardiac index from 2.1 ± 0.1 L/min/m² at baseline to 3.1 ± 0.3 , 3.2 ± 0.4 and 3.2 ± 0.3 L/min/m² at 6, 12 and 24 hrs, respectively ($p < 0.001$ at all time points). This increase was due to a concomitant increase in stroke volume index, as shown in Figure 1, but not in heart rate, which remained unaffected. At the same time, as shown in Table 3 and Figure 2, levosimendan caused significant systemic and pulmonary vasodilation, which was manifested as a marked reduction of systemic and pulmonary vascular resistance and resulted in a significant decrease in central venous, pul-

monary arterial and pulmonary capillary wedge pressure, while a small, albeit statistically significant, decrease in mean arterial pressure was also noted. In addition, levosimendan caused marked improvement of the oxygenation profile by increasing mixed venous oxygen saturation and oxygen delivery index while decreasing oxygen extraction ratio (Table 4). The aforementioned beneficial haemodynamic effects led to a substantial reduction of catecholamine requirements on completion of the levosimendan infusion. As shown in Table 2, the dobutamine dose could be reduced from 6.7 ± 0.7 µg/kg/min at baseline to 2.4 ± 2.2 µg/kg/min at 24 hours ($p < 0.001$).

The numbers of patients receiving concomitant vasoactive medications before, during and at the end of the levosimendan infusion are shown in Table 5. As shown in this table, on completion of the levosimendan infusion five patients were completely weaned off any inotropic support. Postoperative atrial fibrillation was recorded in three patients, whereas no other arrhythmic complications were observed. As shown in Table 1, the mean length of postoperative mechanical ventilation was 24 hours (range 15-57 hours) while the mean length of ICU stay was 4 days (range 39-172 hours). No major neurological, nephrological or other organ dysfunction was noted during the ICU stay. In-hospital and 30-day mortality were zero.

Table 1. Patients' characteristics.

	Patients
Female (N)	4
Male (N)	8
Age (years)	65.6 ± 9.4^1
Body mass index (kg/m ²)	29.2 ± 2.6^1
Body surface area (m ²)	1.6 ± 0.1^1
Preoperative beta-blockers	7 (58.3) ²
Preoperative ACE inhibitors	9 (75) ²
LVEF (%)	47.5 ± 11.6^1
EuroSCORE (points):	
0 - 2 (low risk)	1 (8) ²
3 - 5 (medium risk)	5 (42) ²
≥ 6 (high risk)	6 (50) ²
PDR (%)	$5.6 (1.5-12)^3$
APACHE II score (points)	10.8 ± 2.0^1
Surgical procedure (N):	
Revascularisation	8
Valve surgery	4
CPB (minutes)	$156 (99-218)^3$
ACC (minutes)	$100 (61-134)^3$
MV (hours)	$23.6 (15-57)^3$
ICU LOS (hours)	$96.3 (39-178)^3$

¹Mean \pm standard deviation; ²N (%); ³Mean (range)

ACC – aortic cross clamp; ACE – angiotensin converting enzyme; CPB – cardiopulmonary bypass; ICU LOS – length of stay in intensive care unit; LVEF – left ventricular ejection fraction; MV – mechanical ventilation; PDR – predicted death rate.

Discussion

Post-CPB low cardiac output syndrome due to transient ventricular dysfunction after cardiac surgery is characterised by an improvement in ventricular function during the first hour after CPB termination, followed by a deterioration that reaches a maximum approximately 4 to 6 hours after surgery. A subsequent phase of gradual recovery then usually begins, with full recovery obtained at 24 hours.¹ Transient myocardial dysfunction induced by ischaemia through clamping of the aorta followed by reperfusion seems to be the cause of postoperative myocardial stunning. The pathogenetic mechanisms believed to be involved are intracellular calcium overload, depletion of high energy phosphates, generation of oxygen free radicals and impairment of coronary microcirculation.² Once post-CPB low cardiac output syndrome ensues, pharmacological inotropic support is deemed necessary.^{1,3,4}

There seems to be no ideal inotrope at present, although levosimendan appears promising. Beta-adrenergic agonists are widely used and well docu-

Table 2. Haemodynamic parameters and catecholamine requirements before and during levosimendan infusion.

	Baseline		6hrs		12hrs		24hrs	
	Mean ± SD	Mean ± SD	Mean Change	Mean ± SD	Mean Change	Mean ± SD	Mean Change	
CO	3.5 ± 0.3	5.0 ± 0.7	1.5*	5.1 ± 0.7	1.7*	5.1 ± 0.6	1.7*	
CI	2.1 ± 0.1	3.1 ± 0.3	0.9*	3.2 ± 0.4	1.0*	3.2 ± 0.3	1.0*	
MAP	78.1 ± 6.4	73.3 ± 5.0	-4.8*	74.8 ± 5.7	-3.3+	72.8 ± 5.4	-5.3*	
HR	85.4 ± 4.6	88.0 ± 5.0	2.6+	85.4 ± 3.7	0+	84.8 ± 4.8	-0.6	
SV	40.5 ± 4.6	56.6 ± 8.6	16.1*	59.8 ± 7.4	19.3*	60.4 ± 7.8	19.8*	
SVI	24.9 ± 1.7	34.8 ± 4.7	9.9*	36.8 ± 3.9	12.0*	37.2 ± 4.1	12.3*	
LVSWI	20.1 ± 2.7	27.5 ± 4.3	7.4*	30.5 ± 5.1	10.4*	30.4 ± 5.1	10.2*	
RVSWI	3.8 ± 1.1	4.9 ± 1.6	1.1*	4.4 ± 0.6	0.6+	4.6 ± 1.4	0.8*	
DOB	6.7 ± 0.7	5.4 ± 0.5	-1.3*	4.3 ± 1.5	-2.3*	2.4 ± 2.2	-4.3*	
NE	0.09 ± 0.11	0.12 ± 0.11	0.03+	0.03 ± 0.06	-0.06+	0.01 ± 0.03	-0.08*	

Paired sample t-test: * p < 0.05, + p-value not significant.

CI – cardiac index (L/min/m²); CO – cardiac output (L/min); DOB – dobutamine dose (µg/kg/min); HR – heart rate (beats/min); LVSWI – left ventricular stroke work index (g·m·m⁻²/beat); MAP – mean arterial pressure (mmHg); NE – norepinephrine dose (µg/kg/min); RVSWI – right ventricular stroke work index (g·m·m⁻²/beat); SV – stroke volume (mL/beat); SVI – stroke volume index (mL/m²/beat).

Table 3. Filling pressures and vascular resistance before and during levosimendan infusion.

	Baseline		6hrs		12hrs		24hrs	
	Mean ± SD	Mean ± SD	Mean Change	Mean ± SD	Mean Change	Mean ± SD	Mean Change	
CVP	14.8 ± 2.9	12.8 ± 2.5	-2.0*	12.3 ± 2.4	-2.5*	11.5 ± 2.1	-3.3*	
MPAP	26.0 ± 3.9	23.1 ± 2.7	-2.9*	22.1 ± 2.9	-3.9*	20.7 ± 3.0	-5.3*	
PCWP	18.0 ± 2.6	15.2 ± 1.8	-2.8*	14.0 ± 2.0	-4.0*	12.8 ± 2.0	-5.2*	
SVR	1477 ± 200	987 ± 128	-490*	993 ± 155	-484*	982 ± 163	-495*	
SVRI	2387 ± 285	1602 ± 209	-785*	1606 ± 227	-781*	1590 ± 248	-797*	
PVR	186 ± 46	131 ± 37	-55*	129 ± 26	-56*	125 ± 26	-62*	
PVRI	286 ± 81	213 ± 58	-73*	209 ± 43	-77*	203 ± 45	-84*	

Paired sample t-test: *p < 0.05.

CVP – central venous pressure (mmHg); MPAP – mean pulmonary artery pressure (mmHg); PCWP – pulmonary capillary wedge pressure (mmHg); PVR – pulmonary vascular resistance (dyn·s/cm⁵); PVRI – pulmonary vascular resistance index (dyn·s/cm⁵/m²); SVR – systemic vascular resistance (dyn·s/cm⁵); SVRI – systemic vascular resistance index (dyn·s/cm⁵/m²).

Table 4. Oxygenation profile before and during levosimendan infusion.

	Baseline		6hrs		12hrs		24hrs	
	Mean ± SD	Mean ± SD	Mean Change	Mean ± SD	Mean Change	Mean ± SD	Mean Change	
SVO ₂	65.7 ± 4.9	71.7 ± 5.5	6.0*	72.8 ± 5.2	7.1*	72.7 ± 4.1	7.0*	
DO ₂	525 ± 107	730 ± 116	205*	767.8 ± 118.6	242*	787.6 ± 93.9	262*	
DO ₂ I	324 ± 64	449 ± 66	126*	469.8 ± 63.2	146*	485.4 ± 53	162*	
OER	32.2 ± 5.4	26.9 ± 6.1	-5.3*	25.7 ± 5.2	-6.4*	25.5 ± 4.1	-6.7*	

Paired sample t-test: *p < 0.05.

DO₂ – oxygen delivery (mL/min); DO₂I – oxygen delivery index (mL/min/m²); OER – oxygen extraction ratio (%); SVO₂ – mixed venous oxygen saturation (%).

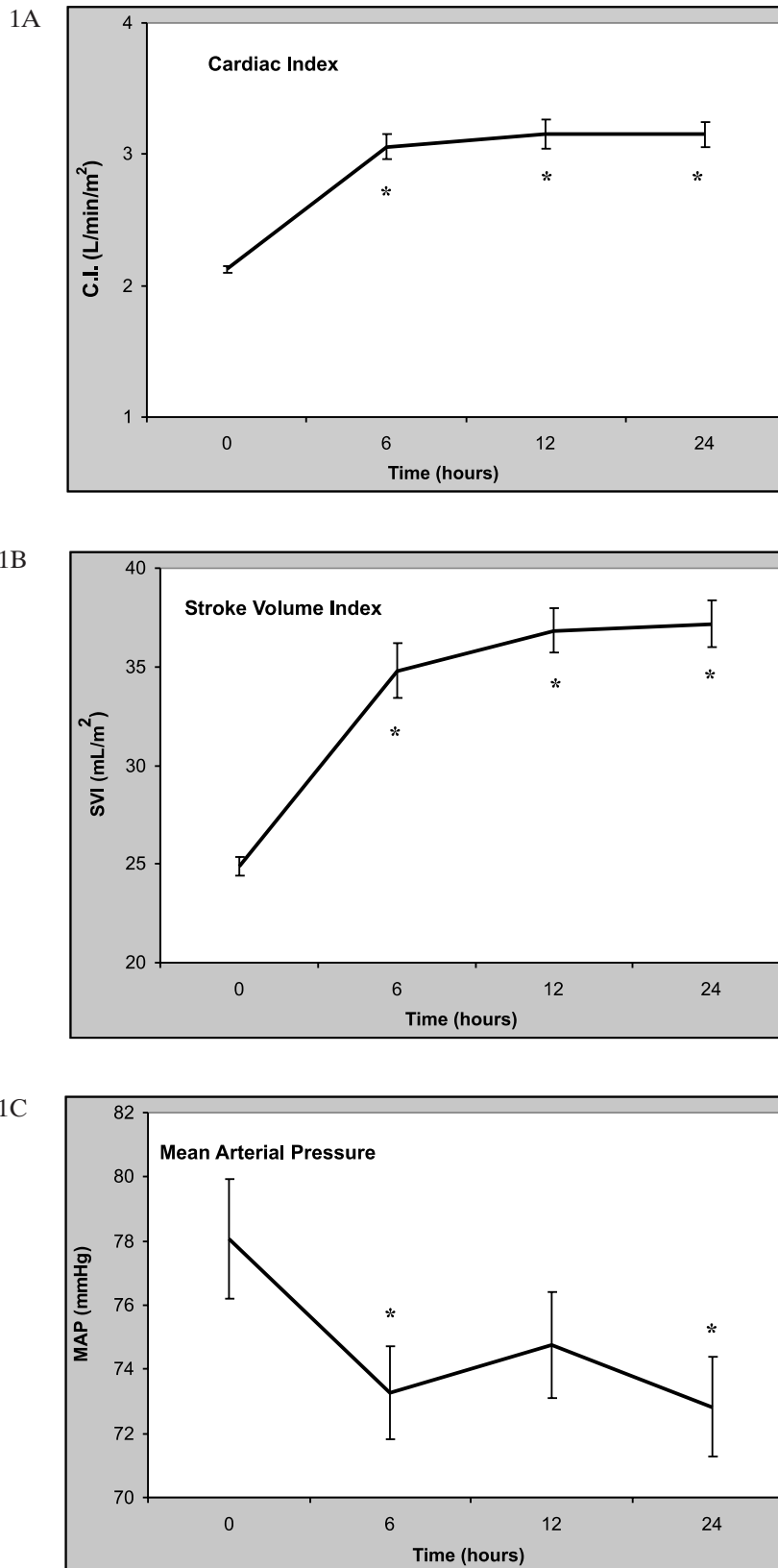


Figure 1. Changes in cardiac index (A), stroke volume index (B) and mean arterial pressure (C) during levosimendan infusion. Values are expressed as mean ± standard error. *Statistically significant compared with baseline value.

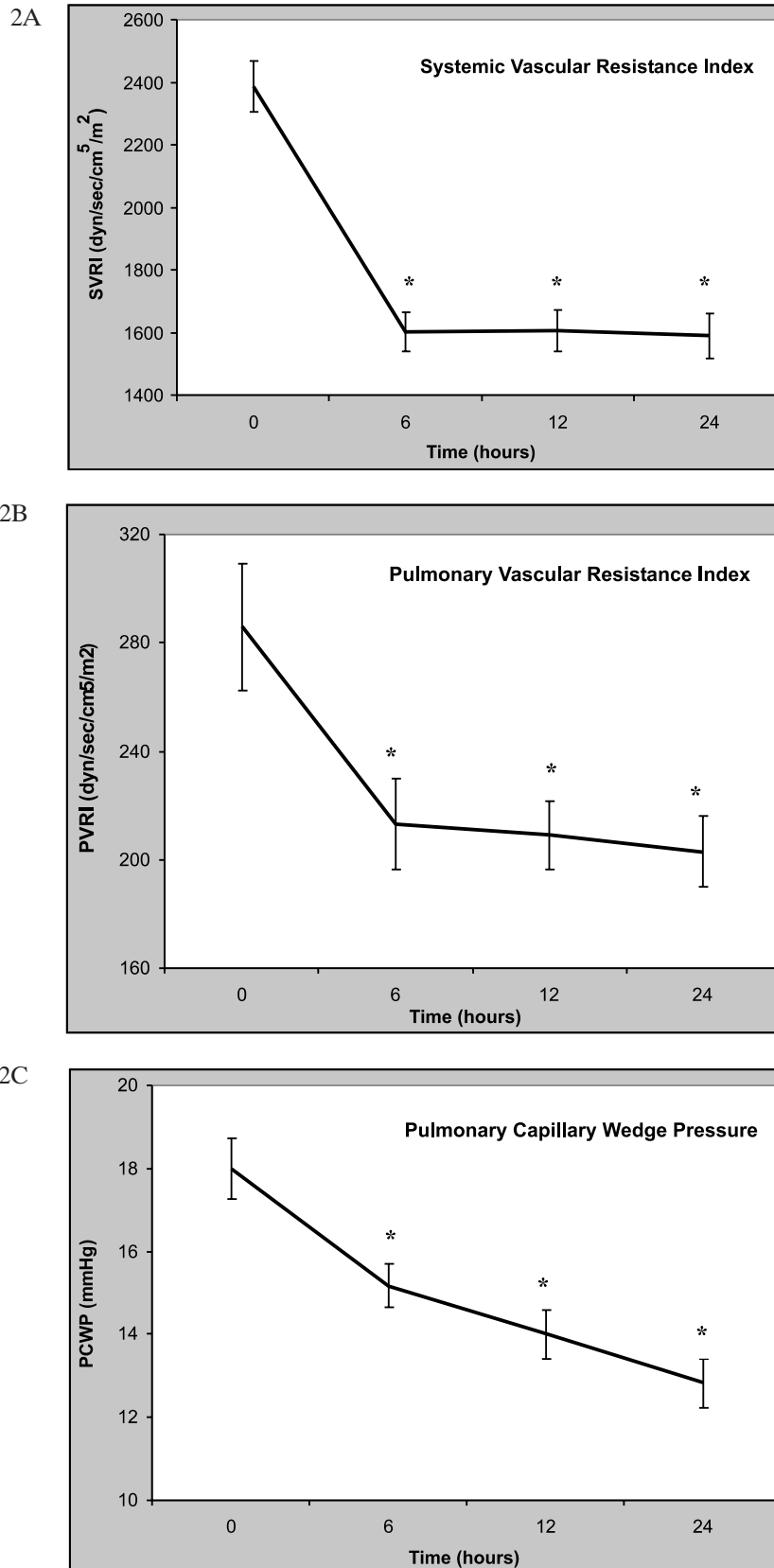


Figure 2. Changes in systemic vascular resistance index (A), pulmonary vascular resistance index (B) and pulmonary capillary wedge pressure (C) during levosimendan infusion. Values are expressed as mean \pm standard error. *Statistically significant compared with baseline value.

Table 5. Concomitant use of vasoactive drugs before and during levosimendan infusion.

	Baseline (N)	6 hrs (N)	12 hrs (N)	24 hrs(N)
Dobutamine	12	12	11	7
Norepinephrine	6	10	3	2
Epinephrine	1	1	0	0
No medication	0	0	1	5

N: Number of patients

mented. Their short half-life permits immediate discontinuation if side effects occur. However, they enhance myocardial contractility by increasing concentrations of cyclic adenosine monophosphate and intracellular calcium, which leads to an increase in myocardial oxygen consumption and increased arrhythmogenesis.²⁹ Furthermore, the clinical response to this class of agents may be attenuated by beta-receptor downregulation.

Phosphodiesterase III/IV inhibitors are, in addition to their inotropic effects, potent pulmonary vasodilators. They have also been reported to prevent internal mammary artery spasm⁶ and to exert certain anti-inflammatory effects.³⁰ On the other hand, systemic hypotension and negative long-term effects on survival are important drawbacks of these agents. However, beta-adrenergic agonists as well as phosphodiesterase inhibitors are commonly used in cardiac surgical patients since other agents, such as vasodilators and beta-blockers, may be contraindicated given the haemodynamic instability frequently encountered during the immediate postoperative period.² Factors like myocardial stunning, anaesthetic agents, hyperthermia and vasodilation caused by the systemic inflammatory response associated with CPB all contribute to this instability.³¹

Several human studies involving the use of levosimendan in cardiac surgery have recently been published, suggesting that this agent may be beneficial in low-output states after cardiac surgery.²²⁻²⁷ Although differing loading and maintenance dosing schemes were used in those studies, their common finding was a significant increase in cardiac index accompanied by a marked decrease in systemic vascular resistance and ventricular filling pressures. These findings are in agreement with the results observed in our study population, strengthening the conclusion that the observed increase in cardiac index produced by levosimendan probably resulted from the combined actions

of reduced left ventricular afterload and modestly increased stroke volume.

Postoperative contractility was not measured in the present study; this was only recorded before surgery (Table 1). Postoperative assessment of contractility, if deemed necessary, is usually carried out by echocardiographic determination of LVEF. This was not performed in our study population because recent sternotomy and the presence of mediastinal drainage tubes render transthoracic echocardiography rather difficult. Transoesophageal echocardiography was not performed in our patients, since most of them were extubated and conscious before the end of the study, and in the absence of major haemodynamic instability it was deemed to be contraindicated.

In some cases, the resulting systemic vasodilation caused by levosimendan is not fully compensated for by the increased cardiac index, leading to arterial hypotension. Indeed, a mild but statistically significant decrease in mean arterial pressure was observed in all our patients and was successfully managed by crystalloid and/or colloid infusion. Nevertheless, in four CABG patients additional use of norepinephrine was deemed necessary in order to maintain a mean arterial pressure above 70 mmHg to prevent arterial graft spasm. Given this fact, avoiding administration of a loading dose in order to prevent excessive hypotension in patients with marginal blood pressure might be more prudent.

As noted earlier, a dobutamine infusion was initiated in all our patients during weaning from CPB. The need for inotropic support to facilitate weaning from CPB is often necessary. It has been shown that if during cardiac surgery the LVEF decreased below 46%, the need for inotropes ranged from 71% to 100%,³² but even patients with a normal LVEF may need inotropic support because of regional wall motion abnormalities and an increase in left ventricular end-diastolic pressure. The most common factors correlating with the need for inotropic or vasoactive support at the time of CPB separation are female sex, older age, low ejection fraction, cardiac enlargement, diastolic dysfunction, longer duration of CPB, and longer duration of aortic cross clamp (ACC).^{32,33} Angiotensin-converting enzyme (ACE) inhibitors are also thought to increase the need for inotropic support.³⁴ It has therefore been suggested that, in the presence of one or more of these prognostic factors, prophylactic inotropic support to facilitate uncomplicated weaning from CPB should be instituted.³⁵ It is noteworthy that eight of our patients were female,

nine were preoperatively on ACE inhibitors and all of them experienced relatively long CPB and ACC times.

Combinations of vasoactive drugs are often used in various clinical settings. In the present case series, levosimendan added to dobutamine and other vasoactive agents for managing a postoperative low cardiac output state resulted in significant haemodynamic improvement with concomitant reduction of catecholamine requirements. As noted earlier, on completion of the levosimendan infusion five out of twelve patients were completely weaned off any inotropic support. In the remaining seven patients discontinuation of inotropic support was accomplished during the next 24 hours. These findings are in line with previous studies. In patients with dobutamine-resistant, decompensated congestive heart failure the addition of levosimendan caused significant haemodynamic improvement, confirming the assumption that the simultaneous infusion of dobutamine and levosimendan would have the cumulative haemodynamic effects of each individual agent, plus those attributable to levosimendan in the presence of an increased calcium concentration induced by dobutamine.³⁶

Furthermore, it was recently shown that levosimendan was able to improve haemodynamic function in critically ill patients with cardiogenic shock already receiving catecholamine treatment.³⁷ In another case series of patients with severe post-CPB cardiogenic shock under pharmacological and mechanical inotropic support, the addition of levosimendan resulted in successful discontinuation of mechanical assistance and reduction of catecholamine requirements.³⁸

The present study has the limitations inherent to a case series study: the small number of patients and the lack of a control group are certainly serious drawbacks, since the presence of several confounding factors (e.g. mode and parameters of mechanical ventilation, amount of fluids or blood products infused during the observation period, administration of other medications, such as beta-blockers or nitrates) that might have affected our results cannot be ruled out. Nevertheless, the results seem quite uniform and are in concordance with similar studies.

Conclusions

In this series of patients with dobutamine-resistant post-CPB low cardiac output syndrome levosimendan treatment resulted in significant haemodynamic im-

provement. On the basis of the present results we conclude that levosimendan may be a beneficial drug in low output states after cardiopulmonary bypass and its role in this important patient group merits further investigation in a large, randomised controlled trial.

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