

# Hemodynamic Effects of Levosimendan Compared With Dobutamine in Patients With Low Cardiac Output After Cardiac Surgery

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**Introduction and objectives.** Levosimendan is an inotropic agent that is effective in the treatment of heart failure. However, experience with levosimendan in patients with reduced cardiac output following cardiopulmonary bypass is limited. The objective of this study was to compare the short-term hemodynamic effects of levosimendan with those of dobutamine in managing low cardiac output after cardiac surgery.

**Methods.** Forty-one patients who had low cardiac output after cardiopulmonary bypass were randomly assigned to dobutamine (n=20), 24-hour infusion of 7.5 µg/kg per min, or levosimendan (n=21), at a loading dose of 12 µg/kg followed by 24-hour infusion of 0.2 µg/kg per min. The following parameters were determined during a 48-hour observation period: arterial, central venous, pulmonary arterial and pulmonary capillary wedge pressure, cardiac index, heart rate, stroke volume, and systemic and pulmonary vascular resistance.

**Results.** Although both dobutamine and levosimendan improved the cardiac index, the increase was significantly greater with levosimendan (2.4 [0.2] l/min/m<sup>2</sup> vs 2.9 [0.3] l/min/m<sup>2</sup>, respectively, at 24 h; *P*<.05). Moreover, levosimendan significantly reduced systemic and pulmonary vascular resistance, and significantly decreased systemic arterial, pulmonary arterial, pulmonary capillary wedge, and central venous pressure.

**Conclusions.** Both dobutamine and levosimendan are effective in managing postoperative low cardiac output. However, levosimendan induces non-specific systemic, venous and pulmonary vasodilation which can result in hypotension as a adverse event. In these patients, it is advisable to omit or reduce the loading dose.

**Key words:** *Levosimendan. Heart failure. Cardiopulmonary bypass.*

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## Comparación de los efectos hemodinámicos del levosimendán con la dobutamina en pacientes con bajo gasto después de cirugía cardíaca

**Introducción y objetivos.** El levosimendán es un fármaco inotrópico positivo eficaz en la insuficiencia cardíaca. Sin embargo, la experiencia con levosimendán en pacientes con bajo gasto después de una cirugía cardíaca es reducida. El propósito de este estudio es comparar a corto plazo los efectos hemodinámicos del levosimendán frente a la dobutamina después de la cirugía cardíaca.

**Métodos.** Se estudió a 41 pacientes con bajo gasto después de una cirugía cardíaca bajo circulación extracorpórea divididos en 2 grupos. Un grupo (n = 20) recibió una infusión continua de 7,5 µg/kg/min de dobutamina durante 24 h. Otro grupo (n = 21) recibió una dosis de carga de levosimendán de 12 µg/kg seguida de una infusión de 0,2 µg/kg/min durante 24 h. Se determinaron el gasto cardíaco, la frecuencia cardíaca, la presión arterial, la presión venosa central, la presión arterial pulmonar, la presión capilar, la resistencia vascular pulmonar y sistémica, y el volumen sistólico.

**Resultados.** Ambos fármacos aumentaron significativamente el índice cardíaco aunque fue más marcado con el levosimendán (a las 24 h, 2,4 ± 0,2 frente a 2,9 ± 0,3 l/min/m<sup>2</sup>; *p* < 0,05). El levosimendán redujo significativamente la resistencia vascular sistémica y pulmonar y ocasionó un descenso significativo de la presión arterial sistémica, pulmonar, venosa central y capilar pulmonar.

**Conclusiones.** El levosimendán y la dobutamina son eficaces en el tratamiento del bajo gasto después de la cirugía cardíaca. Sin embargo, el levosimendán ejerce un efecto vasodilatador inespecífico capaz de provocar hipotensión arterial. En estos pacientes es recomendable reducir o suprimir la dosis de carga.

**Palabras clave:** *Levosimendán. Insuficiencia cardíaca. Circulación extracorpórea.*

## ABBREVIATIONS

ECC: extracorporeal circulation.

## INTRODUCTION

Patients who have undergone heart surgery involving extracorporeal circulation (ECC) with global myocardial ischemia induced by aortic clamping show different degrees of transitory ventricular dysfunction without myocardial infarction in the immediate post-operative period.<sup>1,2</sup> This dysfunction can cause post-operative low cardiac output syndrome with a prevalence of about 10%. The mortality rate among those who develop this complication is 17%.<sup>3</sup> Treatment includes the administration of positive inotropic drugs and vasodilators, balloon counterpulsation, and the use of mechanical devices that assist circulation.<sup>2</sup> The most widely used inotropic drugs are beta-adrenergics and inhibitors of phosphodiesterase III/IV.<sup>4</sup> Levosimendan, a positive inotropic drug belonging to the group of agents that increase the sensitivity of contractile proteins to calcium,<sup>5</sup> has recently been introduced. The use of this drug in the treatment of heart failure is based on its double mechanism of action: the improvement of myocardial contractility through the sensitization of troponin C to calcium, and the systemic, pulmonary and coronary arterial and venous vasodilation induced by activation of the ATP-sensitive potassium channels of smooth muscle fibers.<sup>5</sup> Levosimendan increases cardiac output, coronary and renal blood flow, and heart rate, and reduces the pre- and postload. It also has an anti-arrhythmia effect and can revert myocardial stunning.<sup>5-10</sup>

Several studies have shown the effectiveness of levosimendan in both acute and decompensated chronic heart failure.<sup>8,11-13</sup> However, experience with this drug in the treatment of low cardiac output after surgery involving ECC is limited to studies with very few patients and isolated clinical observations; no studies have been undertaken to compare its effects with those of other inotropic agents.<sup>8,14-18</sup> The aim of the present work was to compare the short-term hemodynamic effects of levosimendan and dobutamine in a group of patients with post-operative low cardiac output after surgery involving ECC. The secondary aims were to assess the efficacy and safety of both treatments, expressed as the number of patients showing a normalized cardiac index and the number of subjects dropped from the study because of continued low cardiac output or the appearance of adverse effects.

## METHODS

This prospective, randomized, open study involved 50 consecutive patients with low cardiac output after heart surgery involving ECC. Post-operative low cardiac output was defined as a cardiac index of  $<2.2$  L/min/m<sup>2</sup> plus a pulmonary capillary pressure of  $>15$  mm Hg despite adequate control of heart rhythm, and in the absence of myocardial ischemia, valve dysfunction or cardiac tamponade. The patients were enrolled between May 2002 and November 2004; all showed signs of low cardiac output within a 4 h period after surgery.

The study was approved by the Clinical Research Ethics Committee of Galicia. All patients gave their consent to be included before surgery.

Demographic data, the preoperative diagnosis, the left ventricular ejection fraction in the week before surgery (determined by transthoracic echocardiography) and the surgical technique employed were recorded for each subject.

The anesthetic and surgical techniques used were similar in all patients. After anesthetic induction a Swan-Ganz catheter (Opti-Q CCO/SvO<sub>2</sub>, Abbott Laboratories, IL, USA) was introduced and cardiac output and mixed venous oxygen saturation determined continuously. Surgery was performed with ECC and global myocardial ischemia induced by aortic clamping, and with electromechanical heart arrest using intermittent cold, hyperpotassic cardioplegic solution. After surgery, all patients were taken to a post-surgical intensive care unit.

The patients were then divided into 2 groups of 25. The members of one group were administered 7.5 µg/kg/min dobutamine (Dobutamine Abbott, EFG, Madrid, Spain) by continuous infusion for 24 h (dobutamine group-DG), whereas those of the other group received levosimendan (Simdax, Spoo, Finland) administered as a loading dose of 12 µg/kg over 15-20 min, followed by infusion of 0.2 µg/kg/min for 24 h (levosimendan group-LG).

The inotropic treatment protocol was deemed not to have been complied with when patients suffered any of the following problems: *a*) a need to reduce the dose or suspend the use of the agent due to secondary effects, *b*) a need to continue treatment for longer than 24 h due to persistent signs of low cardiac output, or *c*) the need to use other inotropic or vasoactive agents concomitantly. Neither the initiation of fluid therapy nor the administration of digoxin, blood derivatives nor diuretics was considered a break of protocol. The hemodynamic data of those patients who did not meet the requirements of the protocol were not included in the final analysis.

In both LG and DG patients, the heart rate, central venous blood pressure, pulmonary capillary pressure, cardiac output, mixed venous oxygen saturation, and hourly diuresis were monitored continuously for the

first 48 h following surgery. Any arrhythmias were also recorded.

The systemic vascular resistance, pulmonary arteriolar resistance, systolic volume and oxygen supply and consumption were measured immediately before starting treatment with the inotropic drugs and again at 6, 12, 24, and 48 h.

SPSS software for Windows v. 10 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Numerical results are presented as means±SD; means were compared by the Student *t* or Mann-Whitney test. Significance was set at *P*<.05. The size of the sample required was determined bearing in mind the criterion that an increase in the cardiac index of >20% over baseline be obtained after 24 h of treatment for an  $\alpha$  error of 5% and a  $\beta$  error of 20%.

## RESULTS

Five DG patients (20%) were dropped from the study within the first 6 h due to persistent signs of low cardiac output requiring the dobutamine dose be increased or concomitant treatment with another agent be initiated (4 patients), or low blood pressure requiring the administration of vasoconstrictors (1 patient). Of the 20 patients who completed the study, 1 died after >15 days (late post-operative death) due to respiratory complications. Four LG patients (16%) were excluded within the first hour of treatment due to low blood pressure requiring levosimendan perfusion be reduced or suspended and vasoconstrictors and other positive inotropic drugs be administered. Of the 21 patients who completed the protocol, 1 died after >15 days (late post-operative death) due to respiratory

complications.

Table 1 shows the clinical and demographic data of all patients initially included in the study. Those of the patients who did and who did not complete the protocol are given separately. No significant differences were seen between them.

Treatment with either dobutamine or levosimendan led to a significant increase in the heart rate and cardiac index at the administered doses (Figures 1 and 2). However, these effects were more prolonged among the LG patients. Table 2 shows heart rate, cardiac index and systolic volume of patients who complied with the protocol, both before the start of inotropic treatment and at 6, 12, 24, and 48 h.

Levosimendan had a systemic and pulmonary vasodilatory effect that led to vascular resistance and blood pressure reduction; this was maintained even after treatment with the drug was ended. Treatment with dobutamine led to no significant changes in this respect (Figure 3). Table 3 shows the systemic and pulmonary arterial blood pressure, the central venous pressure, the pulmonary capillary blood pressure, and the systemic and pulmonary vascular resistance at baseline and at 6, 12, 24, and 48 h.

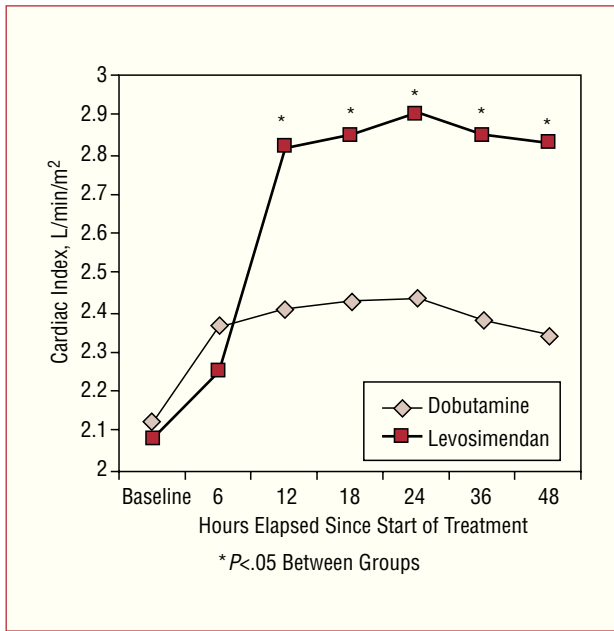
Both drugs increased the mixed venous oxygen saturation, although this effect was greater and more prolonged with levosimendan. Table 4 shows the mixed venous oxygen saturation plus the oxygen supply and consumption of the patients who adhered to the treatment protocol.

Post-operative atrial fibrillation was recorded in four DG patients and 3 LG patients (Table 1). No malignant ventricular arrhythmias were recorded in any patient.

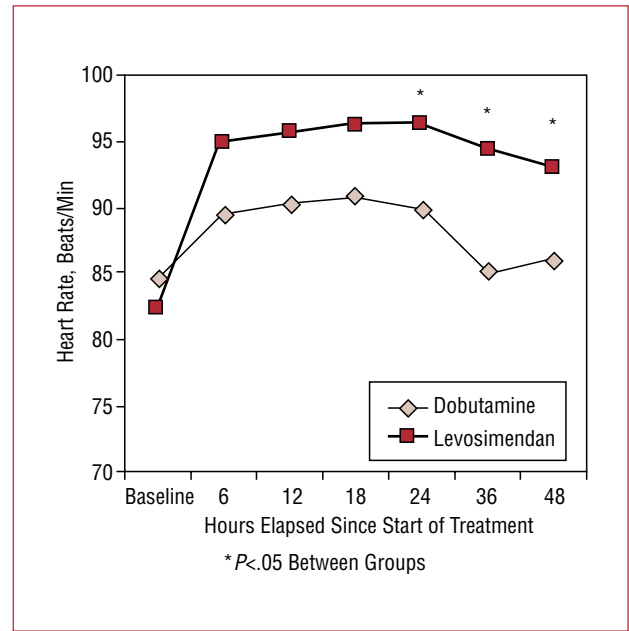
**TABLE 1. Patient Characteristics\***

	Total Patients		Patients Included		Patients Excluded	
	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan
Patients, n	25	25	20	21	5	4
Age, mean±SD, y	67.01±8.01	71.15±7.22	66.24±5.18	71.15±8.40	70.09±8.46	70.60±4.30
Sex						
Women	14 (56%)	12 (48%)	12 (60%)	11 (52.38%)	2 (40%)	1 (25%)
Men	11 (44%)	13 (52%)	8 (40%)	10 (48%)	3 (60%)	3 (75%)
Body surface area, mean±SD, m <sup>2</sup>	1.66±0.22	1.74±0.17	1.65±0.24	1.73±0.15	1.68±0.14	1.76±0.21
Pre-surgery sinus rhythm	18 (72%)	16 (64%)	16 (80%)	15 (71%)	2 (40%)	1 (25%)
LVEF, mean±SD, %	33.58±4.94	35.41±4.38	33.19±5.24	35.54±4.20	35.12±3.68	34.70±4.45
Surgical procedure						
Revascularization	11 (44%)	13 (52%)	9 (45%)	12 (57%)	2 (40%)	1 (25%)
Valve surgery	14 (56%)	12 (48%)	11 (55%)	9 (43%)	3 (60%)	3 (75%)
Duration of ECC, mean±SD, min	74.3±17.8	71.6±18.5	72.6±15.8	79.5±20.5	76.8±19.7	81.2±19.3
Duration of ischemia, mean±SD, min	63.1±15.9	68.4±17.4	62.2±14.4	67.8±17.5	66.6±16.4	68.2±17.3
Postoperative atrial fibrillation	4 (16%)	3 (12%)	2 (10%)	2 (9.5%)	2 (40%)	1 (25%)

\*ECC indicates extracorporeal circulation; SD, standard deviation; LVEF, left ventricular ejection fraction.



**Figure 1.** Changes in the cardiac index over the study period. Dobutamine: dobutamine group; levosimendan: levosimendan group. \*Significant difference between treatment groups.



**Figure 2.** Change in heart rate over the study period. Dobutamine: dobutamine group; levosimendan: levosimendan group. \*Significant difference between treatment groups.

## DISCUSSION

Post-operative low cardiac output syndrome due to transitory ventricular dysfunction after surgery involving ECC is characterized by an improvement in ventricular function during the first hour after ECC is terminated, followed by a deterioration that reaches a maximum at 4-5 h after surgery. A gradual recovery then usually begins, with full recovery at 24 h.<sup>1</sup>

Transitory myocardial dysfunction induced by ischemia through clamping of the aorta followed by reperfusion is the cause of post-operative myocardial stunning. This condition involves depletion of high energy phosphates, intracellular calcium overload, generation of free radicals, and impairment of the coronary microcirculation.<sup>2</sup> Patients with this

condition respond to positive inotropic agents, the treatment of choice in post-operative low cardiac output syndrome.<sup>1,3,4</sup>

Beta-adrenergic agonists and inhibitors of phosphodiesterase III/IV induce good early hemodynamic values, but favor myocardial ischemia and arrhythmias and are associated with high mid-term mortality in non-surgically treated patients with heart failure.<sup>5,19,20</sup> However, they are habitually used in patients who undergo heart surgery since other agents—vasodilators and beta-blockers—may be contraindicated given the hemodynamic instability commonly seen in the immediate postoperative period.<sup>2</sup> Myocardial stunning, anesthetic agents, vasodilation, and hyperthermia caused by the inflammatory response associated with ECC all contribute to this instability.<sup>21</sup>

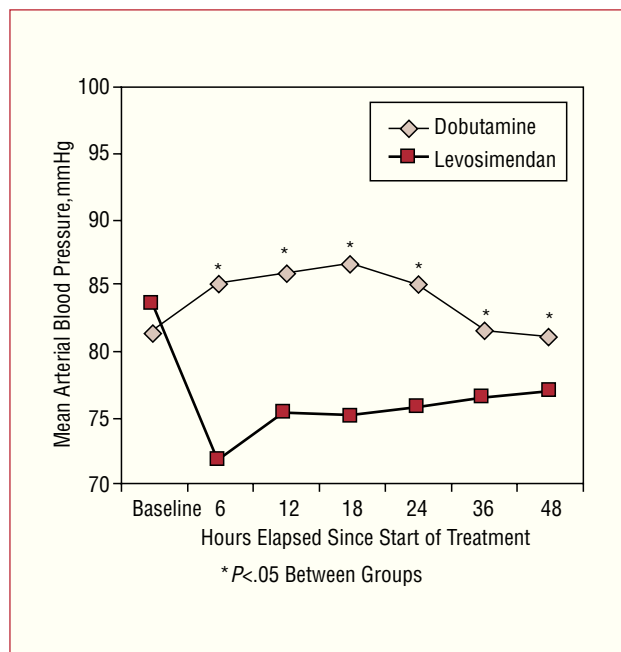
**TABLE 2. Heart Rate, Cardiac Index, and Systolic Volume in Patients in Whom the Criteria of the Treatment Protocol Were Met\***

Group	Baseline		6 h		12 h		24 h		48 h	
	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan
HR	84.6±8	82.2±12	89.7±6	95.1±11†	90.4±8†,‡	95.7±9†	90±10‡	96.4±10†	85.9±7‡	93±9†
CI	2.1±0.1	2±0.2	2.3±0.2†,‡	2.2±0.2†	2.4±0.2†,‡	2.8±0.2†	2.4±0.2†,‡	2.9±0.3†	2.3±0.2†,‡	2.8±0.3†
SV	42.4±6	43.1±6	44.3±5‡	39.9±6‡	44.6±5‡	49.7±5†	45.6±5‡	50.5±6†	45.8±4‡	51.1±6†

\*HR indicates heart rate (beats/min); CI, cardiac index (L/min/m²); SV, left ventricular systolic volume (mL).

†P<.05 with respect to the baseline value for the same group.

‡P<.05 with respect to comparisons between the 2 treatment groups.



**Figure 3.** Change in mean arterial blood pressure over the study period. Dobutamine: dobutamine group; levosimendan: levosimendan group. \*Significant difference between treatment groups.

Few studies on the use of levosimendan in the immediate post heart surgery period have been undertaken.<sup>14-17</sup> The loading and maintenance doses used in the present study are within the therapeutic margins recommended by the European Society of Cardiology.<sup>22</sup> A perfusion rate of 0.2 µg/kg/min (the high end of the range) was chosen since the present study was designed in the last three months of 2001 when the administration of higher doses<sup>11</sup> than those currently used<sup>22</sup> were contemplated.

Dobutamine was chosen as the inotropic control drug since its effects on low cardiac output syndrome following surgery involving ECC have been described in detail.<sup>22-24</sup> The dose used was lower than that administered by other authors,<sup>23</sup> similar to that administered by others<sup>8,24-26</sup> (and within the range recommended by the European Society of Cardiology),<sup>22</sup> and higher than that used in other studies.<sup>27,28</sup> The dose of 7.5 µg/kg/min was chosen because this was previously administered in a large study that compared the hemodynamic effects of levosimendan and dobutamine.<sup>8</sup>

Levosimendan and dobutamine both normalized the cardiac index, although the former allowed higher

**TABLE 3. Systemic, Central Venous, Pulmonary Arterial, and Pulmonary Capillary Blood Pressure, and the Systemic and Pulmonary Vascular Resistance of Patients in Whom the Criteria of the Treatment Protocol Were Met**

Group	Baseline		6 h		12 h		24 h		48 h	
	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan
MABP	81.4±7	83.6±6	85±7	71.9±4†,‡	85.8±7	75.4±5†,‡	85±8	75.8±6†,‡	81±7	77±5†,‡
CVBP	16.2±2	16.6±2	15±1	12.5±2†,‡	14.8±1	12.2±2†,‡	15±2	12.4±2†,‡	15.2±2	13±2†,‡
MPAP	32.6±4	31±4	31.9±4	22.4±3†,‡	31.6±4	23.8±3†,‡	31.4±4	23.28±3†,‡	31.7±4	23.9±4†,‡
PCBP	19.1±3	18±2	19.2±2†	13.4±1†	18.9±2†	13.4±2†	18.8±2†	13.2±1†	19.5±2†	14.5±1†
SVR	1.462±2.216	1.562±270	1.429±226	1.274±174†,‡	1.225±226	1.078±149†,‡	1.383±237	1.055±149†,‡	1.350±184	1.091±155†,‡
PAR	305±122	302±119	262±107	198±101†	254±96	80±81†	249±100	169±84†	250±96	178±83†

\*MABP indicates mean arterial blood pressure (mm Hg); CVBP, central venous blood pressure (mm Hg); MPAP, mean pulmonary arterial blood pressure (mm Hg); PCBP, pulmonary capillary blood pressure; SVR, systemic vascular resistance (dyn·s/cm<sup>5</sup>); PAR, pulmonary arteriolar resistance (dyn·s/cm<sup>5</sup>).  
 †P<.05 with respect to the baseline value for the same group.  
 ‡P<.05 with respect to comparisons between the two treatment groups.

**TABLE 4. Mixed Venous Oxygen Saturation and Oxygen Supply and Consumption in Patients in Whom the Treatment Protocol Criteria Were Met\***

Group	Baseline		6 h		12 h		24 h		48 h	
	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan	Dobutamine	Levosimendan
SvO <sub>2</sub>	62±6	61.8±6	64.8±4	65.5±5†,‡	64.6±4	71.4±3†,‡	65.2±3†	71.9±3†,‡	61.8±5	70.9±5†,‡
DO <sub>2</sub>	268±33	257±42	284±40	275±32†,‡	288±36	342±41†,‡	292±32	345±46†,‡	279±25	333±41
VO <sub>2</sub>	95.4±20	92.3±25	92±18	88.3±19	93.1±16	86.8±17	91.8±15	86.5±21	94.1±13	85.7±20

\*SvO<sub>2</sub> indicates mixed venous oxygen saturation (%); DO<sub>2</sub>, oxygen supply (mL/min/m<sup>2</sup>); VO<sub>2</sub>, oxygen consumption (mL/min/m<sup>2</sup>).  
 †P<.05 with respect to the baseline value for the same group.  
 ‡P<.05 with respect to comparisons between the two treatment groups.

values to be obtained. However, the cardiac index increased more slowly in the LG than in the DG patients. This delayed response of levosimendan has been described in non-surgically treated patients.<sup>8</sup> However, in other studies it is reported that the increase in cardiac index is quicker with levosimendan in both patients with heart failure and those who have undergone surgery involving ECC.<sup>7,16</sup>

The improvement in the cardiac index induced by levosimendan is due to 2 mechanisms: vasodilation (Table 3) and increased contractility.<sup>5</sup> In some cases the reduction in systemic vascular resistance is not compensated by an increased cardiac index, resulting in hypotension. The administration of a loading dose is the cause of most of these hypotensive episodes, in conjunction with the vasodilation associated with the post-ECC inflammatory response.<sup>21</sup> It has been reported that levosimendan greatly reduces the plasma concentration of proinflammatory cytokines in patients with chronic heart failure,<sup>29</sup> but this has not been confirmed in patients who have undergone surgery involving ECC.<sup>30</sup> Some authors have described the use of levosimendan in continuous perfusion without a loading dose as a means of measure to low blood pressure in surgical patients with low cardiac output and ventricular dysfunction.<sup>31</sup>

In the present study the blood pressure was continuously monitored, especially the mean arterial blood pressure. This was made possible by the introduction of an intra-arterial catheter that measured the systolic, diastolic and mean arterial blood pressures. The systolic and diastolic blood pressures varied from one beat to the next, but the mean arterial blood pressure remained more stable. The systemic vasodilation caused by the postoperative inflammatory response is often accompanied by a reduced diastolic blood pressure. Thus, the mean arterial blood pressure shows a closer relationship with the perfusion pressure (especially the myocardial perfusion pressure) and is systematically used to monitor of patients recovering from heart surgery.

Postoperative contractility was not measured in the present study; this was only recorded before surgery (Table 1). The normal way to assess contractility in the clinic is to determine the left ventricular ejection fraction by echocardiography. This was not performed after surgery because the recent sternotomy and the mediastinal (and sometimes pleural) drainage tubes render transthoracic echocardiography rather difficult. Transesophageal echocardiography was not performed since the majority of patients were extubated before the end of the study, and this is contraindicated in such patients who are conscious and show no great hemodynamic problems.

The heart rate is of great importance in patients recovering from heart surgery. Both agents administered in the present study increased heart rate,

but levosimendan increased it more strongly and for a more prolonged period. Indeed, this effect persisted 24 h after withdrawing treatment. The increased heart rate induced by dobutamine, however, disappeared immediately after drug was withdrawn. The prolonged effects of levosimendan are owed to the pharmacokinetic properties of its metabolites, especially the molecule known as OR-1896. This has a pharmacodynamic profile identical to that of levosimendan, with a half life of approximately 80 h and an activity period of 2 weeks.<sup>5,6,8,31,32</sup>

Levosimendan provokes an early and maintained reduction of the systemic, pulmonary, central venous and pulmonary capillary blood pressures along with a reduction in the systemic vascular and pulmonary arteriolar resistance. In agreement with other authors,<sup>15,33</sup> no selective pulmonary vasodilatory action was noted.

The preload of both ventricles was significantly reduced in the LG patients from the beginning of treatment. During the initial hours this was accompanied by a reduction in the systolic volume; the initial increase in cardiac index is therefore dependent on the heart rate. This initial reduction in systolic volume is probably explained by venous and arterial vasodilation, plus the extravasation of liquid to the interstitium owed to a reduction in the colloidal oncotic pressure and an increased permeability due to the post-ECC inflammatory response. Other authors report levosimendan to induce an early increase in the cardiac index without changes in systolic volume.<sup>7</sup> After the first few hours of treatment a significant increase in systolic volume was seen due to increasing contractility and recovery of the blood volume. This contributes to the increase in cardiac index obtained.

The incidence of postoperative atrial fibrillation was similar in both groups (Table 1); the very small numbers allowed no significant difference to be detected.

The oxygen supply increased in both LG and DG patients in line with the cardiac index, but oxygen consumption did not change significantly. This may be due to the fact that, while all the patients showed low cardiac output values, none suffered tissue ischemia.

## CONCLUSIONS

Dobutamine and levosimendan are both effective in the treatment of low cardiac output syndrome following heart surgery. Both agents increase the heart rate. The increase in cardiac output achieved with levosimendan is owed to a vasodilatory and positive inotropic and chronotropic mechanism that is maintained after the drug is suspended. The vasodilatory effect of levosimendan is nonspecific,

and if administered as a bolus this agent could provoke low blood pressure. This can be avoided by eliminating the loading dose, while the drug's favorable hemodynamic effects can be obtained by initiating continuous infusion.

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