

# The clinical experience with levosimendan in anesthesiology and in the intensive care unit

Marco Cavana, Claudia Pignataro, Amanda Fraticelli, Alexandre Mebazaa

*Department of Anesthesiology and Critical Care Medicine, Hôpital Lariboisière, Paris, France*

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In the present review striking data showing that intensive care unit patients with acute heart failure and high-risk surgical patients may markedly benefit from the use of levosimendan are presented. Indeed, levosimendan is an effective new agent that acts via two complementary mechanisms. It enhances cardiac contractility by improving the response of the myofilaments to intracellular calcium, and it reduces the cardiac workload by opening the adenosine triphosphate-dependent potassium channels for the dilation of blood vessels. Because the therapeutic levels of levosimendan do not increase the intracellular calcium concentrations, levosimendan is less likely than traditional inotropes (beta-agonist inotropes or phosphodiesterase inhibitors) to elicit arrhythmias or impair diastolic relaxation. In fact, the results of recent clinical studies indicate that levosimendan offers significant hemodynamic and survival benefits when given to patients who are hospitalized for acute heart failure.

Indeed, in the near future, it is likely that levosimendan may also prove effective for the treatment of patients with diastolic heart failure or for those with a low cardiac output following coronary artery bypass grafting. In addition, levosimendan has the potential of supporting the cardiac function during the initiation of beta-blocker therapy, for weaning patients from cardiopulmonary bypass, for individuals with valvular abnormalities and for those with myocarditis. Preliminary results also suggest that levosimendan may be beneficial for the treatment of patients with right ventricular heart failure. Although the use of levosimendan has been fully validated for the most common causes of acute heart failure, additional clinical trials are needed to safely broaden its therapeutic indications.

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*Address:*

Prof. Alexandre Mebazaa

*Department of  
Anesthesiology and  
Critical Care Medicine  
Hôpital Lariboisière  
2 Rue Ambroise Pare  
75475 Paris Cedex 10  
France  
E-mail:  
alexandre.mebazaa@  
lrb.ap-hop-paris.fr*

## Epidemiology of heart failure

The term acute heart failure commonly refers to an episode of severe cardiac dysfunction<sup>1,2</sup>. Around the world, the problem of congestive heart failure (CHF) is growing despite declining cardiovascular mortality rates and improvements in care. Although the age at which patients develop CHF has shifted upward, newer therapeutic strategies have not reduced – and may actually have increased – the global burden. A recent study of a Swedish population, for example, showed that 10% of 75 year-olds had evidence of left ventricular systolic dysfunction or clinical symptoms of heart failure<sup>3</sup>. Not only is CHF common, but the mortality rate is high when decompensation occurs. Indeed, patients with CHF can decompensate for reasons such as the occurrence of atrial fibrillation, myocardial ischemia or infection. Nearly half of patients who are hospitalized for acutely decompensated CHF die within the next 3 years<sup>4,5</sup>.

Alternatively, acute heart failure may onset suddenly, in patients with no history of

heart failure, as occurs during myocardial infarction. The term acute heart failure could also apply to cardiogenic shock, a syndrome characterized by a low cardiac output, low arterial pressure, severely impaired tissue oxygenation, and associated oliguria. The latter condition is associated with a very poor prognosis.

## The traditional approaches to the treatment of acute heart failure are probably not valid

Heart failure has long been thought to be principally due to an impaired contractility (systolic dysfunction) and so drugs that increase contraction (positive inotropes) have been used as first-line therapy. Unfortunately, the inotropes traditionally used in cardiac care units and intensive care units – catecholamines and phosphodiesterase inhibitors – are now recognized as having serious therapeutic drawbacks, including a decreased long-term survival<sup>6,7</sup>. These inotropes act through the common mechanism of increas-

ing the levels of cytoplasmic cyclic adenosine monophosphate (cAMP) in cardiac myocytes. In turn, elevated cAMP levels promote the release of calcium from the sarcoplasmic reticulum with a consequent rise in the peak intracellular calcium – an action that increases the generation of the contractile force by the actin-myosin interactions. Catecholamines such as dobutamine or epinephrine stimulate adenylate cyclase for an increased production of cAMP, while phosphodiesterase inhibitors such as milrinone prevent cAMP breakdown. Unfortunately, such therapeutic agents also increase the risk of death because the sustained elevation of the intracellular calcium concentration in an already-failing heart can further increase the oxygen demand, impair relaxation, and exacerbate ischemia and arrhythmias. Furthermore, treatment with beta-agonist inotropes such as dobutamine and dopamine can lead to tachyphylaxis (drug tolerance) or dependence, thus compromising the long-term efficacy. New strategies are therefore urgently needed for the treatment of acute heart failure.

### Levosimendan in acutely decompensated congestive heart failure

Levosimendan is currently used to improve the hemodynamic and clinical signs of acute decompensated CHF in cardiology and non-cardiologic intensive care units, heart failure clinics and in the emergency rooms of several European and American countries. This was supported by several studies assessing the beneficial clinical effect of levosimendan in patients with acutely decompensated heart failure. A beneficial effect of levosimendan on the cardiac output, pulmonary artery occlusive pressure (PAOP) and on clinical signs such as dyspnea was further confirmed in a large study, named LIDO, recently published in *Lancet*<sup>8</sup>. In this multicen-

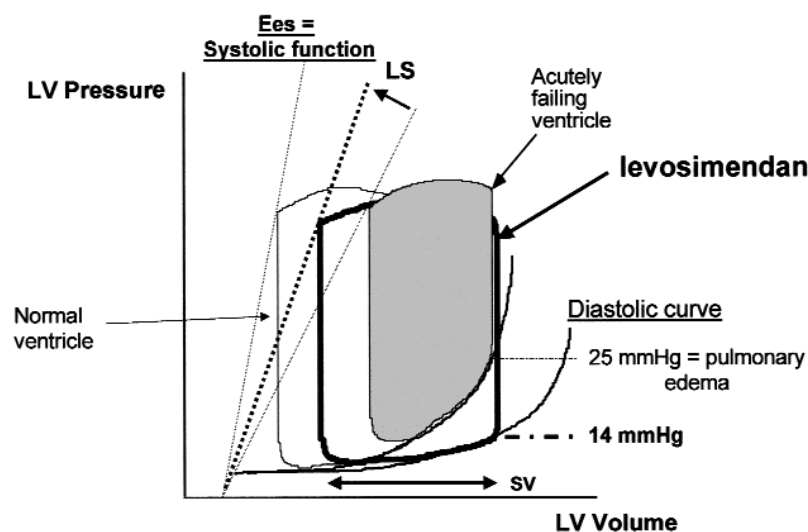
ter randomized, double-blind, double-dummy, parallel group trial, the authors showed that levosimendan, given to 103 patients at a dose of 24 µg/kg over 10 min followed by a continuous infusion of 0.1 µg/kg/min for 24 hours, increased the cardiac output by more than 1.2 l/min and decreased the PAOP by more than 7 mmHg within 1 hour. These data also suggest that levosimendan improved both the systolic and diastolic functions in these CHF patients. Indeed, the increase in cardiac output is in accordance with an improvement in systolic function. In addition, the decrease in the PAOP that represents a decrease in the left ventricular end-diastolic pressure may indicate an increase in left ventricular compliance (Fig. 1).

Another interesting property of levosimendan is that its hemodynamic effects were maintained for more than 24 hours, usually for 3-5 days after the 24-hour infusion<sup>9</sup>.

Thus, there is consensus among cardiologists and intensive therapy physicians in many European and Latin American countries that levosimendan should be used as a first-line therapy after nitrates and/or diuretics and/or non-invasive ventilation (continuous positive airway pressure) in acutely decompensated CHF patients.

### Levosimendan in patients on beta-blocker therapy

An increasing number of CHF patients around the world receive beta-blockers as a standard therapy since these have been shown to improve the survival rate. The incidence of CHF patients ranges between 15 and 80%. The frequency of CHF patients treated with beta-blockers is expected to reach > 50% worldwide within a couple of years. Thus, an increasing number of patients admitted in the emergency room for acutely decompensated CHF are under beta-blocker therapy. The administration of beta-adrenergic agonists such as dobu-



**Figure 1.** Beneficial effects of levosimendan (LS) on the systolic and diastolic functions. Congestive heart failure combines an impairment of both systolic (rightward shift of the elastance-Ees slope) and diastolic functions (upward shift of the diastolic curve). LS improves both dysfunctions: it shifts the Ees slope to the left and decreases the end-diastolic pressure (here from 25 to 14 mmHg). LV = left ventricular; SV = stroke volume.

tamine, is therefore either ineffective or may be even harmful since emergency physicians need to use much higher doses than those administered to patients without beta-blocker therapy to obtain a similar hemodynamic effect.

The LIDO study showed that levosimendan is the ideal drug to improve the clinical and hemodynamic status in CHF patients already under beta-blocker therapy when hospitalized in the emergency room for acutely decompensated CHF<sup>8</sup>. Indeed, levosimendan significantly increased the cardiac output and decreased the PAOP in 33 patients under beta-blocker therapy while dobutamine (at 5-10 µg/kg/min) had no hemodynamic effect in 28 patients who were also on long-term beta-blocker therapy.

### Levosimendan in cardiogenic shock

An increasing number of studies are assessing the beneficial effects of levosimendan on cardiogenic shock. A recent report at the European Society of Intensive Care Meeting in Barcelona (2002), described a beneficial effect of levosimendan in 10 patients with critically ill catecholamine-dependent cardiogenic shock<sup>10</sup>. These patients, with a high APACHE II score (27 on average), a high plasma lactate level (3.6 mmol/l) and a cardiac index < 2.2 l/min/m<sup>2</sup>, were treated with a levosimendan infusion at 0.1 µg/kg/min (and no bolus dose) in combination to norepinephrine or epinephrine when needed. Although no bolus dose was given, the cardiac index increased from 1.8 to 2.5 l/min/m<sup>2</sup>, on average, within 8 hours with no change either in the mean arterial pressure (78 to 73 mmHg) or in the heart rate (96 to 101 b/min). No adverse events were associated with the levosimendan infusion. In our opinion, it is very likely that a bolus dose of 3-6 µg/kg/min would have further increased the cardiac index and shortened the delay to achieving an optimal hemodynamic effect without any significant alteration in blood pressure or in heart rate.

Levosimendan also has beneficial effects in case of severe hemodynamic failure related to a rapidly progressive cardiomyopathy. We recently admitted 2 female patients with cardiogenic shock related to a decompensated *peri-partum* cardiomyopathy and to a viral cardiomyopathy respectively, both successfully treated with levosimendan in our intensive care unit. The first patient developed a severe pulmonary edema and cardiogenic shock within hours of delivery. She was first treated with intubation, mechanical ventilation, nitrates, diuretics, and dobutamine at 10 µg/kg/min. Despite this adequate treatment, the patient remained in cardiogenic shock (heart rate 140 b/min, stroke volume < 50 ml, PAOP > 18 mmHg, and left ventricular ejection fraction < 25%). Levosimendan was therefore introduced and administered for 24 hours. The PAOP decreased rather quickly, down to < 8 mmHg within 24 hours and the stroke volume and urinary output increased. This dra-

matic hemodynamic improvement allowed us to extubate the patient within a couple of days. A similar improvement was seen in a young active women, with no clinically relevant episode in her medical history, who was hospitalized for a rapid occurrence of dyspnea. Chest X-ray showed a pulmonary edema while echocardiography showed a left ventricular ejection fraction < 25%. A Swan-Ganz catheter confirmed the severity of heart failure: cardiac index < 2 l/min/m<sup>2</sup>, mixed venous oxygen saturation < 60%, PAOP > 20 mmHg; heart rate 115 b/min, and blood pressure 115/64 mmHg. After initial treatment with nitrates and continuous positive airway pressure (diuretics failed to increase the urinary output), levosimendan was introduced at 12 µg/kg over 10 min as bolus dose followed by a continuous infusion of 0.1 µg/kg/min for the following 24 hours. All hemodynamic parameters dramatically improved allowing the patient to leave the intensive care unit at day 4.

### Levosimendan to wean intensive care unit patients from mechanical ventilation

Mechanical ventilation as well as non-invasive ventilation are known to improve the hemodynamic function and specially the left ventricular function in patients with heart failure. Indeed, the increase in the intrathoracic pressure is known to decrease the left ventricular afterload and to improve left ventricular-aortic coupling. Furthermore, the addition of a positive end-expiratory pressure will further increase intrathoracic pressure and improve arterial oxygenation.

In contrast, weaning a heart failure patient from the ventilator could be problematic because it may worsen heart dysfunction. Despite the lack of data, levosimendan could be a good therapeutic adjuvant in these patients. Indeed, as performed in several European intensive care units, levosimendan is given before the weaning period to improve left ventricular function. In addition, the long lasting effects of its metabolite (> 5 days) help to maintain left ventricular function during the whole period of weaning including the first hours after extubation that are often problematic.

It is also likely that levosimendan may be beneficial in patients with chronic obstructive pulmonary disease in whom the difficulty in weaning may be related to an exacerbation of the right ventricular failure. In these patients, levosimendan will improve the right ventricular (and if needed left ventricular) contraction but also reduce the right ventricular afterload by decreasing the pulmonary vascular resistance via its K<sub>ATP</sub> channel opening effect<sup>11</sup> and as mentioned above, via the long lasting effect of its metabolite.

### Levosimendan in the perioperative period

**Cardiac surgery.** In 1999, Nijhawan et al.<sup>12</sup> showed that levosimendan enhanced cardiac performance after car-

diopulmonary bypass. Levosimendan increased the cardiac output and stroke volume and decreased the pulmonary and systemic vascular resistances. No differences in arterial oxygenation and perioperative arrhythmia (Holter analysis) were observed between levosimendan and placebo groups. In several European countries, levosimendan is increasingly used in post-cardiac surgery. It is given to wean patients from cardiopulmonary bypass or in cardiosurgical intensive care units. Levosimendan is also beneficial for right ventricular failure, specially that occurring after heart transplantation. In case of vascular dysfunction, as often occurs after cardiopulmonary bypass, norepinephrine can be associated with no harmful effects.

**High-risk surgical patients.** High-risk surgical patients may benefit in the future from the hemodynamic properties of levosimendan. The term high-risk surgical patients defines the patients with a high perioperative morbidity and mortality. It includes patients with severe heart failure and/or coronary artery disease. In addition to their already present cardiac disease, additional myocardial ischemia may frequently manifest during the perioperative course. Myocardial ischemia mostly occurs during the early postoperative phase. The peak incidence of perioperative myocardial infarction (the most severe consequence of myocardial ischemia) occurs within the first 3 postoperative days and more precisely between 12 and 32 hours after surgery. This complication is always preceded by myocardial ischemic events. In addition, compared to what observed in control patients, the survival rate 2 years after non-cardiac surgery is reduced in patients with coronary artery disease (79 vs 93%, respectively). The postoperative decompensation of coronary disease is usually silent even in non-diabetic patients and is often detected only when myocardial ischemia is advanced and ventricular failure is manifest.

A typical scenario is that pain-related tachycardia may increase myocardial oxygen demand and further decrease myocardial oxygen supply by reducing the left coronary diastolic filling time, within 12 hours of major surgery. A vicious cycle may ensue with the tachycardia worsening the myocardial ischemia and inducing left ventricular dysfunction. Ventricular failure becomes manifest with pulmonary edema during the first 24 postoperative hours. Pulmonary congestion is often related to an exacerbation of the diastolic dysfunction due to myocardial ischemia. An analysis of cardiac physiology can explain why patients with coronary artery disease and particularly those with left ventricular hypertrophy, are susceptible to diastolic heart failure. When hemodynamically challenged by stress, such as in case of tachycardia, persons with coronary artery disease and left ventricular hypertrophy are unable to adequately supply oxygen to the left ventricular wall. Tachycardia and the subsequent myocardial ischemia may therefore worsen left ventricular relaxation and compliance, both

already reduced by left ventricular hypertrophy. Consequently, a cascade begins, in which the left ventricular end-diastolic pressure rises, the left atrial pressure increases, and pulmonary edema develops.

Yet, the treatment of patients with left ventricular diastolic dysfunction remains empirical. Current treatment includes avoiding excessive sodium intake, the cautious use of diuretics (to relieve pulmonary congestion without an excessive reduction of the preload), the restoration and maintenance of sinus rhythm at a heart rate that optimizes ventricular filling and the correction of precipitating factors such as acute ischemia and an elevated blood pressure. Levosimendan appears to be an ideal treatment for myocardial ischemia and pulmonary edema in the postoperative period of major surgery. Indeed levosimendan may improve relaxation and left ventricular compliance (by its anti-stunning effect) while the cardiac output remains stable or is improved.

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