

# Prospective observational study of levosimendan and weaning of difficult-to-wean ventilator-dependent intensive care patients

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Although mechanical ventilation is fundamental to modern intensive care, its well-established drawbacks mean it should not be used for longer than absolutely necessary. In patients recovering from critical illness, weaning from mechanical ventilation should begin as soon as the indication for initiating mechanical ventilation starts to resolve. Weaning is usually a relatively uncomplicated process, followed by extubation of the intubated patient. In 10%–20% of cases, weaning may be difficult and the patient requires longer-term ventilatory support, often with multiple failed weaning attempts. This subset of intensive care patients exhibits high morbidity and mortality,<sup>1</sup> with prolonged ICU stay and substantial economic implications. In these patients, successful weaning requires optimisation of the function of several organ systems, with the cardiovascular system playing a key role.<sup>1</sup>

Drugs traditionally used to optimise cardiac function are vasodilators, diuretics and inotropes. The novel calcium-sensitiser levosimendan appears a promising alternative to conventional inotropic agents, such as catecholamines (dobutamine) or phosphodiesterase III inhibitors (amrinone and milrinone), particularly in light of their possible adverse effects, including tachydysrhythmias, increased oxygen consumption, worsening of diastolic dysfunction, tolerance, downregulation of  $\beta$  receptors<sup>2</sup> and potentially detrimental long-term effects.<sup>3,4</sup> There is evidence of improved long-term prognosis of patients with impaired cardiac function treated with levosimendan compared with those treated with dobutamine.<sup>5,6</sup>

In spite of the increasing number of reports of the use of levosimendan in the critically ill,<sup>7,8</sup> little has been published on its potential role in improving cardiac function in difficult-to-wean ventilated ICU patients with impaired cardiac function.<sup>9</sup> We undertook a prospective observational study to evaluate the efficacy and safety of levosimendan in difficult-to-wean, ventilator-dependent ICU patients, with regard to improving their cardiac function and the success rate of weaning from ventilatory support.

## Methods

This prospective observational study was performed over the 22-month period, January 2003 to October 2004, in the

## ABSTRACT

**Objective:** To evaluate the role of levosimendan in improving cardiac performance and the success rate of weaning from mechanical ventilation in ventilator-dependent, difficult-to-wean patients with impaired cardiac function in the intensive care unit.

**Design and setting:** Prospective, observational study in the ICU of Westmead Hospital, a university-affiliated tertiary referral hospital in Sydney, NSW, between January 2003 and October 2004.

**Patients and interventions:** 47 ICU patients who were ventilator-dependent for  $\geq 10$  days and had failed a weaning or extubation attempt due to respiratory insufficiency were identified as difficult to wean from mechanical ventilation. All were assessed by transthoracic or transoesophageal echocardiography. Twelve who had impaired left ventricular performance (demonstrated by left ventricular ejection fraction [LVEF]  $< 40\%$ ) and were already established on diuretic and vasodilator treatment were given a 24-hour infusion of levosimendan. LVEF was measured again within 24 hours after infusion, and weaning from mechanical ventilation and extubation were re-attempted, when clinically deemed feasible.

**Results:** Levosimendan administration was associated with significantly improved LVEF (28.3% before v 34.6% after,  $P=0.04$ ) and  $\text{PaO}_2/\text{FiO}_2$  ratio (179 mmHg v 197 mmHg,  $P=0.002$ ) and reduced  $\text{FiO}_2$  (0.45 v 0.39,  $P=0.01$ ). These changes were associated with significant improvement in the success rate in weaning from mechanical ventilation ( $P=0.02$ ), with seven of the 12 patients successfully weaned after levosimendan therapy, and six surviving to hospital discharge. There was no significant difference in any other important parameter between pre- and post-levosimendan weaning attempts.

**Conclusions:** Levosimendan may provide significant benefit to ventilator-dependent patients with impaired left ventricular function. Randomised controlled trials appear justified.

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20-bed tertiary-referral, general ICU of an Australian university hospital (Westmead Hospital, Sydney, NSW). This ICU

provides critical care for a mixed population of medical and surgical patients requiring mechanical ventilation or haemodynamic support. There are no high-dependency beds, and the ICU operates as a closed unit.

The Hospital Drug Committee approved use of levosimendan for this indication, and the inclusion of each patient in the study required further independent approval by two Drug Committee members. Consent was obtained from each patient or the patient's next of kin. Ventilation used Siemens Servo i and Siemens Servo 300 ventilators.

### Study design

In the absence of a universally accepted definition of the "difficult-to-wean patient", we included all patients who were ventilated for 10 days or more, and had failed at least one weaning or extubation attempt because of respiratory insufficiency.

Patients categorised as difficult to wean were assessed by echocardiography. The subgroup of patients with left ventricular ejection fraction (LVEF) <40% was identified and established on diuretic and vasodilator therapy. All patients were further assessed for the presence of other contributing factors, such as decreased level of consciousness and critical illness polyneuromyopathy.

Patients with LVEF <40%, on established diuretic and vasodilator (angiotensin-converting enzyme inhibitor) treatment, who were fully conscious and without any significant clinical signs of critical illness polyneuromyopathy, were treated with a 24 h infusion of levosimendan. The average dose of levosimendan was 0.108–0.21 µg/kg/min, according to tolerance of the loading dose and haemodynamic stability during infusion. The loading dose of 12 µg/kg was given to six of 12 studied patients.

Twenty-four hours later, LVEF was reassessed by transthoracic or transoesophageal echocardiography (TTE or TOE), and weaning from ventilatory support plus extubation (in non-tracheostomised patients) were again attempted, when clinically deemed feasible by the treating intensivist. Level of consciousness, muscle strength, ability to cough and protect airways, serum levels of magnesium, potassium, phosphate and calcium, renal function, fluid balance and thyroid function were compared between the first (before levosimendan) and second attempt to wean.

Successful weaning was defined as no requirement for ventilatory support for 48 hours after extubation, or (in tracheostomised patients) discontinuation of ventilatory support.

### Statistical analyses

Statistical analyses were performed with GraphPad software and the QuickCalc calculator. All data entered for analysis were normally distributed. The distribution of con-

**Table 1. Baseline characteristics and diagnoses of the 12 patients treated with levosimendan**

Characteristic	
Male : female ratio	8 : 4
Age (years): mean (SD)	69 (13)
Weight (kg): mean (SD)	81.4 (9)
APACHE II score: mean (SD)	23.2 (3)
No. of patients with	
Ischaemic heart disease (acute coronary syndrome)	6
Congestive cardiac failure	5
Toxic/septic cardiomyopathy	1
Tracheostomy in situ	3
Translaryngeal intubation	9

APACHE II = Acute Physiology and Chronic Health Evaluation.

tinuous variables was checked with the Shapiro–Wilk *W* test. Continuous variables were assessed with paired Student's *t* tests, and the mean ± SD are reported. Paired categorical variables were assessed with McNemar's test. For all parameters, differences at the level of *P* < 0.05 were considered statistically significant.

### Results

A total of 1569 patients were admitted to Westmead ICU during the study period. Their average APACHE II score was 20.2, average length of stay was 6.7 days, and average number of ventilator days was 5.2.

Of the 1569 patients, 47 (3%) were classified as difficult to wean from ventilation. All were assessed by TTE or TOE; 27 of the 47 had impaired left ventricular function as demonstrated by LVEF <40%; 11 of the 27 had a persistently decreased level of consciousness, and four others were diagnosed with critical illness polyneuromyopathy.

The 12 patients with decreased LVEF and a satisfactory neurological profile were treated with levosimendan infusion. Their baseline characteristics and diagnoses are summarised in Table 1. Parameters before the first and second weaning attempts are compared in Table 2. There were no statistically significant differences in important baseline characteristics — patient physiological condition and ventilator settings — between the first and second weaning attempts. None of the 12 patients had any clinical or radiological evidence of chest infection before or during either weaning attempt.

Haemodynamic and oxygenation parameters before and after levosimendan infusion are summarised in Table 3. Levosimendan had no major adverse effect and was gener-

**Table 2. Characteristics of 12 patients before attempts at ventilator weaning, related to levosimendan therapy\***

Parameter	Attempt pre-levosimendan	Attempt post-levosimendan	P
Consciousness (GCS) <sup>†</sup>			
Muscle strength <sup>‡</sup>	4	3.92	0.33
No. able to cough	12/12	12/12	–
Serum levels (mmol/L)			
PO <sub>4</sub>	1.08 (0.148)	1.13 (0.114)	0.26
Mg	1.1 (0.123)	1.07 (0.119)	0.61
K	4.14 (0.093)	4.27 (0.122)	0.27
Ca	2.46 (0.126)	2.49 (0.068)	0.56
No. with renal dysfunction <sup>§</sup>	3/12	2/12	1.00
No. with thyroid dysfunction <sup>¶</sup>	5/12	5/12	0.68
Arterial pH	7.39 (0.088)	7.37 (0.118)	0.77
PEEP (cmH <sub>2</sub> O)	6.25 (0.629)	6 (1.08)	0.51
Pressure support (cmH <sub>2</sub> O)	7.75 (1.451)	7.68 (1.098)	0.88
FiO <sub>2</sub>	0.40 (0.289)	0.39 (0.050)	0.63
No. successfully weaned	0/12	7/12	0.02

GCS = Glasgow Coma Scale score.

PEEP = positive end-expiratory pressure.

\* All values are mean (SD) unless otherwise indicated.

† Median value; verbal response on GCS was replaced by ability to adequately communicate via written messages or letter table.

‡ Clinical assessment on a scale of 1–4, where 1 = total paralysis or flicker of movement; and 4 = ability to overcome resistance.

§ Requirement for continuous renal replacement therapy for raised serum levels of urea, creatinine and/or fluid overload.

¶ Sick euthyroid syndrome, based on levels of thyroid-stimulating hormone and thyroxine (T4).

**Table 3. Haemodynamic and oxygenation parameters before and after levosimendan therapy**

	Before levosimendan	After levosimendan	P
SaO <sub>2</sub> (%)*	96.1	96.4	0.30
Systolic BP (mmHg)*	123.1	122.7	0.90
Diastolic BP (mmHg)*	64.4	69.4	0.07
Mean arterial BP (mmHg)*	83.9	87.2	0.51
Heart rate (per min)*	90	89	0.60
Serum potassium (mmol/L)*	4.27	4.22	0.54
FiO <sub>2</sub> <sup>†</sup>	0.45 (0.10)	0.39 (0.10)	0.01
LVEF (%) <sup>†</sup>	28.3 (5.37)	34.6 (8.65)	0.04
PaO <sub>2</sub> /FiO <sub>2</sub> ratio (mmHg) <sup>†</sup>	179 (6.5)	197 (16.5)	0.002

BP = blood pressure. FiO<sub>2</sub> = inspired fraction of oxygen.

LVEF = left ventricular ejection fraction.

PaO<sub>2</sub> = arterial partial pressure of oxygen. \* Mean. † Mean (SD).

**Table 4. Comparison of patient characteristics before levosimendan therapy between responders and non-responders**

	Levosimendan responders	Levosimendan non-responders	P
FiO <sub>2</sub> *	0.4688 (0.0651)	0.4375 (0.1797)	0.66
PaO <sub>2</sub> /FiO <sub>2</sub> ratio (mmHg)*	181 (12.5)	177 (3.5)	0.56
LVEF (%)*	28.00 (4.17)	28.60 (4.79)	0.77
Complications <sup>†</sup>	4	3	–

FiO<sub>2</sub> = inspired fraction of oxygen. PaO<sub>2</sub> = arterial partial pressure of oxygen. LVEF = left ventricular ejection fraction.

\* Mean (SD). † Number of complications per group: transitory hypotension with mean arterial pressure < 65 mmHg and/or self-terminating episode of atrial fibrillation and/or sinus tachycardia > 120 beats/min.

ally well tolerated. Temporary decreases in mean arterial pressure (MAP, < 65 mmHg) occurred in 25% (3/12) of patients but were easily corrected by a low-dose noradrenaline infusion. Transient, self-terminating episodes of atrial fibrillation occurred in 17% (2/12) during the infusion, but required no specific therapeutic intervention. There was an association between levosimendan-attributable complications (temporary decrease of MAP, atrial fibrillation and sinus tachycardia) and the use of a loading dose of levosimendan, but it did not reach statistical significance ( $P=0.25$ ).

Among the 12 patients who received levosimendan, we observed:

- a significant increase in LVEF ( $P=0.04$ ), from 28.3% (95% CI, 24.9%–31.7%; SD, 5.37%) to 34.6% (95% CI, 29.1%–40.1%; SD, 8.65%);
- a significant increase in PaO<sub>2</sub>/FiO<sub>2</sub> ratio ( $P=0.002$ ), from 179 mmHg (95% CI, 175–183; SD, 6.5 mmHg) to 197 mmHg (95% CI, 186–207; SD, 16.5 mmHg); and
- a significant reduction in FiO<sub>2</sub> ( $P=0.01$ ) from 0.45 (95% CI, 0.42–0.48; SD, 0.10) to 0.39 (95% CI, 0.35–0.44; SD, 0.10).

Most importantly, seven of the 12 patients who were previously difficult to wean from ventilatory support were successfully weaned and/or extubated within 51.14 hours (SD, 29.97 hours) of cessation of levosimendan infusion. Four of the seven were extubated within the first 24 hours of cessation of the infusion. All seven survived to discharge from the ICU, and six to discharge from hospital (the other patient died from massive pulmonary embolism 10 days after successful weaning). An eighth patient also responded to levosimendan, but failed to be weaned from ventilatory support and died in the ICU.

Four of the 12 patients did not respond to levosimendan administration, in that cardiac performance measured as

LVEF remained unchanged. None of these patients were successfully weaned and none survived to ICU discharge. However, we did not identify any significant difference between levosimendan-responders and non-responders in any of the important characteristics before administration of levosimendan or in the occurrence of levosimendan-attributable complications (Table 4).

Total ICU mortality in the patients treated with levosimendan was 42% (5/12), and total hospital mortality was 50% (6/12). Overall costs related to levosimendan administration were less than the cost of one ICU bed-day in an Australian tertiary referral centre.

## Discussion

Few case reports have been published on optimisation of cardiac function with levosimendan in ICU patients who are difficult to wean from ventilatory support. Our study is, to our knowledge, the first prospective observational study investigating this topic. Levosimendan acts through direct binding with troponin-C, thereby increasing its affinity for calcium in a calcium-dependent manner, enhancing actin-myosin cross-bridging. Hence, it increases the strength of systole<sup>10</sup> without additional energy and oxygen requirements. During diastole (under low prevailing calcium concentrations), levosimendan — unlike other calcium sensitisers — does not show a calcium-sensitising effect.<sup>10</sup> Thus, levosimendan is both positively inotropic and lusitropic,<sup>11</sup> independently of heart rate.<sup>12</sup> In addition, the long-lasting pharmacodynamic effects of the levosimendan metabolite OR-1896 (5–9 days) may help maintain improved cardiac performance<sup>13</sup> during prolonged weaning, and even during the first 24–48 hours after extubation, which is often a problematic phase.

By opening ATP-dependent K channels, levosimendan causes clinically significant vasodilatation, including within the coronary and pulmonary vasculature,<sup>14</sup> improves O<sub>2</sub> supply to the myocardium and reduces right ventricular afterload. An increasing number of patients with congestive heart failure who are receiving long-term  $\beta$ -blockade<sup>15</sup> present to ICUs with acute decompensation. Administration of  $\beta$ -agonists, such as dobutamine, may be ineffective or even harmful in these patients, because of the competing mechanisms of action and the need for much higher doses of  $\beta$ -agonists to obtain the desired haemodynamic effect.<sup>14</sup> Levosimendan appears more beneficial in patients receiving  $\beta$ -blockade.<sup>16</sup> This may be another rationale for levosimendan as a therapeutic option for ventilator-dependent patients with a failing myocardium. Positive haemodynamic effects have also been shown in a group of patients undergoing cardiac surgery with cardiopulmonary bypass.<sup>17</sup> While two large studies have failed to show a mortality

benefit for levosimendan in heterogeneous populations of patients with acute decompensated heart failure, they did show improvements in plasma brain natriuretic peptide (a marker of ventricular dysfunction) compared with both placebo<sup>18</sup> and dobutamine.<sup>19</sup> One of these studies also reported a reduction in hospital stay.<sup>19</sup>

Our study shows that levosimendan can be used safely and may improve the success rate of weaning in patients with impaired left ventricular function who are difficult to wean from ventilatory support in the ICU. There was a statistically significant improvement in LVEF, which was accompanied by an increase in Pao<sub>2</sub>/Fio<sub>2</sub> ratio and subsequent reduction in Fio<sub>2</sub>. None of the other monitored parameters (level of consciousness, renal and thyroid function, muscle strength, ability to cough, or serum levels of significant ions) showed any statistically significant difference between the first (before levosimendan) and second (after levosimendan) weaning and/or extubation attempt.

The number of patients fulfilling the criteria for difficult to wean comprised only 3% of all ventilated patients admitted to the ICU during this study, probably due to the strict definition applied, limiting levosimendan administration to patients with markedly prolonged and difficult weaning.

Although the multifactorial and complex nature of the weaning process makes study design in this field difficult, we conclude that the improved success rate of weaning from ventilatory support is likely to be attributable to the improvement in cardiac performance. Patients who responded to levosimendan, as shown by an increased LVEF, had a markedly higher success rate for weaning and ICU and hospital discharge than non-responders; of the patients who showed no increase in LVEF after levosimendan therapy, none were successfully weaned, and all died in the ICU. We can only speculate whether responsiveness to levosimendan could be used as a prognostic marker in this context. The loading bolus of levosimendan appeared associated with the few negative effects of the drug and should probably be avoided, contributing nothing to the longer-term effects desired in this scenario. Cost analysis comparing the total costs related to levosimendan administration with the costs of a standard ICU bed-day suggests that a reduction in ICU stay by even a single day justifies the use of levosimendan in difficult-to-wean ICU patients.

Nevertheless, the study had limitations. It was a small observational study without blinding, randomisation or placebo control. Thus, although it suggests a beneficial effect of levosimendan in this patient population, the findings must be regarded as hypothesis-generating for an appropriately powered, double-blind, prospective, randomised, placebo-controlled trial.

In conclusion, levosimendan appears to provide significant benefit to ventilator-dependent patients with impaired

left ventricular function, increasing the likelihood of successful separation from ventilation and survival to hospital discharge, and also potentially reducing the total costs of ICU and hospital stay. The results of this study might be used to help design an appropriately powered, double-blind, prospective, randomised, placebo-controlled trial.

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