

New positive inotropic agents in the treatment of left ventricular dysfunction

Leonardo De Luca, Paola Proietti, Gian Luca Palombaro, Alessandro Battagliese, Annalisa Celotto, Chiara Bucciarelli Ducci, Francesco Fedele

Department of Cardiovascular and Respiratory Sciences, "La Sapienza" University, Rome, Italy

Key words:

Heart failure;
Inotropic agents;
Levosimendan;
Milrinone;
Myocardial infarction;
Vesnarinone.

Three major classes of inotropic agents have been clinically evaluated in patients with left ventricular dysfunction: a) agents that increase the intracellular concentration of cyclic adenosine monophosphate by stimulating the beta-adrenergic receptor or inhibiting phosphodiesterase; b) drugs that increase the intracellular sodium concentration; c) the new calcium-sensitizing drugs.

This review will focus on the newest drug for each of the above-mentioned classes of inotropic agents. Moreover, we present a new protocol which provides the use of levosimendan in patients with post-ischemic left ventricular dysfunction.

(Ital Heart J 2004; 5 (Suppl 6): 63S-67S)

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Address:

Dr. Leonardo De Luca

Dipartimento di Scienze
Cardiovascolari
e Respiratorie
Università degli Studi
"La Sapienza"
Policlinico Umberto I
Viale del Policlinico, 155
00161 Roma
E-mail:
leodeluca@virgilio.it

Introduction

At the moment, three major classes of inotropic agents have been clinically evaluated in patients with left ventricular dysfunction: agents that increase the intracellular concentration of cyclic adenosine monophosphate (AMP) by stimulating the beta-adrenergic receptor or inhibiting phosphodiesterase, drugs that increase the intracellular sodium concentration¹ and the new calcium-sensitizing drugs.

This review will focus on the newest drug for each of the above-mentioned classes of inotropic agents: milrinone, vesnarinone and levosimendan, respectively. Moreover, we present the preliminary data of a protocol which provides the use of levosimendan in patients with post-ischemic left ventricular dysfunction.

Milrinone

The phosphodiesterase inhibitor milrinone is both an inotropic agent and a vasodilator that acts by inhibiting the breakdown of intracellular cyclic AMP. Milrinone also increases myocardial contractility without increasing regional myocardial oxygen consumption^{2,3}. The hemodynamic effect of milrinone is to increase the cardiac index and to decrease pulmonary artery and pulmonary wedge pressures⁴.

Decompensated heart failure. Oral agents that increase intracellular levels of cyclic

AMP have not proved beneficial effects^{5,6} and some studies suggest that long-term administration is associated with increased mortality in patients with left ventricular dysfunction^{7,8}.

On the contrary, the efficacy of oral inotropic agents as short-term treatments for heart failure (HF) exacerbations has been recently demonstrated and have definitely changed the treatment of worsening chronic HF resulting in hospitalization^{9,10}.

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study was the first trial to systematically evaluate a strategy of short-term inotrope use during exacerbations of chronic HF and firstly showed that milrinone may have a bidirectional effect based on etiology in decompensated HF¹¹. This trial randomized 949 patients with left ventricular systolic dysfunction and decompensated HF to receive 48 to 72 hours of intravenous milrinone or placebo¹¹. The primary endpoint (days hospitalized from cardiovascular causes within 60 days) was 13.0 days for ischemic patients and 11.7 days for non-ischemic patients ($p = 0.2$). Moreover, milrinone-treated patients with ischemic etiology tended to have worse outcomes than those treated with placebo in terms of the primary endpoint (13.6 days for milrinone vs 12.4 days for placebo, $p = 0.055$) and the composite of death or rehospitalization (42 vs 36% for placebo, $p = 0.01$). In contrast, outcomes in non-ischemic patients treated with milrinone tended to be improved in

terms of the primary endpoint (10.9 vs 12.6 days for placebo) and the composite of death or rehospitalization (28 vs 35% for placebo). Therefore, milrinone may be deleterious in ischemic HF, but neutral to beneficial in non-ischemic cardiomyopathy¹¹. This finding could be explained because, despite their similar presentations, ischemic and non-ischemic HF represent distinct diseases with different pathophysiology, prognosis and response to therapy^{12,13}. Many potential differences exist in the pathophysiology of HF exacerbations between patients with ischemic and non-ischemic etiology, most notably the presence or absence of ischemia as a trigger for decompensation.

New prospects. Recently, there is evidence of a synergistic effect of milrinone and beta-blockers in advanced congestive HF patients¹⁴, with acceptable mortality rates and a substantially improved quality of life¹⁵. Therefore, combination milrinone and beta-blocker treatment appears to offer hope to some patients with NYHA class IV HF who have no other treatment options¹⁵. Obviously, these data need to be confirmed in a clinical trial with a larger number of patients.

Vesnarinone

Vesnarinone, a quinolinone derivative, is an oral inotropic agent that augments myocardial contractility with little effect on the heart rate or myocardial oxygen consumption¹⁶. By now, its clinical use is restricted because of the occurrence of agranulocytosis as a side effect.

Mechanism of action. The mechanisms of action associated with the inotropic properties of vesnarinone in animals include a decrease in the delayed outward and inward rectifying potassium currents¹⁷; an increase in intracellular sodium caused by the prolonged opening of sodium channels¹⁸; and an increase in the inward calcium current attributable to the mild inhibition of phosphodiesterase¹⁹.

Congestive heart failure. Short-term administration of vesnarinone to patients with HF was associated with limited and variable hemodynamic effects^{20,21}.

In a multicenter study initiated in 1990, with a primary endpoint of combined mortality and major cardiovascular morbidity, 477 patients with NYHA class III or IV HF were randomly assigned to receive placebo or 60 mg of vesnarinone daily for 6 months²². A remarkable and significant 50% reduction in the combined endpoint and a 62% reduction in mortality from all causes were observed in the vesnarinone-treated group²².

Unfortunately, concern was aroused by the occurrence of neutropenia, a dangerous side effect of the drug, in this and earlier clinical trials^{23,24}. Therefore, only two vesnarinone regimens (60 and 120 mg daily) were stud-

ied, and the higher-dose regimen was discontinued early by the data and safety monitoring committee because of a trend toward an adverse effect on mortality.

In a long-term study (Vesnarinone Trial) 3833 patients, who had symptoms of HF (NYHA class III or IV) and a left ventricular ejection fraction $\leq 30\%$ despite optimal treatment, were enrolled to receive 60 or 30 mg of vesnarinone, as compared with placebo, in order to evaluate its effects on mortality and morbidity²⁵. There were significantly fewer deaths in the placebo group (18.9%) than in the 60 mg vesnarinone group (22.9%) and longer survival ($p = 0.02$). The dose-dependent increase in mortality with vesnarinone was attributed to an increase in sudden death, presumed to be due to arrhythmia. The quality of life had improved significantly more in the 60 mg vesnarinone group than in the placebo group at 8 weeks ($p < 0.001$) and 16 weeks ($p = 0.003$) after randomization. The contrasting effects of vesnarinone on the quality of life and on mortality raise profound issues about its mechanisms of action in HF.

Relevant to the above discussion is the observation that vesnarinone inhibits the production of proinflammatory cytokines in a variety of human cell lines^{26,27}, as well as in lipopolysaccharide-stimulated whole blood from HF patients²⁸. Based on these observations, it was postulated that at least some of the beneficial effects of vesnarinone in HF patients were secondary to the anti-cytokine effects of this drug^{27,29}. In contrast to this hypothesis a clinical study³⁰, measuring circulating levels of tumor necrosis factor (TNF), soluble TNF-receptor type 1, soluble TNF-receptor type 2, as well as interleukin-6 and soluble interleukin-6 receptor on plasma samples, suggested that vesnarinone does not have any measurable anticytokine effects *in vivo* in patients with moderate to advanced HF.

Levosimendan

Levosimendan, a pyridazinone-dinitrile derivative, is a calcium sensitizer in cardiac muscle that produces enhanced myocardial contractility³¹.

Mechanism of action. At therapeutic concentrations, levosimendan induces enhanced myofilament contractility mainly via its calcium-sensitizing actions by binding to cardiac troponin C in a calcium-dependent manner^{32,33}. It does not affect intracellular free calcium and cyclic AMP levels and should, therefore, possess no arrhythmogenic potential. This mechanism of action appears to differ from that seen with other calcium sensitizers such as pimobendan and EMD 53998^{34,35}.

Hemodynamic effects. The dose-dependent enhanced contractility effects of levosimendan shown in *in vitro* and *in vivo* have been confirmed in clinical trials in which single doses of levosimendan (0.25 to 5 mg) were given to healthy patients³⁶, patients with left ven-

tricular dysfunction³⁷, and patients who underwent coronary artery bypass³⁸.

Furthermore, levosimendan seems to have no significant effects on myocardial oxygen consumption or on utilization of free fatty acids, lactate, pyruvate and glucose and, at the same time, it reduces coronary vascular resistance and coronary perfusion pressure³⁸.

Effects on diastolic function. A concern regarding calcium sensitizers has been the possibility that they delay the dissociation of calcium from the contractile apparatus, leading to slowing of ventricular relaxation. Conversely, levosimendan has been shown to decrease or have no effects on myocardial relaxation time in a study involving dogs³⁵ and in *in vitro* studies involving failing human myocardium³⁹ and guinea pig hearts⁴⁰. Moreover, levosimendan, compared to placebo, had no clinically relevant influence on diastolic function in 16 patients who had undergone successful percutaneous transluminal coronary angioplasty⁴¹. The mechanism responsible for this phenomenon is not well known but is probably due to the fact that it binds strongly to troponin C in the presence of high systolic intracellular calcium concentrations and binds less avidly when cytosolic calcium levels decrease during diastole⁴². Finally, levosimendan also causes vasodilation attributed to the activation of adenosine triphosphate-regulated potassium channels⁴³.

Congestive and decompensated heart failure. Levosimendan has been evaluated in patients with congestive HF and decompensated HF in several large, multicenter, randomized, double-blind trials compared with placebo or dobutamine.

In the Levosimendan Infusion versus Dobutamine (LIDO) trial⁴⁴, 203 patients with severe, low-output decompensated HF were randomized to levosimendan or dobutamine. Significantly more patients treated with levosimendan than dobutamine achieved an increase from baseline in cardiac index $\geq 30\%$ and a decrease in pulmonary capillary wedge pressure $\geq 25\%$ (28 vs 15%, $p = 0.022$). At 30 days of follow-up, the relative risk of worsening HF or death was significantly lower ($p = 0.039$) with levosimendan than with dobutamine⁴⁴.

In another trial involving 151 patients with congestive HF, 5 different dosages of levosimendan were compared with dobutamine and placebo. At least 50% of patients treated with levosimendan, at all doses, had favorable hemodynamic response in terms of stroke volume, decrease in pulmonary capillary wedge pressure and increase in cardiac output⁴⁵.

Myocardial infarction. Positive inotropic agents, especially phosphodiesterase inhibitors and adrenergic agonists such as dobutamine, may be associated with increasing myocardial oxygen demand and the potential to induce myocardial ischemia or malignant arrhythmias⁴⁶⁻⁴⁹.

Levosimendan, with its little effect on myocardial oxygen demand, is better tolerated by patients with ischemic cardiomyopathy, as demonstrated by an open-label dose-controlled study with three different bolus doses of levosimendan in patients with acute myocardial infarction⁵⁰.

These findings led to the RUSSLAN trial⁵¹ which randomized 504 patients with left ventricular failure complicating an acute myocardial infarction to receive levosimendan at different doses or placebo. Levosimendan-treated patients experienced lower risk of death and worsening HF than patients receiving placebo (2.0 vs 5.9%, $p = 0.033$ over 6-hour and 4.0 vs 8.8%, $p = 0.044$ over 24-hour infusion). Moreover, mortality was lower with levosimendan compared with placebo at 14 days (11.7 vs 19.6%, $p = 0.031$) and the reduction was maintained at the 180-day retrospective follow-up (22.6 vs 31.4%, $p = 0.053$)⁵¹. These interesting findings were in accordance with previous pharmacological results. In a dog study, levosimendan was found to reduce myocardial infarct size, suggesting cardioprotective effects⁵². In another recently published study, racemic simendan improved survival in rats with healed myocardial infarction⁵³.

Our experience. We sought to evaluate the effects of levosimendan (bolus of 12 $\mu\text{g/kg}$ for 10 min and continuous i.v. infusion of 0.1 $\mu\text{g/kg/min}$ for 24 hours) on systolic and diastolic left ventricular function (using echocardiographic parameters for the first time in the literature) and on coronary flow reserve in patients who underwent percutaneous coronary interventions for an acute myocardial infarction with left ventricular dysfunction (ejection fraction $< 40\%$).

At the moment, our data suggest that levosimendan, given intravenously after a percutaneous coronary intervention procedure in patients with acute myocardial infarction, is safe and efficacious and produces a short-term augmentation of the coronary flow reserve and ejection fraction with a concomitant reduction of preload and left ventricular volumes.

Conclusions

Positive inotropic agents are an efficacious and incomparable tool in the short-term treatment of patients with severe left ventricular dysfunction.

Data suggest that positive inotropy by calcium sensitization should be considered as an evolving approach for the treatment of congestive HF and myocardial infarction.

Riassunto

Attualmente tre sono le classi di agenti inotropi valutate in trial clinici e randomizzati su pazienti con dis-

funzione ventricolare sinistra: quelli che aumentano la concentrazione intracellulare di adenosinmonofosfato ciclico attraverso la stimolazione di recettori beta-adrenergici o l'inibizione delle fosfodiesterasi; farmaci che aumentano la concentrazione intracellulare di sodio; ed i nuovi sensibilizzanti all'azione del calcio. In questa rassegna è stato considerato un farmaco (il più nuovo e studiato) per ognuna delle tre sovraindicate classi di agenti inotropi: rispettivamente il milrinone, il vesnarinone e il levosimendan.

L'OPTIME-CHF trial è stato il primo studio che ha dimostrato, in 949 pazienti con disfunzione ventricolare sinistra e scompenso cardiaco cronico, che il trattamento a breve termine con milrinone può avere un effetto bidirezionale: deleterio in pazienti con scompenso cardiaco ad eziologia ischemica ed innocuo o benefico in pazienti con cardiomiopatia ad eziologia non ischemica.

Il vesnarinone è un agente inotropo che incrementa la contrattilità miocardica con scarsi effetti sulla frequenza cardiaca e sulla richiesta miocardica di ossigeno. Attualmente il suo utilizzo clinico è scarso a causa dell'elevata incidenza riscontrata di agranulocitosi.

Il levosimendan fa parte dei farmaci cosiddetti sensibilizzanti all'azione del calcio che incrementano la contrattilità miocardica con scarsi effetti sulla funzione diastolica ventricolare sinistra e pochi effetti aritmogeni. L'effetto inotropo positivo dose-dipendente del levosimendan è stato dimostrato in studi *in vitro* ed *in vivo* e confermato in trial clinici su pazienti con scompenso cardiaco congestizio, infarto miocardico, sottoposti a bypass o angioplastica coronarica.

Gli agenti inotropi positivi sono dunque un efficace ed insostituibile strumento nel trattamento a breve termine della disfunzione ventricolare sinistra severa ed i nuovi farmaci sensibilizzanti al calcio possono essere considerati una nuova frontiera nella terapia dello scompenso cardiaco.

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