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

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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.

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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 concentration[1] 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 pressures[4].

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 HF[11]. This trial randomized 949 patients with left ventricular systolic dysfunction and decompensated HF to receive 48 to 72 hours of intravenous milrinone or placebo[11]. 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 cardiomyopathy[11]. 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 patients[14], with acceptable mortality rates and a substantially improved quality of life[15]. Therefore, combination milrinone and beta-blocker treatment appears to offer hope to some patients with NYHA class IV HF who have no other treatment options[15]. 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 consumption[16]. 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 currents[17]; an increase in intracellular sodium caused by the prolonged opening of sodium channels[18]; and an increase in the inward calcium current attributable to the mild inhibition of phosphodiesterase[19].

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 months[22]. 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 group[22].

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 studied, 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 ≤ 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 morbidity[25]. 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 patients[28]. Based on these observations, it was postulated that at least some of the beneficial effects of vesnarinone in HF patients were secondary to the anticytokine effects of this drug[27,29]. In contrast to this hypothesis a clinical study[30], 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 contractility[31].

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 patients[36], patients with left ven-

tricular dysfunction[37], and patients who underwent coronary artery bypass[38].

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 pressure[38].

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 dogs[35] and in *in vitro* studies involving failing human myocardium[39] and guinea pig hearts[40]. Moreover, levosimendan, compared to placebo, had no clinically relevant influence on diastolic function in 16 patients who had undergone successful percutaneous transluminal coronary angioplasty[41]. 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 diastole[42]. Finally, levosimendan also causes vasodilation attributed to the activation of adenosine triphosphate-regulated potassium channels[43].

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) trial[44], 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 ≥ 30% and a decrease in pulmonary capillary wedge pressure ≥ 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 dobutamine[44].

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 output[45].

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 arrhythmias[46-49].

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 infarction[50].

These findings led to the RUSSLAN trial[51] 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 effects[52]. In another recently published study, racemic simendan improved survival in rats with healed myocardial infarction[53].

Our experience. We sought to evaluate the effects of levosimendan (bolus of 12 μg/kg for 10 min and continuous i.v. infusion of 0.1 μg/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 calciun 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.

References

1. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure: mechanisms of action and recent clinical developments. N Engl J Med 1986; 314: 349-58.
2. Jaski BE, Fifer MA, Wright RF, et al. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside. J Clin Invest 1985; 75: 643-9.
3. Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossman W. Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. Circulation 1985; 71: 972-9.
4. Benotti JR, Lesko LJ, McCue JE, et al. Pharmacokinetics and pharmacodynamics of milrinone in chronic congestive heart failure. Am J Cardiol 1985; 56: 685-9.
5. Uretsky BF, Jessup M, Konstam MA, et al. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. Enoximone Multicenter Trial Group. Circulation 1990; 82: 774-80.
6. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989; 320: 677-83.
7. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. Lancet 1990; 336: 517-8.
8. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991; 325: 1468-75.
9. Gheorghiade M, Gattis WA, Klein L. OPTIME in CHF trial: rethinking the use of inotropes in the management of worsening chronic heart failure resulting in hospitalization. Eur J Heart Fail 2003; 5: 9-12.
10. Jain P, Massie BM, Gattis WA. Current medical treatment for the exacerbation of chronic heart failure resulting in hospitalization. Am Heart J 2003; 145 (Suppl): S3-S17.
11. Felker GM, Benza RL, Chandler AB, et al, for the OPTIME-CHF Investigators. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol 2003; 41: 997-1003.
12. Adams KF Jr, Dunlap SH, Sueta CA, et al. Relation between gender, etiology and survival in patients with symptomatic heart failure. J Am Coll Cardiol 1996; 28: 1781-8.
13. Likoff MJ, Chandler SL, Kay HR. Clinical determinants of mortality in chronic congestive heart failure secondary to idiopathic dilated or to ischemic cardiomyopathy. Am J Cardiol 1987; 59: 634-8.
14. Bohm M, Deutsch HJ, Hartmann D, Rosee KL, Stablein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. J Am Coll Cardiol 1997; 30: 992-6.
15. Zewail AM, Nawar M, Vrtovec B, Eastwood C, Kar MN, Delgado RM 3rd. Intravenous milrinone in treatment of advanced congestive heart failure. Tex Heart Inst J 2003; 30: 109-13.
16. Hori M, Inoue M, Tamai J, et al. Beneficial effect of OPC-8212 (3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone) on myocardial oxygen consumption in dogs with ischemic heart failure. Jpn Circ J 1986; 50: 659-66.
17. Iijima T, Taira N. Membrane current changes responsible for the positive inotropic effect of OPC-8212, a new positive inotropic agent, in single ventricular cells of guinea pig heart. J Pharmacol Exp Ther 1987; 240: 657-62.
18. Cavusoglu E, Frishman WH, Klapholz M. Vesnarinone: a new inotropic agent for treating congestive heart failure. J Card Fail 1995; 1: 249-57.
19. Yatani A, Imoto Y, Schwartz A, Brown AM. New positive inotropic agent OPC-8212 modulates single Ca^{2+} channels in ventricular myocytes of guinea pig. J Cardiovasc Pharmacol 1989; 13: 812-9.
20. Sasayama S, Inoue M, Asanoi H, et al. Acute hemodynamic effects of a new inotropic agent, OPC-8212, on severe congestive heart failure. Heart Vessels 1986; 2: 23-8.
21. Asanoi H, Sasayama S, Iuchi K, Kameyama T. Acute hemodynamic effects of a new inotropic agent (OPC-8212) in patients with congestive heart failure. J Am Coll Cardiol 1987; 9: 865-71.
22. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. Vesnarinone Study Group. N Engl J Med 1993; 329: 149-55.
23. Kubo SH, Rector TS, Strobeck JE, Cohn JN. OPC-8212 in the treatment of congestive heart failure: results of a pilot study. Cardiovasc Drugs Ther 1988; 2: 653-60.

24. Asanoi H, Sasayama S, Kameyama T, Ishizaka S, Iuchi K. Sustained inotropic effects of a new cardiotonic agent: OPC-8212 in patients with chronic heart failure. Clin Cardiol 1989; 12: 133-8.
25. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. N Engl J Med 1998; 339: 1810-6.
26. Shioi T, Matsumori A, Matsui S, Sasayama S. Inhibition of cytokine production by a new inotropic agent, vesnarinone, in human lymphocytes, T cell line, and monocytic cell line. Life Sci 1994; 54: PL11-PL16.
27. Matsumori A, Ono K, Sato Y, Shioi T, Nose Y, Sasayama S. Differential modulation of cytokine production by drugs: implications for therapy in heart failure. J Mol Cell Cardiol 1996; 28: 2491-9.
28. Matsumori A, Shioi T, Yamada T, Matsui S, Sasayama S. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. Circulation 1994; 89: 955-8.
29. Packer M. The search for the ideal positive inotropic agent. N Engl J Med 1993; 329: 201-2.
30. Deswal A, Petersen NJ, Feldman AM, White BG, Mann DL. Effects of vesnarinone on peripheral circulating levels of cytokines and cytokine receptors in patients with heart failure: a report from the Vesnarinone Trial. Chest 2001; 120: 453-9.
31. Figgitt DP, Gillies PS, Goa KL. Levosimendan. Drugs 2001; 61: 613-27.
32. Haikala H, Kaivola J, Nissinen E, Wall P, Levijoki J, Linden JB. Cardiac troponin C as a target protein for a novel calcium sensitizing drug: levosimendan. J Mol Cell Cardiol 1995; 27: 1859-66.
33. Levijoki J, Pollesello P, Kaivola J, et al. Further evidence for the cardiac troponin C mediated calcium sensitization by levosimendan: structure-response and binding analysis with analogs of levosimendan. J Mol Cell Cardiol 2000; 32: 479-91.
34. Hasenfuss G, Pieske B, Kretschmann B, Holubarsch C, Alpert NR, Just H. Effects of calcium sensitizers on intracellular calcium handling and myocardial energetics. J Cardiovasc Pharmacol 1995; 26 (Suppl 1): S45-S51.
35. Pagel PS, Harkin CP, Hettrick DA. Levosimendan (OR-1259), a myofilament calcium sensitizer, enhances myocardial contractility but does not alter isovolumetric relaxation in conscious and anesthetized dogs. Anesthesiology 1994; 81: 974-87.
36. Sundberg S, Lilleberg J, Nieminen MS, Lehtonen L. Hemodynamic and neurohumoral effects of levosimendan, a new calcium sensitizer, at rest and during exercise in healthy men. Am J Cardiol 1995; 75: 1061-6.
37. Lilleberg J, Sundberg S, Nieminen MS. Dose-range study of a new calcium sensitizer, levosimendan, in patients with left ventricular dysfunction. J Cardiovasc Pharmacol 1995; 26 (Suppl 1): 63-9.
38. Lilleberg J, Nieminen MS, Akkila J, et al. Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J 1998; 19: 660-8.
39. Hasenfuss G, Pieske B, Castell M, Kretschmann B, Maier LS, Just H. Influence of the novel inotropic agent levosimendan on isometric tension and calcium cycling in failing human myocardium. Circulation 1998; 98: 2141-7.
40. Edes I, Kiss E, Kitada Y, et al. Effects of levosimendan, a cardiotonic agent targeted to troponin C, on cardiac function and on phosphorylation and Ca^{2+} sensitivity of cardiac myofibrils and sarcoplasmic reticulum in guinea pig heart. Circ Res 1995; 77: 107-13.
41. Sonntag S, Opitz C, Wellnhofer E, et al. Effects on the calcium sensitizer levosimendan on stunned myocardium after percutaneous transluminal coronary angioplasty. (abstr) Eur Heart J 2000; 21 (Suppl): 40.
42. Haikala H, Nissinen E, Etemadzadeh E. Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol 1995; 25: 794-801.
43. Lehtonen L. Levosimendan: a promising agent for the treatment of hospitalized patients with decompensated heart failure. Curr Cardiol Rep 2000; 2: 233-43.
44. Follath F, Cleland JG, Just H, et al, for the Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002; 360: 196-202.
45. Nieminen MS, Akkila J, Hasenfuss G, et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000; 36: 1903-12.
46. Caldicott LD, Hawley K, Heppel R, Woodmansey PA, Channer KS. Intravenous enoximone or dobutamine for severe heart failure after acute myocardial infarction: a randomized double-blind trial. Eur Heart J 1993; 14: 696-700.
47. Karlsberg RP, DeWood MA, DeMaria AN, Berk MR, Lasher KP. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. Milrinone-Dobutamine Study Group. Clin Cardiol 1996; 19: 21-30.
48. Gillespie TA, Ambos HD, Sobel BE, et al. Effects of dobutamine in patients with acute myocardial infarction. Am J Cardiol 1977; 39: 588-94.
49. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999; 138 (Part 1): 78-86.
50. Luotalahti M, Lammintausta O, Ukkonen H, et al. Levosimendan, a calcium sensitizer and potassium channel opener, is safe and improves left ventricular function in acute myocardial infarction. (abstr) Circulation 1998; 98 (Suppl I): 105.
51. Moiseyev VS, Poder P, Adrejevs N, et al, for the RUSSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J 2002; 23: 1422-32.
52. Kersten JR, Montgomery MW, Pagel PS, et al. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K_{ATP} channels. Anesth Analg 2000; 90: 5-11.
53. Levijoki J, Pollesello P, Kaheiner P, et al. Improved survival with simendan after experimental myocardial infarction in rats. Eur J Pharmacol 2001; 419: 243-8.