Reviews

Inotropes in Heart Failure: Novel Aspects

ATHANASIOS G. TRIKAS, CHRISTOS A. FOURLAS, CHRISTODOULOS I. STEFANADIS

Department of Cardiology, Medical School of Athens University, Hippokration Hospital, Athens, Greece

Key words:
Heart failure, inotropes, adrenergic agonists, phosphodiesterase inhibitors, calcium sensitizers.

Manuscript received:
February 13, 2003;
Accepted:
July 25, 2003.

Address:
Athanasios G. Trikas

52 Bizaniou St.,
166 73, Panorama
Voulas
Athens, Greece
e-mail:
atrikas@otenet.gr

The development of neurohormonal hypothesis during the last decades has provided a new aspect in the understanding of the pathophysiology and therapeutics of heart failure (HF). It has been postulated that HF is not a problem of "pump dysfunction", as was previously supported by the hemodynamic model. HF is a clinical syndrome with a complicated pathophysiology, which develops and progresses as a consequence of neurohormones and cytokines activation, leading to myocyte alterations, receptor deterioration, apoptosis and structural remodeling[1].

The modern therapeutic strategy in chronic HF has focused on symptom limitation (with diuretics and digitalis) and survival improvement (with angiotensine converting enzyme (ACE) inhibitors and beta-blockers)[2]. Inotropes are in use in decompensated HF with low-output. Adrenergic agonists and phosphodiesterase III (PDE) inhibitors are the two basic categories of inotropic agents, which both increase cardiac muscle contractility by a common final pathway, that results in increased intracellular cyclic adenylate monophosphate (cAMP) levels.

Although inotropic therapy appears to increase mortality, as supported by several clinical trials[3,4], it is still in wide use in clinical practice. Furthermore, adrenergic agonist administration is no longer the treatment of choice in patients with HF receiving beta-blockers. While "classic" inotropic therapy in decompensated HF is under reconsideration, novel inotropic agents are under clinical evaluation.

Adrenergic agonists

Adrenergic agonists are agents that stimulate adrenergic receptors (α, β_1, β_2), affecting both the myocardium and the peripheral vessels. They have been in clinical use for several decades, as a short-term intravenous inotropic support in acute or decompensated HF, although long-term intermittent therapeutic schemes in chronic HF have also been suggested. Despite their favourable hemodynamic effects, adrenergic agent administration is followed by increased frequency of arrhythmiologic events, while rapid beta-receptor desensitization has also been reported. In addition, adrenergic treatment in patients with HF, who are under beta-blockers, is presented as a novel, complicated clinical problem[5].

Dopamine is an endogenous catecholamine, that stimulates both adrenergic and dopaminergic (D_1 and D_2) receptors. It is well-known that hemodynamic effects of dopamine are directly correlated with the infusion rate. Low-dose infusion (<5 μg/kg/min) was reported as "renal dose" and was considered to have renal protective effects. It was thought to induce intrarenal vasodilatation and renal blood flow augmentation, via direct stimulation of renal dopaminergic receptors. Inter-

mediate doses (5-10 μg/kg/min) cause positive inotropic and chronotropic effects, by stimulating myocardial β_1-receptors and inducing norepinephrine release. Higher doses (>10 μg/kg/min) are characterized as "vasoconstrictive", as they induce peripheral vasoconstriction and vascular resistance elevation, via α-adrenergic receptor stimulation.

Dopamine is no longer considered as a first line adrenergic agent for inotropic support of critically ill patients, due to the superior pharmacodynamic properties of dobutamine. However, dopamine is still in wide use in clinical practice, especially the "renal dose" infusion, although its renal protective action has never been proved[6,7]. Furthermore, there is evidence of tolerance development after 48-hour low-dose dopamine infusion[8]. In addition, prolonged dopamine infusion has been accused of inducing hypoxemia, impairing ventilatory response and gas exchange, worsening splachnic oxygenation and impairing gastrointestinal, endocrine and immunologic function[9].

Dobutamine is a β-adrenergic agonist, with positive inotropic and peripheral vasodilative properties, especially when it is administered in low-dose infusion (<5 μg/kg/min). Significant hemodynamic improvement has been reported after tailored therapy, using dobutamine and nitroglycerine in patients with advanced HF[10]. The combination of left ventricular contractility improvement and afterload reduction, with a decrease of pulmonary vascular resistance, has established dobutamine as a first line therapeutic choice in patients with decompensated HF. Furthermore, a recent study reports indices of sympatholytic action of dobutamine in myocardium of patients with HF, attributed to ventricular filling pressure reduction and /or myocardial baroreceptors stimulation[11].

In the presence of beta –blockade in patients with decompensated HF, there is a necessity of high-dose dobutamine infusion (>10 μg/kg/min), in order to achieve adequate increase in cardiac output, with a consequential increase of vascular resistance and left ventricular afterload[12]. In these patients, PDE inhibitors seem to have an advantage in comparison to dobutamine[13].

Long-term intermittent infusion of inotropic agents in patients with severe HF or in pretransplant stage has been reported to be well-tolerated and to improve hemodynamic status, but has been demonstrated to increase mortality[4,14]. This therapeutic strategy, although not evidence-based, may play a role as palliative therapy in end-stage patients. In the multicenter trial DICE, a six-month intermittent low-dose dobutamine infusion was shown to reduce patient hospitalizations, although there was no significant improvement of functional status or mortality[15]. Long-term intermittent dobutamine infusion in patients with HF of New York Heart Association (NYHA) functional class III or IV was demonstrated to lack of improvement concerning quality of life and to increase mortality, as shown by the FIRST study[16]. Combined administration of intermittent inotropes and amiodarone seems to reduce sudden cardiac death incidence and to improve survival[17]. Intermittent inotropic therapy is not a first line therapy in patients with severe HF and is not indicated by the Guidelines for the Evaluation and Management of Chronic Heart Failure.

Ibopamine is a dopaminergic agonist, that is administered orally and induces positive inotropic effects as well as peripheral and intrarenal vaso-dilatation. Although it was initially believed that this agent could contribute to symptomatic and hemodynamic improvement of patients with advanced HF (functional class NYHA III and IV), ibopamine is not currently in use in clinical practice, as a significant increase of mortality was shown by PRIME II study[18,19]. The clinical use of other adrenergic agonists (epinephrine, norepinephrine, isoprotrenole) has been almost substituted by dobutamine, with certain exceptions[20].

Phosphodiesterase inhibitors

Phosphodiesterase (PDE) inhibitors are a category of inotropic agents, that use the adrenergic pathway, as they induce PDE III inhibition, leading to increased intracellular cAMP levels and augmented calcium release from the sarcoplasmic reticulum. PDE inhibition in cardiac muscle cells results in positive inotropic activity, while PDE inhibition in vascular smooth muscle cells results in vasodilatation of peripheral and pulmonary vessels. PDE inhibitors are frequently characterized as "inodilators", due to this combined action. The main agent in clinical use remains milrinone, as enoximone is not widely in use and novel agents (enoximone, vesnarinone) are under clinical evaluation.

As becomes obvious, this "postreceptor" mechanism of action is a great advantage of this category, as it is well-known that adrenergic receptor system is downregulated and desensitized in chronic HF. This

property, in combination with the pulmonary vascular resistance decrease and the limited heart rate augmentation, was a theoretic advantage of this category, in comparison with adrenergic agonists[2!]. In addition, the ability of oral administration appeared as a chance for long-term out-hospital treatment for chronic HF.

Milrinone administration to patients with severe HF (NYHA functional class III or IV) improved their hemodynamic parameters[21], while patients of NYHA functional class II and III, who received enoximone, demonstrated an increase in exercise capacity[23]. Milrinone has also been studied in patients with end-stage HF, who were candidates for heart transplantation and had pulmonary hypertension, as the presence of pulmonary hypertension is an index of poor prognosis in these patients[24].

However, it is well-documented that the symptomatic and hemodynamic improvement, after PDE inhibitors treatment, is an "exchange" of reduced survival[3,25]. The results of the recent OPTIME-CHF study, in which 951 patients with deteriorated HF were enrolled, confirmed the increased frequency of hypotensive events and tachyarrhythmias, while no significant clinical benefit was shown, as there was no decrease in rehospitalizations or mortality[26,27]. These results do not support the short-term milrinone treatment for patients with decompensated HF. However, analysis of study results has shown that milrinone effect may be bidirectional, based on the etiology of the HF, as it may be deleterious in ischemic HF, but neutral to beneficial in non-ischemic cardiomyopathy[28]. Furthermore, in a retrospective analysis of the outcome of dobutamine versus milrinone treatment in 329 patients with advanced decompensated HF, there was no significant difference in clinical benefit or adverse events, while dobutamine based treatment had a significantly reduced economic cost[28].

Novel inotropic agents

Several novel inotropic agents are currently being developed and studied. The most interesting and promising group includes agents that are characterized as "calcium sensitizers", as they exert their action by increasing the sensitivity of contractile apparatus (especially troponine-T) to intracellular calcium[30]. This mechanism of action does not use the adrenergic pathway, that leads to increased intracellular cAMP and calcium concentrations. Thus, serious adverse events, especially proarrhythmic activity, seem to be less common. Furthermore, some of these agents are reported to induce peripheral, pulmonary and coronary vasodilatation, via ATP-sensitive potassium channels, although they were initially supposed to have PDE inhibition properties[31].

Levosimendan is the best clinically evaluated agent of this category (pimobendan and toborinone are still under evaluation). Intravenous infusion of levosimendan in patients with deteriorated chronic HF improved rapidly the hemodynamic parameters (stroke volume and cardiac output), with simultaneous improvement of the clinical situation of the patients, with no significant increase of heart rate or serious adverse events, except hypotension[31,32]. In the LIDO study, the investigators compared the effects of dobutamine and levosimendan on hemodynamic performance and clinical status of patients with low-output HF, that needed hemodynamic support. The majority of patients (circa 90%) received diuretics and ACE inhibitors, 2/3 of them received digitalis and 40% were on beta-blockers. Levosimendan administration was associated with a greater improvement of cardiac output and more pronounced decrease in pulmonary-capillary wedge pressure and peripheral vascular resistance, than dobutamine[33]. These levosimendan effects were not attenuated by the concomitant use of beta-blockers, unlike to dobutamine. Furthermore, a lower six-month mortality was noticed in levosimendan group. This long-acting benefit was attributed to the lack of proarrhythmic effects of levosimendan and to a possible "anti-stunning" effect, as levosimendan does not increase myocardial oxygen demand. From the other hand, dobutamine is reported to induce an irreversible myocardial "damage", that is correlated with increased intracellular concentrations of cAMP and calcium, that leads to increased risk of death.

Levosimendan was proved to be both well-tolerated and effective in patients with left ventricular failure, complicating acute myocardial infarction. According to the results of RUSSLAN study, low-dose levosimendan infusion (0.1-0.2 μg/kg/min) reduced mortality and decreased the incidence of worsening HF, with no increase of clinically significant hypotension or ischemia[34]. This is the first study that demonstrates a decrease of mortality in postinfarct patients, that was achieved by the administration of a positive inotropic agent. In these patients there was previously a crucial "exchange" of

improving cardiac contractility at the expense of an increase of oxygen demand and ischemia incidence.

Inotropes and beta-blockers

Beta-blockade in patients with mild to moderate HF is presently supported by several large trials, that have shown a significant reduction in morbidity and mortality. Despite these impressive results, beta-blockers remain underused by clinical cardiologists (36.9% of patients enrolled in Euro Heart Failure Survey Trial were on beta-blockers)[35,36]. However, the implementation of beta-blockers in clinical practice has given rise to a novel therapeutic problem: what therapeutic strategy is indicated in patients with decompensated HF that are chronically beta-blockaded and need inotropic support? Combined administration of an inotropic agent and a beta blocker may be recommended, as a recent study reports that beta-blocker withdrawal in these patients is correlated with increased adverse events[37].

As it was previously mentioned, dobutamine administration is not indicated in these cases, because increased infusion rates (>10 μg/kg/min) that are usually required to achieve adequate hemodynamic improvement, can also induce peripheral vasoconstriction and left ventricular afterload augmentation[12,13,38]. PDE inhibitors administration in these patients is supported by recent studies, as it has been demonstrated that their potency can be even enhanced by chronic beta-blockade, as a possible consequence of beta-receptor system normalization[39]. A therapeutic combination of PDE inhibitor and short-acting intravenous beta-blocker has been suggested as a pharmaceutical "bridging" to the initiation of long-term beta-blocker therapy in patients with HF of functional class NYHA IV[40]. This therapeutic strategy has also been suggested for patients in pretransplant stage, or as a palliative treatment for end-stage patients, with contraindications for heart transplantation[41].

The hesitations about PDE inhibitors administration in HF, that have been demonstrated by several clinical trials, have settled the novel category of calcium sensitizers as promising candidates for future. Therapeutic combination with beta-blockers seems to be attainable, as their mechanism of action is independent of the beta-adrenergic pathway. LIDO study provided the first positive results of this combination, which obviously need further clinical evaluation.

Conclusions

The role of inotropes in decompensated HF therapeutic is crucial, although controversial. Dopamine has been largely replaced in clinical practice by dobutamine, while the clinical value of "renal dose" is no longer supported. The implementation of beta-blockers as standard treatment of HF makes adrenergic unfavourable for inotropic support of these patients. Adrenergic agonists and PDE inhibitors are demonstrated to improve hemodynamic status and quality of life "in exchange" for reduced survival. Increased intracellular cAMP levels that result in augmented calcium release from the sarcoplasmic reticulum has been considered as the common etiologic mechanism of their proarrhythmic activity. Calcium sensitizers are a novel category of agents with positive inotropic and vasodilative effects, that seem to lack proarrhythmic activity, as they do not increase intracellular calcium levels. Furthermore, they are reported to be well-combined with beta-blocker treatment. However, they are drugs that not been completely evaluated as first line treatment. The goal of an "ideal" inotropic agent for decompensated HF seems unattainable, while therapeutic strategy remains a consequence of patient characteristics and physician's clinical experience.

References

1. Francis GS: Pathophysiology of chronic heart failure. Am J Med 2001; 110: 37S-46S.
2. Abraham WT, Wagoner LE: Medical management of mild-to-moderate heart failure before the advent of beta blockers. Am J Med 2001; 110: 47S-62S.
3. Thackray S, Easthaugh J, Freemantle N, Cleland JG: The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure - a metaregression analysis. Eur J Heart Fail 2002; 4: 515-529.
4. Felker GM, O'Connor CM: Inotropic therapy for heart failure: an evidence-based approach. Am Heart J 2001; 142: 393-401.
5. Bristow MR, Shakar SF, Linseman JV, Lowes BD: Inotropes and beta-blockers: is there a need for new guidelines? J Card Fail 2001; 7: 8-12.
6. Varriale P: Role of dopamine in congestive heart failure: a contemporary appraisal. Congest Heart Fail 1999; 5: 120-124.
7. Van De Borne P, Somers VK: Dopamine and congestive heart failure: pharmacology, clinical use and precautions. Congest Heart Fail 1999; 5: 216-221.
8. Ichai C, Passeron C, Carles M, Bouregba M, Grimaud D: Prolonged low-dose dopamine infusion induces a transient improvement in renal function in hemodynamically stable, critically ill patients: a single-blind, prospective, controlled study. Crit Care Med 2000; 28: 1329-1335.

9. Holmes CL, Walley KR: Bad medicine: low-dose dopamine in the ICU. Chest 2003; 123: 1266-1275.
10. Drazner MH, Solomon MA, Thompson B, Yancy CW: Tailored therapy using dobutamine and nitroglycerin in advanced heart failure. Am J Cardiol 1999; 84: 941-943.
11. Al-Hesayen A, Azevedo ER, Newton GE, Parker JD: The effects of dobutamine on cardiac sympathetic activity in patients with congestive heart failure. J Am Coll Cardiol 2002; 39: 1269-1274.
12. Lowes BD, Simon MA, Tsvetkova TO, et al: Inotropes in the beta-blocker era. Clin Cardiol 2000; 23: III 11-16.
13. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, et al: Beta-blocker therapy influences the hemodynamic response to inotropic agents with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. J Am Coll Cardiol 2002; 40: 1248-1258.
14. Silver MA, Lawn O: Intermittent inotropes for advanced heart failure: inquiring minds want to know. Am Heart J 1999; 138: 191-192.
15. Oliva F, Latini R, Politi A, Staszewsky L, Maggioni AP, Nikolis E, et al: Intermittent 6-month low-dose dobutamine infusion in severe heart failure : DICE Multicenter Trial. Am Heart J 1999; 138: 247-253.
16. O'Connor CM, Gattis WA, Uretsky BF, Adams KF Jr, McNulty SE, Grossman SH, et al: Continuous intravenous dobutamine infusion is associated with an increased risk of death in patients with advanced heart failure: insights of the Flolan International Randomized Survival Trial. Am Heart J 1999; 138: 78-86.
17. Nanas JN, Kontoyiannis DA, Alexopoulos GP, Anastasiou-Nana MI, Tsagalou EP, Stamatelopoulos SF, et al: Long-term intermittent dobutamine infusion combined with oral amiodarone improves the survival of patients with congestive heart failure. Chest 2001; 119: 1173-1178.
18. Hampton JR, van Veldhuisen DJ, Kleber FX, Cowley AJ, Ardia A, Block P, et al: Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Lancet 1997; 349: 971-977.
19. Feenstra H, Grobbee RE, in't Veld BA, Stricker BH: Confounding by contraindication in a national cohort study of risk for death in patients taking ibopamine. Ann Intern Med 2001; 134: 569-572.
20. Young JB: New therapeutic choices in the management of acute congestive heart failure. Rev Cardiovasc Med 2001; 2: S19-S24.
21. Quigg RJ: Rationale for the short term use of intravenous milrinone under hemodynamic guidance in patients with severe systolic heart failure. Congest Heart Fail 2000; 6: 202-214.
22. Hatzizacharias A, Makris T, Krespi P, Triposkiadis FK, Voyatzi P, Dalianis N, et al: Intermittent milrinone effect on long-term hemodynamic profile in patients with severe congestive heart failure. Am Heart J 1999; 138: 241-246.
23. Lowes BD, Higginbotham M, Petrovich L, DeWood MA, Greenberg MA, Rahko PS, et al: Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group. J Am Coll Cardiol 2000; 36: 501-508.
24. Pamboukian SV, Carere RG, Webb JG, Cook RC, D'yachkova Y, Abel JG, et al: The use of milrinone in pre-transplant assessment of patients with congestive heart failure and pulmonary hypertension. J Heart Lung Transplant 1999; 18: 367-371.
25. Thackray S, Witte K, Clark AL, Cleland JG: Clinical trials update: OPTIME-CHF, PRAISE-2, ALL-HAT. Eur J Heart Fail 2000; 2: 209-212.
26. Cuffe MS, Califf RM, Adams KF, Bourge RC, Colucci W, Massie B, et al: Rationale and design of the OPTIME CHF trial: outcomes of a prospective trial of intravenous milrinone for exacerbation of chronic heart failure. Am Heart J 2000; 139: 15-22.
27. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, et al: Short-term intravenous milrinone for acute exacerbation of chronic heart failure. JAMA 2002; 287: 1541-1547.
28. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, et al: 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.
29. Yamani MH, Haji SA, Starling RC, Kelly L, Albert N, Knack DL, et al: Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: hemodynamic efficacy, clinical outcome and economic impact. Am Heart J 2001; 142: 998-1002.
30. 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: 2141-2147.
31. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J, et al: Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000; 102: 2222-2227.
32. Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V, et al: Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000; 36: 1903-1912.
33. Follath F, Cleland JGF, Just H, Papp JG, Scholz H, Peuhkurinen K, et al: 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.
34. Moiseyev VS, Pöder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al: 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: 1422-1432.
35. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, et al: The EuroHeart Failure Survey programme-a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003; 24: 464-474.
36. Gheorghiade M, Colucci WS, Swedberg K: β-Blockers in chronic heart failure. Circulation 2003; 107: 1570-1575.
37. Gattis WA, O'Connor CM, Leimberg JD, Felker GM, Adams KF, Gheorghiade M: Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. Am J Cardiol 2003; 91: 169-174.
38. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR: Milrinone versus dobutamine in heart failure subjects

treated chronically with carvedilol. Int J Cardiol 2001; 81: 141-149.
39. Bohm M, Deutsch HJ, Hartmann D, Rosee KL, Stablein A: Improvement of postreceptor events by metoprolol in patients with chronic heart failure. J Am Coll Cardiol 1997; 30: 992-996.
40. Hauptman PJ, Woods D, Prirzker MR: Novel use of a short-acting intravenous beta blocker in combination with inotropic therapy as a bridge to chronic oral beta blockade in patients with advanced heart failure. Clin Cardiol 2002; 25: 247-249.
41. Shakar SF, Abraham WT, Gilbert EM, Robertson AD, Lowes BD, Zisman LS, et al: Combined oral positive inotropic and beta-blocker therapy for the treatment of refractory class IV heart failure. J Am Coll Cardiol 1998; 31: 1336-1340.