

Infusion therapy in severe heart failure. A reappraisal

Carlo Campana, Laura Scelsi, Alessandra Serio

Department of Cardiology, IRCCS Policlinico San Matteo, Pavia, Italy

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Decompensated heart failure is associated with high rates of morbidity and mortality and it is responsible for numerous hospitalizations. The current approach to acute exacerbations is based on diuretics, vasodilators and inotropes. Compared with the impressive development of new therapeutic agents designed for other cardiovascular diseases, little progress has been observed in developing new drugs for the treatment of decompensated heart failure. Moreover, a series of controlled clinical trials failed to show a better outcome or a reduction in morbidity during treatment with inotropes, even though promising results were recently observed in controlled clinical trials with new classes of drugs, such as calcium sensitizers and nesiritide; these agents will probably modify the treatment options of decompensated heart failure in the coming years.

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Address:

Dr. Carlo Campana

*Dipartimento
di Cardiologia
IRCCS Policlinico
San Matteo
Piazzale Golgi, 2
27100 Pavia
E-mail:
C.Campana@smatteo.pv.it*

Intravenous therapy may be indicated to correct the hemodynamic disruption of end-stage heart failure, in the management of the acute exacerbation of chronic heart failure and as a “bridge” to heart transplantation.

Patients with advanced heart failure often show clinical decompensation characterized by a low cardiac output and high ventricular filling pressures. This can occur in the presence of cardiac or extracardiac events or when compliance to medical therapy is inadequate. These conditions represent a cause of increasing hospital admissions and readmissions as well as of a high mortality.

Patients presenting with an acute decompensation of chronic congestive heart failure frequently receive parenteral inotropic drugs during hospitalization, with a significant clinical improvement. These agents generally increase cardiac output and reduce the preload and afterload. In effect they are not a single class of drugs, but in the acute setting they produce similar clinical outcomes by different mechanisms of action.

Ten years ago Feldman¹ proposed a classification system that defines these drugs according to their mechanism of action (Table I).

Class I includes those drugs that increase the intracellular levels of cyclic adenosine monophosphate (cAMP), e.g., beta-adrenergic agonists and phosphodiesterase (PDE) inhibitors.

Class II includes those agents that affect the sarcolemmal ion pumps and channels, e.g., digoxin.

Class III includes those drugs that modulate the intracellular calcium handling mechanisms. The contractile force of the heart may be augmented not only by an increased availability of intracellular calcium for troponin C but also by increasing the sensitivity of the contractile proteins to calcium.

Class IV agents have multiple mechanisms of action, e.g., pimobendan and vesnarinone. Pimobendan increases the affinity of the regulatory site on troponin C for calcium and is also characterized by an inhibitory effect on PDE III. Vesnarinone decreases the outward and inward rectifying potassium current. The drug also increases the intracellular sodium as a result of PDE inhibition.

The role of inotropic therapy is generally considered controversial; these agents may produce marked acute hemodynamic effects; for example, the intravenous infusion of dobutamine and/or PDE inhibitors has been considered the therapy of choice in acute heart failure and for the critical decompensation of chronic heart failure. However, long-term inotropic therapy failed to produce sustained benefits and the chronic administration of these agents was associated with an increased mortality (Table II)²⁻¹².

Table I. Classification of inotropic agents by mechanism of action.

Class	Drugs	Mechanism of action
I	Beta-adrenergic agonists Phosphodiesterase inhibitors	Increase intracellular cyclic adenosine monophosphate
II	Digoxin	Inhibits sarcolemmal ion pumps and channels
III	Calcium sensitizers	Modulate intracellular calcium handling mechanisms (increase of contractile protein sensitivity to calcium)
IV	Pimobendan, vesnarinone	Pimobendan increases the affinity of the regulatory site on troponin C for calcium, vesnarinone decreases potassium current low phosphodiesterase inhibition effect

Table II. Studies dealing with inotropic drugs in heart failure.

Study	Drug	No. patients	Design	Follow-up	Outcome
Miller et al. ³ , 1991	Dobutamine 5 µg/kg/min	25	Case series	54 weeks	↓ hospitalization 6/25 deaths
Dies et al. ⁴ , 1986	Dobutamine 8.1 µg/kg/min	60	Clinical trial	8 weeks	↑ clinical in 50% ↑ exercise time 20/60 deaths
Applefeld et al. ⁵ , 1987	Dobutamine 2.5-7.3 µg/kg/min	21	Case series	32 weeks	↑ clinical 20/21 deaths
DICE ⁶ , 1999	Dobutamine 48 hours/week 4.5 µg/kg/min	38	Clinical trial	6 months	↑ clinical ↓ hospitalization
Anderson et al. ⁷ , 1987	Milrinone loading 37.5 to 75 µg/kg/min maintenance 0.25 to 0.75 µg/kg/min	189	Clinical trial	48 hours	↑ hemodynamics
PROMISE ⁸ , 1991	Milrinone 40 mg	1088	Clinical trial	6.1 months	↑ mortality
OPTIME-CHF ⁹ , 2003	Milrinone 48-72 hours 0.5 µg/kg/min; no loading	949	Clinical trial	60 days	↑ outcome in DCM ↓ blood pressure
Nieminen et al. ¹⁰ , 2000	Levosimendan 6-24 µg/kg/min loading 0.2 µg/kg/min	151	Clinical trial	–	hemodynamics
LIDO ¹¹ , 2002	Levosimendan 24 µg/kg/min loading 0.1 µg/kg/min vs dobutamine	203	Clinical trial	180 days	↑ hemodynamics ↓ mortality
Nesiritide Study Group ¹² , 2000	Nesiritide 0.015 and 0.030 µg/kg/min	127+ 305	Clinical trial efficacy/ comparative	6 hours 7 days	↑ clinical ↑ hemodynamics

DCM = dilated cardiomyopathy.

In the clinical setting dopamine, dobutamine and milrinone are the drugs generally used to sustain severely perturbed hemodynamics in patients with advanced heart failure.

Inotropic drugs

Sympathomimetic agents. Dopamine. The effects of dopamine are mediated either through the direct or indirect activation of the pre- and post-synaptic adrenergic receptors via the release of norepinephrine. The inotropic and chronotropic actions of dopamine are consequent to the activation of the post-synaptic myocardial beta₁ receptors, with dosages ranging from 5 to 10-15 µg/kg/min; the lower dosages (ranging between 0.5-2.5 µg/kg/min) affect the post-synaptic dopaminergic receptors (D1 vascular receptors) whilst they do not stimulate the adrenergic receptors¹³. Its cardiac effects at low and high dosages include the release of endogenous

norepinephrine acting on cardiac tissues; at low dosages the activation of the D1 vascular receptors predominates with vasodilation of the renal vascular bed enhancing the glomerular filtration rate, renal blood flow and sodium excretion. This property may be useful to increase the renal blood flow in heart failure; at mild or intermediate doses the cardiac effects are related to beta₁-adrenergic receptor activation, consequent to the release of norepinephrine. At higher rates of administration, the dopamine-dependent norepinephrine release activates the alpha-adrenergic receptors with vasoconstriction.

In the management of heart failure dopamine is often administered at low dosages and is associated with dobutamine and vasodilators.

Dopexamine. This is a synthetic sympathomimetic agent similar to dopamine and has been evaluated in patients with heart failure. The cardiovascular effects can be attenuated because of a progressive cardiac norepinephrine depletion. Two studies examined the use of do-

pexamine vs placebo in a total group of 63 patients, of whom 45 had chronic heart failure characterized by hemodynamic instability (cardiac index ≤ 2.5 l/min/m², pulmonary wedge pressure ≥ 15 mmHg) and 18 had acute left ventricular failure. The latter included patients presenting with hypertrophic cardiomyopathy, valvular heart disease, angina pectoris, and inflammatory disorders. Dopexamine, administered acutely at dosages ranging between 1 to 4 $\mu\text{g/kg/min}$, improved the hemodynamic profile evaluated at 1 and 8 hours after infusion^{14,15}.

Dobutamine. Dobutamine is a direct-acting sympathomimetic agent with strong beta- and alpha-adrenergic stimulatory effects; beta₂ stimulation generally produces a mild reduction in the peripheral vascular resistance and a significant increase in cardiac output. On the basis of these findings dobutamine can be considered as an inotropic-vasodilating compound. The heart rate is generally not influenced at dosages ranging from 2 to 5 $\mu\text{g/kg/min}$ and titrated to achieve optimal hemodynamic effects. Higher doses (15 $\mu\text{g/kg/min}$) appear to be often associated with arrhythmias.

In clinical practice the most frequent modality of administration of this agent is represented by continuous infusion in hospitalized critically ill patients, often in combination with dopamine, PDE inhibitors and/or vasodilators. Most trials testing the efficacy and safety of dobutamine infusion dealt with the comparison of this agent with other drugs, rather than vs placebo and they will be considered later on. The clinical use of dobutamine also included continuous or intermittent outpatient therapy. This intermittent administration was proposed to overcome the tachyphylaxis due to beta-receptor downregulation or uncoupling that represents a significant clinical problem. The first experience of short-term dobutamine infusion was reported by Leier et al.¹⁶; these authors showed, in 25 patients with a mean follow-up of 24 weeks, the beneficial effects of dobutamine infusion (at a mean dosage ranging between 7.4 and 8.6 $\mu\text{g/kg/min}$) on the clinical parameters and exercise time. Other non-controlled clinical studies of intermittent infusion were performed using dobutamine in moderate-high dosages (6-8 $\mu\text{g/kg/min}$) and showed a clinical improvement which was however unfortunately associated with an increased mortality; Applefeld et al.⁵ reported their experience with 21 patients presenting with severe heart failure; these patients were submitted to long-term outpatient continuous infusion of dobutamine; 6 of them received a mean dosage of 7.3 $\mu\text{g/kg/min}$ continuously infused over 24-hour periods. Among the remaining patients, 4 underwent a combined treatment of dobutamine and dopamine and the remaining 11 patients received 7.1 $\mu\text{g/kg/min}$ of dobutamine 24 hours per week. Though a clinical improvement was initially recorded, 20 deaths were observed after an average follow-up of 32 weeks. Dies et al.⁴ studied, in a clinical trial vs placebo, 60 patients with a mean follow-up of 8 weeks; dobutamine was administered at a mean dosage

of 8.1 $\mu\text{g/kg/min}$ and a clinical improvement was observed in 50% of cases equally distributed among dobutamine and placebo patients; the latter showed a lower tolerance to exercise; 20 patients died during the clinical study, 15 of them were on dobutamine treatment. Miller et al.^{3,17}, in two consecutive case series including 11 and 25 patients respectively, proposed the administration of lower dosages (5 $\mu\text{g/kg/min}$) and showed that the serum levels of potassium must be accurately monitored during treatment; 7/11 patients of the first series were successfully weaned from the infusion after prolonged administration (mean follow-up 13 weeks). In the other patient group 25 patients underwent dobutamine therapy as a bridge to heart transplantation: the infusion therapy was continued for periods ranging from 1 to 44 weeks, with 6 patients dying during the observation interval. However, 6 patients went to heart transplantation without requiring hospitalization for cardiac decompensation during the period of pharmacological treatment. More recently, the randomized Italian trial DICE⁶ enrolled 38 patients with advanced heart failure to intermittent dobutamine infusion (48 to 72 hours/week at a maximum dosage of 5 $\mu\text{g/kg/min}$) or to standard medical therapy; the study showed, in the dobutamine-treated group, a significant reduction in hospital admissions and NYHA functional class, without significant differences in survival between the two groups after 6 months of follow-up.

The effects of dobutamine vs dopamine on the main parameters of sympathetic activation, in particular on heart rate variability, were analyzed after 72 hours of infusion therapy in 20 patients with NYHA class III-IV heart failure. The therapeutic efficacy of 72 hours of infusion of dobutamine was compared with that obtained by placebo in 15 patients with severe, but clinically stable, chronic heart failure secondary to idiopathic or alcoholic dilated cardiomyopathy in a trial with a longer follow-up (4 weeks) than the preceding ones¹⁸.

Overall, analyzing the results of the aforementioned clinical studies a neutral or worse effect on mortality seems to emerge in patients treated with dobutamine.

Phosphodiesterase inhibitors. PDE inhibitors show powerful inotropic and vasodilator effects and in the last years their use has rapidly increased; in fact, the extensive administration of beta-blockers in chronic heart failure may reduce the response to sympathomimetic agents in the presence of an acute deterioration; the effect of PDE inhibitors, which is independent of the availability of beta-receptors, is not impaired in case of concomitant beta-blocker therapy¹⁹.

PDE inhibitors increase the concentration of cAMP via the inhibition of the PDE III isoenzyme present in cardiac myocytes and vascular smooth muscle cells. This results in an increase of the intracellular calcium concentration with a resultant positive inotropic action and peripheral arteriolar relaxation. The peripheral vasodilator action of PDE inhibitors is generally con-

sidered to be more effective than that of dobutamine and these agents also significantly reduce the pulmonary vascular resistance.

Milrinone. This drug is characterized by a long half-life (20 to 45 min) and the therapeutic regimen generally includes a bolus of 50 µg/kg given over 10-20 min followed by a constant infusion of 0.375 to 0.75 µg/kg/min²⁰. In earlier studies milrinone showed favorable effects on survival in patients with mild-to-moderate heart failure, but not in NYHA class IV patients. A preliminary study on the beneficial effects of intermittent home administration of milrinone in end-stage heart failure has been published. The patients seemed to well tolerate the drug without deaths and with a 4-fold decrease in hospitalization, starting the infusion treatment at 3 days a week for 6 hours at a time over a 3-month period²¹. Two studies compared the acute effects of the infusion of milrinone vs dobutamine: Biddle et al.²² enrolled 79 patients who had severe chronic heart failure but who had been clinically stable for at least 2 weeks before entering the trial, while Karlsberg et al.²³ evaluated patients with heart failure secondary to a recent myocardial infarction (from 12 hours to 5 days after the infarct). A trend towards better results in milrinone-treated patients was observed.

The results of PROMISE⁸, a long-term study in which milrinone was administered orally, clearly confirmed that this class of drugs increases mortality; the trial randomly assigned 1088 patients with severe chronic heart failure (NYHA class III-IV) to double-blind treatment with 40 mg of oral milrinone or placebo; the median follow-up was 6.1 months. As compared with placebo milrinone therapy was associated with a 28% increase in mortality from all causes and with a 34% increase in cardiovascular mortality; the greater increase in mortality (53%) was observed in NYHA class IV patients. Moreover, patients treated with milrinone were more often hospitalized and presented with more serious adverse effects than placebo-treated patients.

A large randomized controlled double-blind trial, the OPTIME-CHF study⁹, on the usefulness and safety of milrinone vs placebo in patients admitted to hospital because of worsening heart failure but in whom inotropic infusion therapy was not considered mandatory, has been completed. The study enrolled 949 patients who were treated for 48-72 hours with a continuous infusion of milrinone or placebo in addition to the standard medical therapy already being used to treat the patients with chronic heart failure. The primary aim of the study was to demonstrate a decrease in hospital readmissions due to cardiovascular events in the 2 months following the acute milrinone treatment. The secondary outcome measures were to evaluate the safety of the drug, the efficacy with regard to an acute improvement in the clinical profile and symptoms of the patients and the maintenance of any benefit in the subsequent follow-up and the possibility of being able to optimize medical therapy despite the recent destabilization whilst evaluating its

effects on mortality. At 60 days after the treatment the results in terms of symptoms and quality of life were equivalent; the in-hospital mortality was 3.8% among the patients treated with milrinone and 2.3% in the control group and 10.3% and 8.9% respectively at 60 days; these data confirmed the lack of any benefit and a trend towards an increased mortality in patients treated with milrinone.

Amrinone. Amrinone has been shown to improve compromised hemodynamic states by increasing the cardiac output and increasing the peripheral perfusion, with no significant changes in heart rate or myocardial oxygen consumption; side effects with amrinone are relatively minor with intravenous infusion, but an excessive decrease in the arterial blood pressure or filling pressure may occur, requiring prompt infusion of colloids and/or vasopressors. Amrinone has been considered the drug of choice in perioperative myocardial dysfunction due to ischemia or infarction²⁴.

Three studies compared the acute effects of infusion therapy with amrinone vs dobutamine in three different situations: in patients with left ventricular failure secondary to an acute myocardial infarction (20 patients)²⁵; in elderly patients with NYHA class IV congestive heart failure (14 patients)²⁶; in patients with severe chronic heart failure due to dilated cardiomyopathy (NYHA class III-IV) refractory to treatment with diuretics and vasodilators (46 patients)²⁷. Significant differences were not found in the endpoints between the groups treated with the PDE inhibitor amrinone and dobutamine. In patients with heart failure secondary to an acute myocardial infarction, amrinone treatment may induce an aggravation of ischemia, worsening systemic arterial hypertension.

The administration of amrinone as infusion inotropic therapy is further limited by the possible occurrence of thrombocytopenia.

Enoximone. Enoximone is a PDE inhibitor ascribed to the imidazolones class; the hemodynamic and myocardial effects of enoximone have been extensively studied. A significant increase in oxygen consumption which produces marked acute hemodynamic effects was sometimes observed with enoximone. More recently three trials compared the PDE inhibitor enoximone to dobutamine in a variety of pathological conditions and with a follow-up of variable duration: Galinier et al.²⁸ enrolled 20 patients with severe chronic heart failure and analyzed the short-term effects of treatment with inotropes; Caldicott et al.²⁹ treated about 20 patients with left ventricular failure secondary to an acute myocardial infarction and followed them for 2 years; there were only slight differences in the effects of enoximone compared with dobutamine on patient outcomes. The Italian Multicenter Study on Enoximone in pre-transplant patients was designed as a double-blind randomized placebo-controlled trial; in order to evaluate the effects on survival 121 patients waiting for cardiac transplantation were

enrolled; the study was interrupted prematurely because of the higher mortality in the enoximone (12%) as compared to the placebo group (5%) (1989, unpublished data).

The overall clinical experience with conventional inotropic drugs. Between 1966 and 2000 the results of 21 trials on the safety and efficacy of infusion treatment with conventional inotropes in patients with heart failure were published. A meta-regression analysis of the trials on infusion inotropic therapy was recently reported³⁰. Overall, 632 patients with heart failure were enrolled in these studies. The inotropes used were beta-agonists (dobutamine, dopamine or dopexamine) and PDE inhibitors (amrinone, milrinone, enoximone and toborinone). Of these 21 clinical trials, 16 analyzed the acute effects of inotrope infusions, enrolling a total of 474 patients with heart failure, while the other 5 trials, involving 158 patients, were carried out to evaluate the safety and efficacy of intermittent infusion therapy with dobutamine. Eleven of the trials compared treatment with the infused inotrope against a placebo or no treatment, 9 trials compared different inotropes, and finally 5 studies evaluated the effects of intermittent dopamine infusion as compared with those of a placebo in patients with heart failure.

Overall, the results were inconclusive and the fragmented methodologically weak experiences highlight the need of large studies including short-, medium- and long-term observations. Considering all the trials reported so far on infusion inotropic therapy, including the OPTIME-CHF study, the conclusion that enhancing the heart inotropic activity through the adrenergic pathway is not the right therapeutic approach in patients with heart failure seems inescapable.

Calcium sensitizers. This class of drugs is able to increase the myocyte sensitivity to calcium, in the presence of a slight increase in the total myocardial energy demand; among these, levosimendan enhances calcium sensitivity by a direct action on troponin C and it can produce a significant vasodilation by its action on the adenosine triphosphate-dependent potassium channels.

The clinical experience carried out with levosimendan is reported in detail in other papers in this issue of the Journal.

Vasodilators

Short-term infusion of nitrates or nitroprusside may be efficaciously used in patients with severe symptoms and signs of heart failure in case of an inadequate response to oral therapy or when diuretics do not suffice for clinical improvement.

Nitroprusside. Previous studies have shown that nitroprusside can induce a significant improvement in left ventricular performance. Administered to patients with

a low cardiac output and high filling pressures, nitroprusside is able to ameliorate cardiac output with a concomitant reduction in the systemic and pulmonary resistances, in the right atrial and left ventricular filling pressures, and in mitral regurgitation.

Long-term intermittent infusion has been successfully proposed and it may be considered an effective tool in the acute unloading treatment of patients with end-stage heart failure. The administration of nitroprusside and dobutamine may be considered a useful and effective therapeutic association of intravenous vasodilators and inotropes³¹. However, the safety of long-term nitroprusside infusion is limited because of thiocyanate and cyanide accumulation.

Recently, in patients awaiting heart transplantation nitroprusside infusion has been shown to be more effective and safe than dobutamine in relieving symptoms, facilitating the management of unloading therapy and improving survival; the mean dose of nitroprusside was $0.76 \pm 0.99 \mu\text{g/kg/min}$ and the mean treatment duration of this 12-hour/day infusion was 22 ± 38 days³².

Flosequinan. Studies evaluating other vasodilators showed negative or non-convincing results: in the REFLECT trial flosequinan, which efficaciously improved the clinical and hemodynamic statuses, induced an increase in mortality^{33,34}.

Epoprostenol. The continuous infusion of epoprostenol has been tested in the large-scale FIRST trial in patients with refractory heart failure. However, the trial was interrupted prematurely because of an excess of mortality in the treated group³⁵. Exogenous prostacyclin is effective and is currently used in the treatment of primary pulmonary hypertension; epoprostenol has a marked activity on the pulmonary and systemic arterial tone, reducing pulmonary and systemic resistances. Its action on the neurohormonal pattern remains uncertain.

Nesiritide. Nesiritide is a recombinant human brain, or B-type, natriuretic peptide that is identical to the endogenous hormone produced by the ventricle in response to an increased wall stress, hypertrophy and volume overload. Nesiritide was approved by the Food and Drug Administration for infusion therapy in decompensated heart failure. This drug has venous, arterial and coronary vasodilator properties that reduce the preload and afterload and increase cardiac output without direct inotropic effects. In addition nesiritide does not show arrhythmogenic actions and increases the glomerular filtration rate and filtration fraction, suppressing the renin-angiotensin-aldosterone axis. Its effects in decompensated heart failure have been evaluated in the VMAC trial: intravenous nesiritide added to standard care in patients hospitalized with acutely decompensated chronic heart failure improves the hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin or placebo³⁶. Previously, in an

efficacy study trial patients with decompensated congestive heart failure underwent nesiritide infusion at rates of 0.015 and 0.030 $\mu\text{g/kg/min}$ with evidence of a dose-related hemodynamic effect¹². The effects of nesiritide in terms of safety and of its proarrhythmic action were compared with dobutamine in the PRECEDENT study: this trial enrolled 255 patients with acutely decompensated congestive heart failure randomized to two different dosages of nesiritide (0.015 or 0.03 $\mu\text{g/kg/min}$) or to dobutamine (≥ 5 $\mu\text{g/kg/min}$) administered for at least 24 hours; dobutamine was associated with proarrhythmic effects whereas nesiritide (mainly at the lower dosage) was related with a significantly reduced number of ventricular tachycardia episodes and couplets over 24 hours and with premature ventricular beats for 1 hour³⁷. A comparative effect with dobutamine on the short-term outcome was tested in a clinical study: in patients with acutely decompensated heart failure nesiritide required shorter infusion treatment than dobutamine with a trend towards a lower number of in-hospital readmissions after infusion treatment; even the 6-month mortality was lower in the nesiritide than in the dobutamine group³⁸. Several trials with nesiritide in heart failure patients are ongoing.

Conclusions

The treatment of decompensated heart failure represents a crucial problem in the presence of an increasing prevalence of cardiac failure; generally, treatment with intravenous diuretics and vasodilators (such as nitrates) can effectively provide a clinical improvement; nevertheless, in many cases of end-stage heart failure intravenous inotropic agents are administered. Controlled clinical trials of inotropic agents are small, insufficient and often fail to show a better outcome or a reduction in morbidity, without significant differences among beta-agonists and PDE inhibitors³⁰; with regard to the effects on the clinical outcome, sympathomimetic agents compared to placebo showed a slight increase in mortality. In conclusion, inotropic agents in patients with decompensated heart failure can effectively improve symptoms and the hemodynamic profile but they should be administered with care and only for short or intermittent treatment periods. Calcium sensitizers and nesiritide probably represent new effective drugs not acting through the adrenergic system, useful both as single or combined therapy.

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