

# Inotropic therapy is unsuccessful: wrong conceptual target or wrong therapeutic tools?

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Since a depressed contractility has long been considered the primary defect in patients with heart failure, the use of inotropic agents has been regarded as a logical approach to treat this syndrome. Despite this conceptual framework, these drugs have not yet established themselves in the treatment of chronic heart failure and their long-term use was associated with an excessive mortality while the short-term intravenous administration in critically ill patients produced only acute hemodynamic results without a stable clinical improvement. At least four mechanisms could explain this discrepancy: their arrhythmogenicity, their direct cardiotoxic effects, the downregulation of the beta-adrenoreceptors, and the energetic cost of inotropic intervention. Moreover, in many patients with ischemic cardiomyopathy the reduction in contractility could be considered as a compensatory mechanism since hibernation is able to decrease the metabolic requirements of the heart.

The contractile force of the heart can be augmented not only by an increased availability of intracellular calcium for troponin C but also by an increased sensitivity of the contractile proteins to calcium. A new class of inotropes working with this mechanism is now available and could represent a real improvement in this challenging therapeutic area.

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Since a depressed contractility has long been considered the primary defect in patients with heart failure, the use of inotropic agents has been regarded as a logical approach to treat this syndrome. However, although widely used in the inpatient setting for many years, these drugs have not yet established themselves in the treatment of chronic heart failure (CHF)<sup>1-3</sup>.

## The unfulfilled promise

Inotropic agents produce marked acute hemodynamic effects. The intravenous infusion of dobutamine and/or phosphodiesterase (PDE) inhibitors is the standard therapy for acute heart failure and for the critical decompensation of chronic failure. However, long-term therapy has failed to produce sustained clinical benefits and has been reported to actually increase mortality<sup>3</sup>. A meta-analysis of 21 randomized trials on beta-adrenergic agonists and PDE inhibitors in heart failure patients suggested that the use of these compounds was associated with an excessive mortality (PDE inhibitors: odds ratio 1.58, 95% confidence interval 1.04-2.41; beta-adrenergic agonists: odds ratio 2.07, 95%

confidence interval 1.23-3.49)<sup>4</sup>. Recently, in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, Cuffe et al.<sup>5</sup> randomly assigned 951 patients with an exacerbation of CHF and for whom inotropic therapy was “indicated but not required” to 48-hour intravenous treatment with milrinone or placebo. The primary endpoint was hospitalization for a cardiovascular cause within 60 days. Milrinone was associated with a higher rate of early treatment failure, more sustained hypotension and new atrial arrhythmias, and a non-significant higher number of deaths in hospital (3.8 vs 2.3%,  $p = 0.19$ ) and after 60 days (10.3 vs 8.9%,  $p = 0.41$ ). The authors conclude that milrinone should not be used as an adjunct to the standard treatment of patients with an exacerbation of heart failure.

## Where is the problem? Is inotropic stimulation the wrong target or is the price to be paid too high?

A reduction in contractility or “inotropic state” is generally considered as one of the most frequent and important findings in

CHF. At the cellular level, many of the components of normal cardiomyocyte functioning may become abnormal in patients with CHF, in particular the excitation-contraction coupling, the energy utilization, and the neuro-humoral responsiveness components. In patients with advanced chronic ischemic cardiomyopathies many substrates including cardiomyocyte loss, myocardial stunning and hibernation, and ventricular remodeling often coexist. The latter leads to abnormal loading conditions contributing to reduce the systolic and diastolic performance. Not only is the inotropic state worsened in CHF but a potentially utilizable contractile reserve does exist in many patients with dilated idiopathic or ischemic cardiomyopathy<sup>1,2</sup> which represents the rationale of inotropic drugs in the treatment of critically decompensated CHF. So, from a pathophysiological point of view, myocardial contractility seems to be an appropriate target and the use of inotropic agents a logical approach to treat the syndrome of CHF.

Despite this conceptual framework the chronic use of these compounds was associated with an excessive mortality while their short-term intravenous administration in critically ill patients produced only transient hemodynamic results which did not convert into a stable clinical amelioration.

Several hypotheses may be proposed to explain this discrepancy, including the arrhythmogenic effects of cyclic adenosine monophosphate (cAMP), the direct cardiotoxic effect of cAMP, the downregulation of beta-adrenoreceptors, and the desensitization of the beta-adrenergic pathway and the energetic cost of inotropic intervention.

In recent reports, the metabolic and energetic cost of inotropic stimulation of the heart has received increasing attention<sup>6-9</sup>. Hayashi et al.<sup>6</sup> studied the myocardial oxygen cost of increasing contractility with dobutamine in patients with left ventricular dysfunction after myocardial infarction. The oxygen cost of contractility was proportional to the degree of left ventricular dysfunction and was evident even at low doses of dobutamine. Their findings suggest that the alteration in mechanoenergetics in patients with severe ventricular dysfunction could result from an increased oxygen cost of excitation-contraction coupling rather than from the reduction in the efficiency of the chemomechanical energy transduction<sup>6</sup>.

At our Institution the hemodynamic and myocardial metabolic effects of enoximone in patients with CHF were studied. The intravenous infusion of the drug produced a marked improvement in hemodynamics. However, an increase in myocardial oxygen consumption > 50% was observed in 2 of 10 patients, and in addition, 2 patients converted to myocardial lactate production. In response to inodilator therapy, myocardial oxygen consumption may decrease, increase, or remain unchanged, probably depending on the degree of the energetic cost of the inotropic effect<sup>8</sup>.

Although dobutamine and enoximone efficaciously increase myocardial contractility, they also increase myocardial oxygen demand. Indeed, the energetic cost might offset the improvement in myocardial contractil-

ity and limit the clinical benefits of long-term intermittent inotropic support by prematurely exhausting the bioenergetic reserve. Furthermore, the failing heart is likely to already be in an energy-depleted state as highlighted by a disproportionate increase in the fraction of the cell volume occupied by the energy-consuming myofibrils relative to that occupied by the energy-regenerating mitochondria<sup>10</sup>. Rather than as a defect, the reduction in contractility can be considered as being compensatory, in that it facilitates the survival of the remaining myocardium by attenuating the intrinsic energy demands. Therefore, the administration of an inotropic agent to an energy-starved heart could produce a temporary improvement in contractility at the expense of an increased myocardial energy consumption and hence finally accelerate myocardial cell death. cAMP, whether generated by an increased rate of synthesis or by a decreased rate of degradation, may be toxic to myocardial cells and exacerbates ventricular tachyarrhythmias. The appearance of delayed afterdepolarizations is related to the increased release of calcium from the intracellular stores. An increased intracellular cAMP might also enhance automaticity and triggered responses<sup>10</sup>.

The disadvantages of long-term inotropic therapy, continuous or intermittent, are probably greatest in patients whose heart failure is consequent to an ischemic cardiomyopathy and who may have significant proportions of hibernating myocardium. In this clinical model of heart failure, hibernation may be viewed as a compensatory mechanism which decreases the metabolic requirements of the myocardium and reorients the metabolism of the cell away from contractile activities, thus maintaining the membrane integrity and cell survival<sup>11</sup>. Many recent studies have shown that low-dose dobutamine can elicit the contractile reserve of the hibernating myocardium and that this response can accurately predict the post-revascularization recovery of the myocardial function. The long-term consequences of intermittent inotropic stimulation of the hibernating myocardium have not been specifically evaluated, but it has been reported that the presence of a chronically ischemic but viable myocardium, if left untreated, is associated with an increased mortality in patients with heart failure<sup>12</sup>. Inotropic therapy, by increasing myocardial energy demand, would likely exacerbate this underlying chronic ischemia. Conversely, we cannot ignore the observations that the precisely opposite strategy of decreasing sympathetic activation with beta-adrenergic antagonists resulted in improvements in symptoms and survival as well as in the mechanical and biologic properties of the chronically failing heart<sup>1</sup>.

### **Can we optimize the risk/benefit ratio of inotropic therapy in clinical practice?**

**Choosing the right dose.** It has been suggested that the dose of inotropic drugs is a key factor in establishing the risk/benefit ratio for these agents, with low doses being

generally safer than high doses. In many cases the toxic/therapeutic ratio of inotropic agents is narrow. Alternatively, in instances where the toxic/therapeutic ratio may be relatively wide, doses at the high end of the standard range may result in untoward effects. This may occur because of a tendency to select, for long-term trials, the dose of drug that causes maximally tolerated hemodynamic effects in patients who are at rest in short-term studies. This is in keeping with the "maximal hemodynamic" paradigm that governed the management of heart failure for many years. Though somewhat counterintuitive in this regard, low doses of pimobendan and flosequinan appear to be more effective than high doses. High doses of flosequinan (150 mg/day) were hemodynamically more effective than 75 to 100 mg/day but were less effective in improving exercise tolerance<sup>13</sup>. Furthermore, in a recently completed survival study (PROFILE), 100 mg/day of flosequinan increased the mortality rate, whereas lower doses (75 mg) did not increase the risk of death when compared with placebo in patients with CHF<sup>14</sup>. Data from the Pimobendan Multicenter Research Group demonstrate that 5 mg/day of pimobendan significantly increase exercise duration, peak oxygen consumption, and quality of life of patients with CHF; higher doses (10 mg/day) produce only an increase of borderline significance<sup>15</sup>.

The experience with vesnarinone, a PDE inhibitor with additional interesting properties, is a typical example of the expectations and disappointments generated by the concept of the optimal dosing of an inotropic drug. Vesnarinone exerts positive inotropic effects by inhibiting PDE and increasing the intracellular levels of sodium, possibly by an agonist action on the sodium channel. The relative importance of these two pharmacological actions may depend on the administered dose of the drug. In a recently published prospective randomized trial, 6 months of therapy with 60 mg/day of vesnarinone resulted in lower morbidity and mortality rates and improved the quality of life of patients with CHF<sup>16</sup>. However, a higher dose (120 mg/day) increased the mortality rate suggesting that this drug had an extremely narrow therapeutic range. This observation led the United States Food and Drug Administration to recommend a larger, longer trial, the Vesnarinone Evaluation of Survival Trial (VEST). The trial enrolled approximately 3800 heart failure patients in nearly 200 centers throughout the United States. Unfortunately, preliminary analysis of the study results by the Data Safety and Monitoring Committee demonstrated that even "low-dose" vesnarinone (60 mg/day) increased the mortality rate by 26% compared with placebo<sup>17</sup>. However, analysis of the extensive database of the VEST trial has only begun, and it will be important to ascertain whether improvement occurred in any patient subset.

**Choosing the right way of administration.** To overcome the negative effects of prolonged, continuous administration of inotropic drugs, some investigators have advocated the intermittent administration of dobu-

tamine or PDE inhibitors. The results are in no way conclusive, and the topic remains a field of active research. In 1980, Unverferth et al.<sup>18</sup> first demonstrated that the beneficial effects of a 72-hour infusion of dobutamine in patients with heart failure persisted for up to 4 weeks after the discontinuation of therapy in a substantial number of patients. This prolonged benefit was associated with an amelioration of the ultrastructure of the myocardium. Applefeld et al.<sup>19</sup> were among the first to examine the clinical effects of intermittent outpatient dobutamine therapy in a small group of patients with chronic refractory heart failure. They found that inotropic therapy improved both the quality of life and hemodynamic status. Subsequent studies seemed to confirm these first results<sup>20-23</sup>. Unfortunately, the enthusiasm for intermittent inotropic therapy diminished when the first clinical trial randomizing patients to either intermittent dobutamine infusion or traditional therapy was discontinued prematurely because of the increased mortality among the dobutamine-treated patients<sup>24</sup>.

Enthusiasm for intermittent inotropic support has been rekindled by two subsequent studies<sup>25,26</sup>. Adamopoulos et al.<sup>25</sup> demonstrated that short bursts of dobutamine (5 to 15 mg/kg/min for 30 min) 4 days/week for 3 weeks resulted in pharmacological conditioning with improved symptoms, autonomic function and exercise tolerance, with beta-receptor upregulation and with an enhanced chronotropic responsiveness in CHF. These results differ from those of prior reports of continuous long-term or of traditional intermittent dobutamine administration, raising questions on whether the type of intermittence can influence the clinical effects of the inotropic support.

More recently, the Dobutamine Infusion in Severe Heart Failure (DICE) trial randomized 38 patients with advanced CHF to intermittent dobutamine infusion (48 to 72 hours/week, maximum dose 5 mg/kg/min) or to traditional therapy. A totally implantable infusion system was used<sup>26</sup>. During 6 months of follow-up, the number of hospital admissions and the NYHA functional class were significantly reduced in both groups, but the effect was more evident among the dobutamine-treated patients. Survival did not differ between groups.

We can draw some general considerations from the published experience with outpatient inotropic support in heart failure patients. Dobutamine appears to be the most frequently used drug. Intermittent infusion of low-dose dobutamine in an outpatient setting can be effective in selected patients with advanced heart failure. This strategy can ameliorate symptoms and reduce the number of hospital admissions and the length of stay without necessarily incurring in an increase in mortality. Patients with a propensity for sustained ventricular tachycardia or sudden death probably were excluded from this form of therapy. Careful selection of patients is critical and scrupulous surveillance for arrhythmias and electrolyte abnormalities must be assured throughout the treatment period. Intermittent inotropic therapy in an outpatient setting requires extensive technical

support (totally implantable infusion pumps, tunneled subcutaneous catheters, etc.) and a high level of patient compliance; this further reduces the number of subjects amenable to treatment.

**Choosing the right drug for the right patient.** Part of the debate and of the confusion regarding the use of inotropic agents in managing heart failure derives from the fact that they are generally viewed as a single class in which all the drugs produce the same physiologic outcome and clinical effects. Indeed the term “inotropes” encompasses a wide range of different short- and long-term clinical actions. Feldman<sup>27</sup> has proposed a classification system that categorizes inotropic agents according to their mechanism of action. This system provides a framework for a better understanding of the potential benefits and limitations of the traditional inotropic agents as well as of the increasing number of new experimental drugs:

- class I: agents that increase the intracellular levels of cAMP, e.g., beta-adrenergic agonists and PDE inhibitors;
- class II: agents that interact with the sarcolemmal ion pumps and channels, e.g., digoxin, the prototype for this group, which inhibits sarcolemmal Na-K adenosine triphosphatase;
- class III: agents that modulate the intracellular calcium handling mechanisms. The contractile force of the heart can be augmented not only by the increased availability of intracellular calcium for troponin C but also by the increased sensitivity of the contractile proteins to calcium. So these agents may enhance the cardiac performance without concomitantly increasing myocardial oxygen consumption and arrhythmic risk. Levosimendan, the most potent calcium sensitizer, is now commercially available and could represent a real improvement in this challenging therapeutic area<sup>28-30</sup>;
- class IV: agents that have multiple mechanisms of action, e.g., pimobendan and vesnarinone. Pimobendan increases the affinity of the regulatory site on troponin C for calcium and also has a modest inhibitory effect on PDE III. Vesnarinone decreases the outward and inward rectifying potassium current. The drug also increases the intracellular sodium levels as a result of a modest inhibition of PDE. An anticytokine activity of vesnarinone has also been documented<sup>16,27</sup>.

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