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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(A)Ital Heart J 2003; 4 (Suppl 2): 22S-26S)

Key words: Congestive heart failure; Inotropic agents; Therapy.

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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 abnor-
mal in patients with CHF, in particular the excitation-con-
traction coupling, the energy utilization, and the neuro-
humoral responsiveness components. In patients with
advanced chronic ischemic cardiomyopathies many sub-
stances including cardiomyocyte loss, myocardial stum-
ning and hibernation, and ventricular remodeling often
coexist. The latter leads to abnormal loading conditions
contributing to reduce the systolic and diastolic perfor-
ance. 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, which represents the rationale of
inotropic drugs in the treatment of critically decompens-
ated CHF. So, from a pathophysiological point of view,
myocardial contractility seems to be an appropriate tar-
get 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 mor-
tality while their short-term intravenous administration
in critically ill patients produced only transient hemo-
dynamic results which did not convert into a stable clin-
ical amelioration.

Several hypotheses may be proposed to explain this dis-
crepancy, including the arrhythmogenic effects of cyclic
adenosine monophosphate (cAMP), the direct cardiotoxic
effect of cAMP, the downregulation of beta-adrenergic
receptors, 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. Hayashi et al. studied the myocardial oxy-
gen cost of increasing contractility with dobutamine in
patients with left ventricular dysfunction after myocar-
dial infarction. The oxygen cost of contractility was pro-
portional to the degree of left ventricular dysfunction
and was evident even at low doses of dobutamine. Their
findings suggest that the alteration in mechanoenerget-
cics in patients with severe ventricular dysfunction could
result from an increased oxygen cost of excitation-con-
traction coupling rather than from the reduction in the effi-
ciency of the chemomechanical energy transduction.

At our Institution the hemodynamic and myocardial
metabolic effects of enoximone in patients with CHF
were studied. The intravenous infusion of the drug pro-
duced 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 inotrope therapy, myocardial oxygen consumption
may decrease, increase, or remain unchanged, probably
depending on the degree of the energetic cost of the
inotropic effect.

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 intermit-
tent inotropic support by prematurely exhausting the
bioenergetic reserve. Furthermore, the failing heart is
likely to already be in an energy-depleted state as high-
lighted by a disproportionate increase in the fraction of
the cell volume occupied by the energy-consuming
myofibrils relative to that occupied by the energy-regen-
erating mitochondria. Rather than as a defect, the
reduction in contractility can be considered as being comp-
ensatory, in that it facilitates the survival of the remain-
ing myocardium by attenuating the intrinsic energy
demands. Therefore, the administration of an inotropic
agent to an energy-starved heart could produce a tem-
porary 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 myocard-
dial cells and exacerbates ventricular tachyarrhythmias.
The appearance of delayed afterdepolarizations is relat-
ed to the increased release of calcium from the intra-
cellular stores. An increased intracellular cAMP might
also enhance automaticity and triggered responses.

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 propor-
tions of hibernating myocardium. In this clinical model
of heart failure, hibernation may be viewed as a com-
ensatory mechanism which decreases the metabolic
requirements of the myocardium and reorients the
metabolism of the cell away from contractile activi-
ties, thus maintaining the membrane integrity and cell
survival. 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 asso-
ciated with an increased mortality in patients with heart
failure. Inotropic therapy, by increasing myocardial
energy demand, would likely exacerbate this underly-
ing chronic ischemia. Conversely, we cannot ignore
the observations that the precisely opposite strategy of
decreasing sympathetic activation with beta-adrener-
gic antagonists resulted in improvements in symptoms
and survival as well as in the mechanical and biologic
properties of the chronically failing heart.

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 tolerance13. 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 CHF14. 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 significance15.

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 CHF16. 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 placebo17. 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 dobutamine or PDE inhibitors. The results are in no way conclusive, and the topic remains a field of active research. In 1980, Unverferth et al.18 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.19 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 results20-23. 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 patients24.

Enthusiasm for intermittent inotropic support has been rekindled by two subsequent studies25,26. Adamopoulos et al.22 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 used26. 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. Feldman27 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 sarcoplasmic ion pumps and channels, e.g., digoxin, the prototype for this group, which inhibits sarcoplasmal 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 area28-30;
- class IV: agents that have multiple mechanisms of action, e.g., pimobendan and vesiarnine. Pimobendan increases the affinity of the regulatory site on troponin C for calcium and also has a modest inhibitory effect on PDE III. Vesnarnine 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 vesnarnine has also been documented16,27.

References