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

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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 neurohumoral 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 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-adrenoceptors, 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 oxygen cost of increasing contractility with dobutamine in many patients with dilated idiopathic or ischemic cardiomyopathy which demonstrates 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 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.

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 more effective and safer.
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 inotropes 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 et al. have 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 reticulum and/or the contractile elements, 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 area28-30;
- 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 documented16,27.

References