Positive Inotropic Agent


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4. Positive Inotropic Agents: A Double-Edged Sword for Chronic Heart Failure

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Introduction

Katz (1) previously raised the “milk-wagon” analogy, demonstrating effects of positive inotropic agents on the energy-starved failing heart. While the milkman would whip the horse, which might get the wagon up the hill, the effort could hasten the horse’s demise. These concerns have in part been confirmed by reports from the long-term trials with milrinone (2), raising doubts about the safety and the efficacy of long-term positive inotropic therapy. In many cases, adverse effects of inotropic agents have a common subcellular pathway with the positive inotropic effects per se. Therefore, some believe that inotropic stimulation is inherently all deleterious for the failing heart (3). Recently, promising results were introduced with digitalis glycoside and new agents with mixed mechanisms of inotropic actions (4–7), demonstrating a growing body of evidence of long-term usefulness of inotropic agents.

Pathophysiological consideration

Heart failure could be regarded as a cardiomyopathy of overload, a condition which leads to energy starvation and progressive deterioration of cardiac function (1). In this regard, the effectiveness to transfer the mechanical energy of ventricular contraction would critically affect the long-term prognosis in chronic heart failure. Most of the known positive inotropic agents increase energy expenditure at the cellular level in order to increase myocardial contractility. However, some clinical data suggest that energy expenditure remains unchanged at the organ level, i.e. myocardial oxygen consumption, by administration of a positive inotropic agent, as the metabolic cost of increasing contractility is offset by a concomitant fall in left ventricular wall tension (8). We have examined the relation of baseline inotropic conditions and energy-transfer efficiency of the failing heart (9–11). In patients with less compromised ventricular function, the operating end-systolic pressure was close to the energetically optimal pressure, achieving nearly maximal mechanical efficiency (82% of maximal). As the heart deteriorated, however, the optimal end-systolic pressure became significantly lower than the actual pressure which was maintained within normal range by pressure-raising mechanisms such as sympathetic and renin-angiotensin system. This discrepancy between these two pressures resulted in a fall in actual mechanical efficiency from the theoretical maximum (68% of maximal). Under the circumstances, a reduction in operating pressure with angiotensin-converting enzyme inhibitors or β-blockers, seems to be reasonable to maximize mechanical efficiency. Another strategy to optimize mechanical efficiency of the failing heart is to increase the optimal arterial pressure toward normal range. This corresponds to the use of inotropic agents. Augmentation of contractility could maximize mechanical efficiency of the failing heart, maintain normal arterial pressure, and potentially attenuate endogenous neurohumoral activity (12). Among the drugs currently avail-

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able for the treatment of heart failure, digitalis has ideal properties in terms of optimizing the mechanical efficiency of the failing heart because this agent attenuates pressure-raising mechanisms by restoring the sympathetic-parasympathetic autonomic balance and reducing renin secretion and increases the optimal end-systolic pressure toward normal by enhancing left ventricular contractility.

**Dosage of positive inotropic agents for long-term usefulness**

In many cases, doses for chronic administration have been chosen on the basis of the dose that exerts maximally-tolerated hemodynamic effects at rest. However, the introduction of this hemodynamic concept into chronic heart failure has revealed that this concept is not sufficient for long-term treatment in the majority of patients. Recent clinical trials on positive inotropic therapy demonstrated that selection of the proper dose is critical for long-term outcome. The results of vesnarinone and pimobendan provided an important clinical implication on the risk and benefit of inotropic agent for long-term use (5–7). These two drugs exert different mechanisms of inotropic actions but showed a quite similar clinical outcome in terms of dose-related effects. In the vesnarinone trial (5), vesnarinone at a dose of 60 mg/day caused a 50% reduction in combined endpoints of worsening heart failure and death and a 62% reduction in death. In striking contrast, the high dose of vesnarinone (120 mg/day) caused a more than 2-fold increase in death. Dose-related effects of pimobendan are summarized in Fig. 1, according to the data from a 3-month multicenter trial in USA (6), a 2-month multicenter trial in Japan (7), and a 6-month trial in Toyama, Japan (7). The greatest improvement of quality of life was found for the medium dose, but to a lesser extent, for the high dose. The beneficial effects of the low dose appeared later than those of the medium dose. These studies suggest that the narrow toxic/therapeutic ratio of the dose-relationships for clinical effects exhibits a J-shaped curve with decreasing prognostic benefit at higher doses of inotropic agents.

**Conclusions**

These findings have led to the concept that, in order to be clinically beneficial and well-tolerated, positive inotropic agents should only enhance myocardial contractility to a very modest degree. When a milk wagon is being pulled up a steep hill, whipping the horse gently would make the trip longer but safer. A modest increase in pumping ability with a positive inotropic agent could result in a secondary withdrawal of sympathetic nervous activity and thereby reduce loading conditions. Large clinical trials on the long-term efficacy and safety of positive inotropic agents are warranted to confirm this concept.

![Figure 1. Dose-related effects of pimobendan are summarized according to the data from three clinical trials. The greatest improvement in quality of life was achieved by the medium dose. The beneficial effects of the low dose of this agent appear later than those of the medium dose. These dose-related effects exhibit a J-shaped curve with a decreasing benefit at higher doses.](image-url)