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SPECIAL ARTICLE

Classification of Positive Inotropic Agents

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Although there is increasing recognition that all inotropic agents are not alike, they continue to be viewed in the generic sense because of the lack of a classification system. Analogous to the classification system proposed for the antiarrhythmic agents over 20 years ago, a classification system is proposed that categorizes inotropic agents according to their mechanisms of action. Agents are classified as those that augment contractility by increasing intracellular levels of cyclic adenosine monophosphate (class I); affect ion channels or pumps (class II); modulate intracellular calcium regulation (class III), and augment contractility through multiple pathways (class IV). This classification system does not suggest that some classes of inotropic agents might be more effective than others nor does it imply that potential beneficial effects are shared by all members of each class of drugs. However, it provides a framework for better understanding of the potential benefits and limitations of the traditional inotropic agents as well as the increasing number of new investigational drugs.

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The initiating event in the development of clinical congestive heart failure is myocardial injury with a resulting decrease in cardiac output and an increase in left ventricular filling pressures. However, the role of positive inotropic agents or drugs that enhance pump function in the management of patients with congestive heart failure has been controversial (1–3). Theoretic arguments have been raised that both support and reject the use of inotropic agents in patients with heart failure. Intuitively, it appears that inotropic agents could be beneficial by supporting pump function and in so doing decreasing both adrenergic drive (4) as well as renin-angiotensin activation (5). In contrast, investigators have suggested that in patients with heart failure, inotropic agents may be deleterious because they can be arrhythmogenic, can have adverse effects on myocardial energetics, can potentially impair cardiac relaxation and may accelerate the progression of disease (6–8). However, one factor that has contributed to the confusion regarding the role of therapy with inotropic agents in the management of patients with congestive failure is that these agents have been considered in the generic sense. It has become increasingly clear that all inotropic agents are not alike; therefore, the purpose of this review is to propose a classification of inotropic agents based on their mechanisms of action (Table 1).

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Class I: Inotropic Agents That Increase Intracellular Cyclic Adenosine Monophosphate

Both the beta-adrenergic receptor agonists and the phosphodiesterase inhibitors increase cardiac contractility by increasing intracellular levels of the second messenger cyclic adenosine monophosphate (AMP) (9,10). Stimulation of the beta-adrenergic receptor results in activation of the stimulatory guanine nucleotide-binding regulatory protein (αG_s) and stimulation of the effector enzyme adenylyl cyclase resulting in enhanced production of cyclic AMP (Fig. 1). Once synthesized, cyclic AMP activates a cyclic AMP–dependent protein kinase with subsequent phosphorylation of a group of myocardial proteins leading to both improved contraction and relaxation. Cyclic AMP is metabolized to an inactive by-product by the enzyme phosphodiesterase. In the presence of adequate quantities of intracellular cyclic AMP, inhibition of phosphodiesterase can also result in increased intracellular cyclic AMP levels and enhanced contractility and relaxation.

Intuitively, one would suspect that activation of the adrenergic pathway would provide inotropic support. Although a substantial number of oral adrenergic agonists have been evaluated in the management of congestive heart failure, none have proved consistently efficacious with long-term use (11,12). Indeed, a multicenter trial assessing the efficacy of the long-term administration of the partial beta-adrenergic agonist xamoterol demonstrated a substantial increase in mortality in the xamoterol-treated patients (13). It is unclear why the oral beta-adrenergic agonists fail to benefit patients with congestive failure; however, several hypotheses have been proposed: 1) desensitization of the beta-adrenergic pathway, 2) arrhythmogenic effects of cyclic AMP, and 3) direct cardiotoxic effects of cyclic AMP (14).

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Table 1. Classes of Inotropic Agents by Mechanism of Action

Class	Definition
I	Agents that increase intracellular cyclic adenosine monophosphate
	Beta-adrenergic agonists
	Phosphodiesterase inhibitors
II	Agents that affect sarcolemmal ions pumps/channels
	Digoxin
III	Agents that modulate intracellular calcium mechanisms by either:
	A) Release of sarcoplasmic reticulum calcium (IP_3) or
	B) Increased sensitization of the contractile proteins to calcium
IV	Drugs having multiple mechanisms of action
	Pimobendan
	Vesnarinone

IP_3 = inositol triphosphate.

A group of oral phosphodiesterase inhibitors have also undergone clinical investigation in the United States during the past decade. These have included milrinone, enoximone and imazodan. The long-term use of these phosphodiesterase inhibitors was not associated with improved exercise performance (15–17). Of greater concern was the finding of a trend toward increased mortality in those patients receiving phosphodiesterase inhibitors (15,16). Indeed, those patients receiving milrinone in the large PROMISE trial (18) had a 28% increased mortality over that of patients receiving placebo. Therefore, enthusiasm for oral agents that augment contractility predominantly by increasing intracellular levels of cyclic AMP has diminished.

Although oral inotropic agents that increase intracellular cyclic AMP have not proved beneficial, intravenous adrenergic agonists have become a standard of therapy in the short-term management of patients with congestive heart failure. First introduced in 1975, dobutamine is a beta-adrenergic agonist that provides sustained inotropic support in patients with severe congestive failure (19). Several studies (20,21) suggested potential benefits of intermittent outpatient therapy with dobutamine; however, enthusiasm for this form of therapy was diminished by a report (22) suggesting increased mortality in patients receiving such therapy at high doses. In contrast, a relatively small study (23) has demonstrated beneficial effects of long-term continuous outpatient therapy in patients with end-stage disease. The phosphodiesterase inhibitor amrinone can also provide hemodynamic improvements in patients with acute heart failure (24); however, its cardiotonic effects might be limited by diminished levels of cyclic AMP in the failing myocardium (25). Because the adrenergic agonists enhance intracellular levels of cyclic AMP and phosphodiesterase inhibitors inhibit degradation of the second messenger, the use of an adrenergic agonist and a phosphodiesterase inhibitor could theoretically be additive (26). In fact, several studies have shown the benefits of combined therapy especially as transition therapy in awaiting heart transplantation (27,28).

Class II: Inotropic Agents Affecting Sarcolemmal Ion Pumps and Channels

A second group of inotropic agents are those that augment cardiac contractility by affecting the activity of selective ion pumps and channels within the sarcolemma and in so doing altering intracellular calcium homeostasis. The prototype of this group of agents is digoxin. It is now well

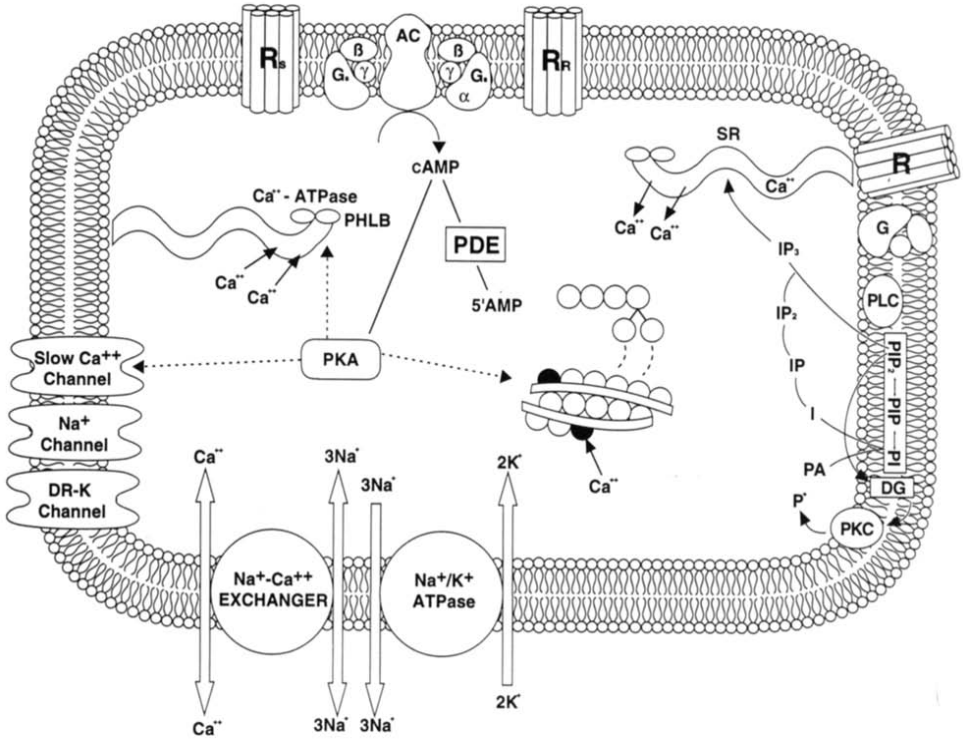

Figure 1. Biochemical pathways important in regulation of cardiac contractility. AC = adenylyl cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; DG = diacylglycerol; DR = delayed rectifier; G = guanine nucleotide–binding regulatory proteins that may stimulate (αG_s) or inhibit (αG_i) adenylyl cyclase; I = inositol; IP = inositol phosphate; IP_2 = inositol diphosphate; IP_3 = inositol triphosphate; PDE = phosphodiesterase; PHLB = phospholamban; PI = phosphotidylinositol; PIP = phosphotidylinositol 4 phosphate; PIP_2 = phosphotidylinositol 4.5-biphosphate; PKA = protein kinase A; PKC = protein kinase C; PLC = phospholipase C; R = sarcolemmal receptor; R_i = inhibitory receptor; R_s = stimulatory receptor; SR = sarcoplasmic reticulum; Tn = troponin.

recognized that digoxin inhibits the sarcolemmal sodium-potassium adenosine triphosphatase resulting in increased levels of intracellular sodium (29) (Fig. 1). This sodium is then exchanged for calcium by the sodium-calcium exchanger resulting in enhanced intracellular calcium levels, enhanced release of calcium from intracellular stores and increased cardiac contractility.

Although digoxin has been administered to patients with congestive heart failure for more than 200 years, its use has remained controversial (30,31). However, several recent multicenter clinical trials (15,32) demonstrate that digoxin improves the ejection fraction, decreases the incidence of worsening heart failure and improves exercise tolerance (15) in patients with chronic congestive heart failure receiving concomitant therapy with a diuretic agent. The recent RADIANCE trial (33) provided even more compelling evidence of the beneficial effects of digoxin. When digoxin was withdrawn from patients who were already receiving an angiotensin-converting enzyme inhibitor, there was a much greater need for cointervention in those patients not receiving digoxin. However, the clinical use of digoxin is limited by a narrow therapeutic index (34) and the long-term effects of digoxin on survival remain undefined.

Class III: Agents That Modulate Intracellular Calcium Mechanisms

A third group of inotropic agents augment cardiac contractility by affecting intracellular calcium homeostasis through increased release of calcium from the intracellular stores in the sarcoplasmic reticulum (35) or by activation of the phosphoinositide cascade (36,37) (Fig. 1). Alternatively, this group of agents can increase the sensitivity of the contractile proteins to calcium particularly at the site of troponin C and in so doing increase the contractile response to any given level of intracellular calcium (38). No agents are currently under clinical investigation that act solely by one of these two pathways. However, it is likely that new investigational agents will be developed that utilize these pathways.

Class IV: Inotropic Agents Having Multiple Mechanisms of Action

A fourth group of inotropic agents are those drugs that augment cardiac contractility by utilizing two or more biochemical pathways. Two prototypes of this group are currently undergoing clinical investigation: pimobendan and vesnarinone. Pimobendan is a benzimidazole-pyridazinone derivative that is thought to augment cardiac contractility by 1) increasing the affinity of the regulatory site on troponin C for calcium (39), and 2) having a modest inhibitory effect on phosphodiesterase III (40). However, in contrast to traditional phosphodiesterase inhibitors, pimobendan prolongs the action potential (41), suggesting the presence of other ancillary effects. Results from recent clinical trials (42) suggest that pimobendan can increase exercise duration, peak oxygen uptake and quality of life in patients with chronic congestive heart failure already receiving standard therapy including a vasodilator. Interestingly, these beneficial effects were noted in patients receiving 5 mg/day but not 10 mg/day.

OPC-8212 or vesnarinone is a quinolinone derivative that has unique mechanisms of action. In model systems, vesnarinone decreased the outward and inward rectifying potassium current (43); in fact, electrophysiologically it closely resembled a class III antiarrhythmic agent (44). Vesnarinone also increased intracellular sodium as a result of prolonged opening of sodium channels (45). And, vesnarinone increased the inward calcium current largely as a result of modest inhibition of phosphodiesterase (46,47). In marked contrast to agents that increase intracellular cyclic AMP, vesnarinone slows heart rate, prolongs the action potential and suppresses the delayed outward potassium current (43). In a randomized placebo-controlled trial (48), vesnarinone improved both quality of life and the combined end point of mortality and major cardiovascular morbidity in patients with symptomatic congestive heart failure. In addition, a recent multicenter randomized placebo-controlled clinical trial (49) demonstrated a substantial decrease in the risk of worsening heart failure or death as well as a decrease in the risk of all-cause mortality alone in patients receiving vesnarinone when compared with those receiving placebo. These beneficial effects were associated with a significant improvement in quality of life; the major risk associated with the use of vesnarinone was reversible neutropenia, which occurred in 2.5% of patients.

Benefits of a Classification System

Classification of the inotropic agents can provide intuitive understanding of the potential benefits and limitations of these agents. For example, inotropic agents that increase intracellular cyclic AMP may improve hemodynamics through ancillary vasodilator effects yet have the disadvantage that they may increase heart rate and have the potential to be either arrhythmogenic or cardiotoxic. In contrast, agents that affect ion channels may slow heart rate and therefore be cardioprotective. However, these agents may also have vasodilator properties (11). Finally, inotropic agents with multiple mechanisms of action may combine vasodilator, negative chronotropic and antiarrhythmic properties. Furthermore, it will be important to identify the effects of these agents on both coronary hemodynamics and myocardial energetics.

Although a classification system can help in understanding the usefulness of inotropic agents, factors outside the classification system may also play a role in determining the efficacy and use of any given agent. Recent evidence suggests that the beneficial effects of many inotropic agents are predicated on the dose of the drug. In studies using low

doses of the phosphodiesterase inhibitor enoximone, there were trends toward increased exercise duration and decreased mortality when results were compared with those achieved with placebo (50). In contrast, higher doses were not associated with improvements in exercise tolerance and there was a significant trend toward increased mortality. Similar dose-related effects have been seen in studies using other investigational inotropic agents (17,49). However, it is also possible that the beneficial effects of some inotropic agents are the result of ancillary properties, including antiarrhythmic or anticytokine activity, that are not associated with their augmentation of cardiac contractility. Recent studies (51) suggest that the vasodilator flosequinan also has inotropic properties; however, the mechanisms responsible for these inotropic properties have not yet been defined. Therefore, it will be important to include in a classification system pharmacologic agents with ancillary positive inotropic effects.

Conclusions

Recent investigations suggest that some inotropic agents may be beneficial in the short-term management of patients with congestive failure as well as in the long-term therapy of patients with chronic myocardial disease. Because many of the new investigational inotropic agents differ in their mechanisms of action from the more traditional adrenergic agonists and phosphodiesterase inhibitors, it has become increasingly important to classify these agents according to their mechanisms of action rather than to view them in the generic sense. This attempt to classify the inotropic agents according to their mechanisms of action is analogous to the classification of antiarrhythmic agents first proposed by Vaughan Williams >20 years ago (52). As with the antiarrhythmic agents, the classification system must remain flexible and not rigid. Furthermore, such a classification does not suggest that some groups of inotropic agents are necessarily more effective than others, but it provides a framework for better understanding of the increasing number of new inotropic agents. The potential benefits of each individual agent within the four groups of inotropic drugs must be thoroughly assessed by scientific analysis as well as by the individual practitioner.

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