PHOSPHODIESTERASE INHIBITORS. IT ROLE IN HEART FAILURE THERAPY

IRA J. KOHN, LAIR G. T. RIBEIRO
Philadelphia, USA

Chronic congestive heart failure (CHF) presently carries a grave prognosis with 6 month mortality rates from time of initial diagnosis being as high as 50% by some estimates. The two major causes of CHF in the United States are currently myocardial infarction secondary to coronary artery disease and long-standing hypertension. Decreased ventricular function and abnormalities of the circulation to both the periphery and organs are pathophysiologically responsible for the progressively debilitating syndrome of CHF, which initially presents with symptoms during exercise and latent rest. Strategies for treating CHF include improving myocardial contractility, reducing ventricular preload and afterload, and reversing counterproductive physiologic compensatory responses such as increased sympathetic activity or fluid retention. Treatment of CHF with conventional inotropic drugs, such as cardiac glycosides and dopamine, have many undesirable effects, including narrow therapeutic index, lack of oral activity and induction of arrhythmias[1].

Myocardial contractility is due to the interaction of the contractile proteins, actin and myosin. The cycle of cross bridge formation between actin and myosin responsible for development of force in the myocardium requires adenosine triphosphate (ATP) and is regulated by a group of proteins collectively known as the troponin-tropomyosin complex. At rest, tropomyosin blocks the interaction of actin and myosin. Prior to muscular contraction, calcium binding to troponin serves as a signal for tropomyosin to change its physical conformation allowing actin and myosin to interact. An increase in the concentration of intracellular free cytoplasmic calcium ([Ca^{2+}]) is directly proportional to increased contractility. [Ca^{2+}] is regulated by the net dynamic interplay between Ca^{2+} influx, efflux and the sequestration and release of Ca^{2+} from intracellular storage sites.

Depolarization of cardiac myocytes leads to increased Ca^{2+} influx via the voltage-dependent slow Ca^{2+} channels. The amount of Ca^{2+} entering through these slow voltage channels triggers the release of a substantially larger pool of Ca^{2+} from intracellular stores to raise $[Ca^{2+}]_2$ thus increasing contractility. Phosphorylation of channel associated proteins increases the functional size of these slow Ca^{2+} channels whe reas dephosphorylation limits Ca^{2+} influx. During times of stress, the sympathetic nervous system enhances cardiac performance by promoting slow Ca^{2+} channel phosphorylation via the following mechanism. When sympathetic nerves to the heart are stimulated, norepinephrine is released from nerve endings and binds b_1-adrenergic receptors on the sarcolema, leading to activation of receptor associated adenyl cyclase, which, in turn converts ATP to the regulatory nu cleotide 3' 5' cyclic adenosine monophosphate (cAMP). Several cytoplasmic protein kinases are activated by cAMP, that in turn phosphorylate the following proteins: l) slow Ca^{2+} channel regulatory proteins that enhance Ca^{2+} influx; 2) phospholamban, a protein within the sarcoplasmic reticulum that increases $Ca^{2.+}$ sequestration following myofilament relaxation thereby accelerating crossbridge recycling, and 3) troponin I, a protein that decreases the sensitivity of the troponin-tropomyosin complex for Ca^{2+} thereby facilitating relaxation (i.e. lusitropic effect)2. Stimulation of the heart via these b_1-adrenergic receptors results in a positive inotropic, positive chronotropic and positive lusitropic effect, while concomitantly increasing atrioventricular conduction. The level of cardiac stimulation produced by variations in sympathetic tone is balanced by enzymatic inactivation of cAMP by cytosolic phosphodiesterase and dephosphorylation of proteins via phosphatase mediated reactions.

By an unknown mechanism, increasing intracellular levels of cAMP in smooth muscle results in vasodilation. This vasodilatory effect of cAMP is postulated to occur via activation of protein kinases, by cAMP that phosphorylate vascular smooth muscle regulatory proteins resulting in alteration of ionic fluxes[3]. Specifically, modulation of sarcolemmal calcium adenosine triphosphatase leads to increased efflux and reduced influx of calcium ions. Normally calcium induces smooth muscle contraction by binding to calmodulin, activating myosin light chain kinase, and phosphorylation of myosin light chain. Therefore, decreased cytosolic concentrations of calcium secondary to increased levels of cAMP results in vasorelaxation. Also, myosin light chain kinase is rendered less sensitive to activation by calcium and calmodulin af ter phosphorylation by a cAMP dependent protein kinase[4]. Finally, it is theorized that

Thomas Jefferson College of Medicine.
Correspondência: Lair G. T. Ribeiro—Jefferson Medical College—1020 Locust Street—Philadelphia, PA 19107—USA.

increased levels of cAMP are linked to enhanced sodium-potassium ATPase activity that secondarily tends to lower intracellular concentrations of Ca^{2+} via sodium-calcium counter transport[5].

Following production of cAMP, this nucleotide maintains its kinase-activating activity until it is inactivated by cytoplasmic phosphodiesterase. Considering the pivotal role that cyclic nucleotides play in the modulation of intracellular metabolism, it is not surprising that at least one of several phosphodies terase isoenzymes are found in the cells of most organ systems. Cardiotonic phosphodiesterase inhibitors (PDEI's) display specificity for the phosphodiesterase isoenzyme peak-III (PDE-III)[5]. Since PDE-III is the predominant phosphodiesterase isoenzyme in both the myocardium and vascular smooth muscle, PDEI's act as inodilators, causing simultaneously increased contractility and vasodilation. The mechanism behind the cardiotonic effects of PDEI's is not fully understood. It is presumed that increased intracellular concentrations of cAMP, resulting from decreased rates of degradation by inhibiting PDE-III activity, leads to increased myocardial contractility by enhancing slow Ca^{2+} inward current. However, alternate mechanisms for the positive inotropic effect of PDEI's have been invoked since it was noted that the maximum increase in contractility occurs prior to the maximum increase in cAMP levels with several of these agents[6]. Four mechanisms have been proposed to explain why increased intracellular concentrations of cAMP enhance myocardial contractility: 1) higher concentrations of intracellular free Ca^{2+} resulting from increased calcium influx through the voltage dependent slow Ca^{2+} channels secondary to phosphorylation of channel associated regulatory proteins; 2) inhibition of Ca^{2+} sequestration by the sarcoplasmic reticulum; 3) sensititization of the contractile proteins actin and myosin to Ca^{2+}; and 4) blockade of receptors for the endogenous negative inotropic mediator adenosine[7]. The relative contribution of increased contractility versus vasodilation to the overall hemodynamic effect of PDEI's has been debated and may vary from agent to agent.

There are 3 major chemical classes of PDEI's used as positive inotropic agents: the bipyridines, e.g. amrinone and milrinone; the imidazole derivatives, e.g. enoximone and piroximone; and the benzimidazoles, e.g. sulmazole and pimobendan. In 1984, the United States Food and Drug Administration (FDA) approved the use of intravenous amrinone for the short-term treatment of patients with severe CHF refractory to the use of conventional therapy or in whom conventional therapy was contraindicated. Recently, the FDA also approved the use of intravenously administered milrinone for similar indications. Neither of these agents are presently approved for oral dosing. Oral amrinone is associated with a substantial risk of severe side effects and clinical studies were discontinued because of a lack of efficacy; however, clinical studies with oral milninone and enoximone have suggested both efficacy and a more favorable side effect profile. Many other PDEI's have been developed and are at various stages of preclinical and clinical investigation.

Experiments with isolated animal myocardium have shown that a positive correlation exists between positive inotropic responses and increased levels of cAMP secondary to administration of various PDEI's'[1, 8]. These correlations were observed at concentrations of PDEI's known to inhibit PDE-III in vivo[8]. These experiments support the hypothesis that PDE-III inhibition by PDEI's lead to increased levels of cAMP, activation of cAMP dependent protein kinases and positive inotropy.

Acute administration of PDEI's to patients with CHF results in a marked improvement in many hemodynamic parameters including; increased: cardiac index; cardiac output; stroke volume; stroke work; left ventricular dP/dt; left ventricular ejection fraction; and concomitantly decreased: left and right sided cardiac filling pressures; left ventricular end diastolic pressure; pulmonary capillary wedge pressure; mean aortic pressure; mean pulmorary arlery pressure; right atrial pressure; negative dP/dt (i.e.lincreased lusitropic effect); and systemic vascular resistance[9, 11, 13]). Heart rate and systemic blood pressure are generally only slightly affected[5], although at higher doses, a positive chronotropic effect and a substantial fall in systemic blood pressure are likely to occur. In fact, the limiting factor in dosage is frequently the decreased filling pressures and potential hypotension.

Since PDEI's exert their effect directly on cAMP by inhibiting catalysis and bypass any receptor mechanisms, tolerance due to receptor down regulation with long-term therapy would not be expected. Also, studies of PDEI readministration following periods of drug withdrawal reveal a prompt return of the hemodynamic effect caused by acute administration of PDEI's[14]. However, it is important to realize that the ability of PDEI's to increase contractility is dependent upon the myocardial cell cAMP concentration which decreases as CHF progresses in severity with time.

Several studies show that with long-term PDEI therapy, hemodynamic improvement is maintained throughout the period of active drug administration[7, 14]. However, 3 of 4 studies in which the long term effects of enoximone on hemodynamic parameters were evaluated, and several uncontrolled hemodynamic studies with amrinone and milrinone, all noted that left ventricular dysfunction progresses during long-term treatment[7, 14]. In one large multi-center, placebo controlled study, 155 patients with CHF underwent invasive hemodynamic testing before and after 12 weeks of therapy with either milrinone or placebo[15]. Compared to baseline, values for cardiac index and stroke volume were lowered and values for left ventricular filling pressure and systemic vascular resistance were higher in patients after 3 months of treatment with milrinone[15]. Progressive deterioration in cardiac per-

formance could be attributed to the natural course of the underlying syndrome, CHF, however patients treated with placebo did not show similar cardiodynamic worsening during the period of study.

The direct vasodilator effects for PDEI's have been evaluated experimentally using impedance plethysmography and have revealed a substantial decrease in vascular resistance accompanied by an increase in blood flow[16]. Arterial dilation results in afterload reduction leading to increased stroke volume that amplifies the direct inotropic action of PDEI's in CHF. Venodilation can markedly reduce left ventricular end diastolic volume and filling pressure and may therefore reduce left ventricular preload.

Administration of PDEI's reduces coronary vascular resistance by 30 to 40%, yet myocardial oxygen consumption remains approximately constant [17, 18], Experiments with isolated coronary arteries and aortic strips of the rabbit clearly support the hypothesis that PHEI's have vasodilating effects on the coronary vasculature[19].

Increased systemic blood flow secondary to administration of PDEI's is not uniformly distributed to all vascular beds. Variation in regional perfusion is most likely proportional to differences in the concentration of PDE-III within the microcirculation of specific organs. PDEI's selectively increase skeletal blood flow at rest, while renal and hepatic splanchnic blood flow and vascular resistances remain unhaltered [5, 20]. Glomerular filtration rate and filtration fraction remain unchanged[2, 20].

Activation of the renin-angiotensin system, the sympathetic nervous system and arginine vasopressin secretion may further compromise cardiac function in CHF. Plasma norepinephrine, arginine vasopressin, and renin concentrations do not change significantly with administration of PDEI's[9]. Plasma atrial natriuretic peptide levels decrease probably secondary to the decrease in atrial filling pressures with administration of PDEI's[9].

Several studies have found that acute administration of PDEI's result in an immediate improvement in exercise function accompanied by a significant increase in maximal oxygen consumption[13]. White et al in a randomized, double-blind, crossover study of intravenous administration of milrinone vs placebo, demonstrated an immediate improvement in exercise tolerance, as did Timmis et al in a similar investigation[14]. Long-term effects of PDEI's on exercise tolerance have been less clear-with 2 of 5 controlled studies showing exercise tolerance is not always improved with long-term therapy[14].

Three controlled trials with enoximone addressed the issue of quality of life as an experimental parameter. There was evidence of significant improvement of quality of life in the enoximone treated groups in all 3 studies[14].

There is concern that potent positive inotropic agents may stress the cardiovascular system to the point that their use may be detrimental to patient survival or well being. Specifically. three major concerns have been raised: 1) positive inotropic stimulation may increase myocardial oxygen requirements thereby stressing myocardial energetics and enhancing severity of CHF; 2) myocardial relaxation and/or diastolic filling may be adversely affected; and 3) risk of lethal arrythmia may increase in response to increased intracellular concentrations of Ca^{2+} or cAMP.

Theoretically, treatment of CHF by positive inotropic agents may increase myocardial oxygen demand beyond the limits of supply from occluded coronary arteries and thus stress myocardial energetics and metabolism in an already failing heart. However, the improvement in contractility that follows PDEI therapy is not associated with an increase in myocardial oxygen demand, presumably because of a reduction in left ventricular systolic wall stress due to afterload reduction via peripheral arteriolar vasodilation, that offsets the increase in myocardial oxygen consumption which would otherwise result from an increased inotropic state[18, 21]. In fact, studies have shown that PDEI's exert a beneficial effect on coronary hemodynamics by improving the oxygen supply-demand ratio[17].

PDEI's do not adversely effect diastolic filling or have a negative lusitropic action. Improved diastolic function, as evidenced by a downward displacement of the left ventricular pressure versus volume curva, has been shown to occur following treatment of CHF with PDEI's[21]. This positive lusitropic action occurs secondary to increased intracellular concentrations of cAMP as previously elaborated.

In approximately 35% of patients with CHF sudden unexpected death is precipitated by lethal ventricular arrythmias[22]. The precise etiologic mechanisms causing these arrythmias have not been discovered, but are theorized to possibly result from increased concentrations of cAMP secondary to PDE-III inhibition, increased cytosolic calcium levels secondary to increased cAMP and/or reflex adrenergic stimulation secondary to peripheral vasodilation caused by PDEI's[23]. Increased levels of intracellular cAMP have also been hypothesized to increase automaticity and thus increase the risk for lethal ventricular arrythmias[15]. Results of many uncontrolled clinical trials report the incidence of ventricular arrythmias to increase after institution of therapy for CHF with various PDEI's[15]. However, since ventricular arrythmias are very common in patients with severe left ventricular dysfunction, these results are ambiguous without reference to a control group. Recently, several large, multicenter, placebo controlled, clinical trials have confirmed an increased risk for arrythmogenesis after administration of PDEI's for the treatment of CHF[15]. In one such study, 103 patients with CHF were treated with either milrinone or placebo. After 3 months of therapy, ambulatory electrocardiograph monitoring revealed worsening of arrythmias more frequently in

the milrinone treated group than in those treated with placebo[15].

Aside from the increased risk of arrythmias,the side effect profile of PDEI's is relatively safe. Gastrointestinal complaints including nausea, vomiting, anorexia, diarrhea, and abdominal pain have been reported in a small percent of patients and are of greater incidence with oral than with parenteral therapy[2,5]. Thrombocytopenia, hypotension, fever, and liver function test abnormalities have also been infrequently reported following treatment with PDEI's[25].

Although none of the controlled clinical trials of PDEI's completed to date were designed to evaluate survival as an experimental parameter, it is nevertheless worthwile examining mortality rates in these studies to see if there were any discouraging or encouraging trends. In a placebo-controlled trial to evaluate the effects of imazodan (CI-914) for the treatment of patients with CHF, 7 of 69 patients, receiving imazodan died, whereas none of the 44 patients randomly assigned to placebo died during the 12 week experimental period ($p < 0.05$)[15]. In a 3 month placebo-controlled trial of 230 patients with CHF, 15 of 119 patients randomly assigned to treatment with milrinone died, compared with only 6 of 111 patients assigned to the control group ($p = 0.06$)[21]. By statistical chance, however, patients with the lowest left ventricular ejection fraction were disproportionately assigned to treatment with milrinone. Another study enrolled 155 patients with moderate to severe CHF. After stabilization on treatment with digitalis and diuretics, patients were randomly assigned to one of 3 treatment groups for 3 months: diuretic plus digoxin, diuretic plus milrinone, or diuretic plus digoxin and milrinone[21]. In this trial, the randomization process resulted in a similar distribution of values for left ventricular ejection fraction among the treatment groups and still milrinone had no significant effect on improving survival[21].

In a study of 186 patients with moderate to severe CHF who were randomly assigned to treatment with either milrinone or placebo for 6 months in addition to their previous therapy with digoxin and diuretic, milrinone had no effect on survival[21]. Di Bianco et al in a study of milrinone versus digoxin concluded that while milrinone significantly increased exercise tolerance and reduced the frequency of worsened heart failure, it also increased the frequency of ventricular arrhythmias and offered no advantage over digoxin alone in the treatment of CHF[24]. These observations have raised concerns that PDEI's may exert a deleterious effect of survival of patients with CHF.

To date, no clinical trial has prospectively evaluated the effect of PDEI's on survival of patients with CHF. In a laboratory animal model of experimentally induced CHF, as well as in large-scale, multicenter, controlled. clinical trials. angiotensin converting en zyme (ACE) inhibitors have been shown to significantly increase survival. Recently, Sweet et al employing this same model, demonstrated that milrinone increased the median survival time of rats with left ventricular dysfunction secondary to coronary artery ligation by 49%[21]. The magnitude of this increase in survival time exceeds that produced by ACE inhibitors in the same model and has raised hope that milrinone may prolong life in patients with CHF. However, it must be kept in mind that milrinone does not inhibit PDE-III or elevate cAMP in the rat heart, and most likely achieves its effect by acting as a vasodilator in this species[15]. Therefore, it may not be accurate to extrapolate results from the rat infarction model to humans since PDEI's act directly on the human heart.

In an effort to assess the effect of PDEI's on survival of patients with CHF in the clinical setting, the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial has been started in 75 to 90 clinical research centers through the United States and Canada[15]. A total of 750 patients with symptoms of class IV heart failure refractory to treatment with conventional agents such as digitalis, diuretics, ACE inhibitors, or vasodilators will be enrolled. Patients will be randomly assigned to additional treatment with either oral milrinone or placebo and followed until death or conclusion of the study. The major variable to be evaluated will be all-cause mortality, but the effect of milrinone on functional capacity will also be evaluated.

In summary, CHF is a common syndrome with an unpredictable, yet progressively downhill course and poor prognosis. PDEI's are both positive inotropes and peripheral vasodilators designed to counteract two of the detrimental cardiovascular effects of CHF, namely decreased contractility and increased vasoconstriction. Clinical studies on the acute administration of PDEI's have revealed favorable effects on hemodynamic parameters, increased myocardial oxygen supply-demand ratio, increased exercise tolerance, and an improvement in symptomatic state. However, results of long-term effects of PDEI's on hemodynamic parameters and exercise tolerance remain controversial, with some clinical studies revealing continued benefit, while others suggest reversal of acute effects. Also, an increased risk of ventricular arrythmias and a high incidence of sudden death has been reported to be associated with use of PDEI's. Finally, no increased survival has been documented in CHF patients treated with PDEI's. More long-term, properly controlled, large-scale, randomized clinical studies, such as the PROMISE Trial, are necessary to definitively determine the role of PDEI's in the treatment of CHF.

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