World Journal of Cardiology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4330/wjc.v8.i7.401

World J Cardiol 2016 July 26; 8(7): 401-412
ISSN 1949-8462 (online)

REVIEW

Novel role of phosphodiesterase inhibitors in the management of end-stage heart failure

Abhishek Jaiswal, Vinh Q Nguyen, Thierry H Le Jemtel, Keith C Ferdinand

Abhishek Jaiswal, Vinh Q Nguyen, Thierry H Le Jemtel, Keith C Ferdinand, Tulane School of Medicine, Tulane University Heart and Vascular Institute, New Orleans, LA 70112, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: Dr. Ferdinand is a consultant with Amgen, Boerhinger Ingelheim, Eli Lilly, Sanofi. All other authors report no relationships relevant to the contents of this paper to disclose.

Manuscript source: Invited manuscript

Correspondence to: Keith C Ferdinand, MD, Tulane School of Medicine, Tulane University Heart and Vascular Institute, 1430 Tulane Avenue, SL# 48, New Orleans, LA 70112, United States. kferdina@tulane.edu
Telephone: +1-504-9885492
Fax: +1-504-9884237

Received: February 26, 2016
Peer-review started: February 26, 2016
First decision: April 15, 2016
Revised: May 2, 2016
Accepted: May 31, 2016
Article in press: June 2, 2016
Published online: July 26, 2016

Abstract

In advanced heart failure (HF), chronic inotropic therapy with intravenous milrinone, a phosphodiesterase Ⅲ inhibitor, is used as a bridge to advanced management that includes transplantation, ventricular assist device implantation, or palliation. This is especially true when repeated attempts to wean off inotropic support result in symptomatic hypotension, worsened symptoms, and/or progressive organ dysfunction. Unfortunately, patients in this clinical predicament are considered hemodynamically labile and may escape the benefits of guideline-directed HF therapy. In this scenario, chronic milrinone infusion may be beneficial as a bridge to introduction of evidence based HF therapy. However, this strategy is not well studied, and in general, chronic inotropic infusion is discouraged due to potential cardiotoxicity that accelerates disease progression and proarrhythmic effects that increase sudden death. Alternatively, chronic inotropic support with milrinone infusion is a unique opportunity in advanced HF. This review discusses evidence that long-term intravenous milrinone support may allow introduction of beta blocker (BB) therapy. When used together, milrinone does not attenuate the clinical benefits of BB therapy while BB mitigates cardiotoxic effects of milrinone. In addition, BB therapy decreases the risk of adverse arrhythmias associated with milrinone. We propose that advanced HF patients who are intolerant to BB therapy may benefit from a trial of intravenous milrinone as a bridge to BB initiation. The discussed clinical scenarios demonstrate that concomitant treatment with milrinone infusion and BB therapy does not adversely impact standard HF therapy and may improve left ventricular function and morbidity associated with advanced HF.

Key words: Milrinone; Advanced heart failure; Bridge to beta blocker; Combination therapy; Inotrope support

Core tip: Heart failure (HF) patients requiring chronic inotropic support are considered hemodynamically labile and may escape the benefits of evidence based HF therapy (HFTx). Chronic milrinone infusion may be bene-

ficial as a bridge to introduction of HFTx. We discuss evidence that intravenous milrinone support may allow introduction of beta blocker (BB). We propose that HF patients who are intolerant to BB therapy may benefit from intravenous milrinone as a bridge to BB initiation. When used together, BB mitigates cardiotoxic effects and decreases the risk of arrhythmias associated with milrinone. Whereas, milrinone does not attenuate the clinical benefits of BB therapy.

Jaiswal A, Nguyen VQ, Le Jemtel TH, Ferdinand KC. Novel role of phosphodiesterase inhibitors in the management of end-stage heart failure. *World J Cardiol* 2016; 8(7): 401-412 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i7/401.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i7.401

INTRODUCTION

Heart failure (HF) is a chronic progressive disease with high morbidity and in advanced stages with an annual mortality > 50%; and prevalence is projected to rise[1-3]. Although the long-term benefit of beta-blocker (BB) in advanced HF is well established[4], many patients may be intolerant due to the negative hemodynamic impact of acute therapy and escape the benefits of HF therapy[4-7]. In such patients with advanced HF, chronic inotrope support is used as a bridge to transplantation, ventricular assist device, or palliation strategy for clinical and hemodynamic improvement. However, the use of chronic inotrope therapy as a bridge to introduction of HF therapy, specifically BB therapy, has not been effectively explored. Furthermore, chronic inotropic support is discouraged in advanced HF patients due to increased sudden death and accelerated disease progression[8,9]. In inotrope dependent advanced HF patients, combination therapy with intravenous milrinone infusion and BB provide a unique opportunity.

Concomitant therapy with BB and inotropes has been reported; however only type ⅢA phosphodiesterase inhibitors (PDEI) such as milrinone and enoximone (an PDEI agent available in oral and intravenous formulations in Europe) have demonstrated a positive impact on hospitalization and functional status[10-15]. Both milrinone and enoxamone have shown to improve left ventricular ejection fraction (LVEF) when used in combination with BBs[12,16,17]. However, latest HF management guidelines do not comment on this dual therapy approach and recommends intravenous milrinone infusion only as bridge to advanced management or palliation in refractory end-stage HF[2,18,19].

This review discusses the beneficial effects of combining milrinone infusion and BB therapy in advanced HF. When used together, BB attenuates the cardiotoxicity and accentuates the hemodynamic effect of milrinone. Wherein, milrinone provides the hemodynamic support for introduction of BB therapy. Further, BB therapy decreases the risk of adverse arrhythmias associated with chronic PDEI. Finally, molecular pathways supporting beneficial effects of combination therapy with milrinone infusion and BB therapy are discussed. The index cases to be discussed demonstrate improvement in LVEF after concomitant treatment with carvedilol and chronic milrinone infusion in end-stage HF with severe functional limitation.

Intravenous milrinone therapy in HF

Intravenous milrinone is typically used in patients with acute systolic HF with signs or symptoms of end organ hypoperfusion[2,18,19]. However, inotropic support may be difficult or impossible to wean and prolonged support may be required.

The earliest use of chronic inotropic infusion as viable management option in end-stage HF patients was in 1987[20]. Mehra *et al*[21] reported a 72% survival on long-term milrinone support with a mean duration of 160 d in advanced HF patients awaiting transplantation. Brozena *et al*[22] found similar results in a study of 60 patients committed to home milrinone with an 88.3% survival rate to heart transplantation. In a prospective randomized study that included 19 hospitalized patients who received milrinone therapy, Aranda *et al*[23] showed that 84% survived to receive heart transplantation with a mean waiting of 60 ± 45 d.

In advanced HF patients who are transplant ineligible, success of long-term inotrope therapy has been modest. Harjai *et al*[24] reported a decrease in the number of hospital admissions from 2.7 ± 2.6 to 1.3 ± 1.3 (P = 0.056) and length of hospital stay from 20.9 ± 12.7 to 5.5 ± 5.4 d (P = 0.0004) with improvement in NYHA functional class from 4.0 ± 0.0 to 2.7 ± 0.9 (P < 0.0001) in 24 patients with LVEF < 30%, chronic inotrope-dependence and intolerance to oral HF agents. The benefit of therapy was at the expense of eight deaths (38%) after 2.8 ± 1.7 mo of home Ⅳ inotropic therapy. Hershberger *et al*[25] showed a 3, 6 and 12 mo mortality of 51%, 26% and 6%, respectively, in 36 inotrope-dependent patients with refractory HF on high-dose milrinone (mean dose: 0.6 ± 0.3 mcg/kg per minute). Additionally, using Medicare data, Hauptman *et al*[26] reported reductions in hospital days at all time points (30, 60 and 180 d) but was negatively counterbalanced by a mortality rate exceeding 40% at 6 mo in 331 patients on chronic inotrope therapy. In a single center retrospective analysis of 56 inotrope dependent, transplant ineligible HF patients, Gorodeski *et al*[27] reported 62% mortality and 48% hospitalization during a median follow-up of 130 d. However, in a recent single center study of 197 contemporary HF patients, Hashim *et al*[28] reported an overall median survival of 18 mo on continuous inotropic therapy. Median survival was 9 mo in whom inotrope therapy was intended as palliation, with a 1-year actuarial survival of 48% and a 2-year actuarial survival of 38%. Among all patients placed on inotropes, those on milrinone had a better survival than on dobutamine. The authors proposed that the modest improvement in survival compared to prior studies may be related to

utilization of HF medical therapy and electrophysiologic devices that treat arrhythmias.

In the largest study to date, the PROMISE (Prospective Randomized Milrinone Survival Evaluation) trial randomized 1088 HF patients with NYHA functional class Ⅲ or Ⅳ to placebo or oral milrinone[29]. The milrinone group had 28% higher mortality at 6 mo. However, it is noteworthy that patients did not have defibrillators, and those requiring BB were excluded. Moreover, the study did not evaluate hemodynamics at enrollment with milrinone therapy. Secondary analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study revealed a neutral to beneficial effect of milrinone on 60 d cardiovascular hospitalizations and composite of death and readmission in nonischemic cardiomyopathy but harmful effect in ischemic cardiomyopathy[30]. In addition, it is not clear whether the mortality on chronic inotropic therapy is above and beyond that of patients with end-stage HF where medical options are limited, specifically those with resting hemodynamic decompensation who are not candidates for advanced management[9].

In the light of existing evidence (Table 1), the American Heart Association/American College of Cardiology HF management consensus guideline classifies chronic inotrope infusion in refractory HF as a class Ⅱb indication/level of evidence B due to a lack of randomized controlled trials supporting morbidity and mortality benefits[2,18].

Combination of intravenous milrinone infusion with beta-blocker

Patients whose BB dosages have to be reduced or stopped have worse clinical outcomes than those in whom BB is maintained[31]. The use of intravenous PDEI permits successful initiation and up titration of BBs in HF patients who are intolerant to BB therapy[13,32-34]. Milrinone provides hemodynamic support by improving systolic and diastolic function, along with decreasing afterload and filling pressures, correcting some of the adverse effects of acute BB therapy[14]. Whether these hemodynamic benefits translate into clinical improvement has not been extensively studied. Kumar *et al*[33] assessed the tolerability of carvedilol titration and ability to wean inotrope support in a retrospective review of 32 patients with HF. Seventeen patients with NYHA functional class Ⅲb/Ⅳ HF (group Ⅰ) who received intermittent milrinone infusion were compared to 15 patients with NYHA functional class Ⅱ/Ⅲa symptoms (group Ⅱ) who did not. Both groups were started on carvedilol 3.125 mg twice daily and titrated to 25 mg twice daily every 2 wk as tolerated. Milrinone infusion had no impact on carvedilol titration (88% *vs* 93%). At 8 wk, 53% patients in group Ⅰ were successfully weaned off milrinone infusion. Those who could not be weaned had a 50% decrease in the frequency of infusions. The majority (63%) of group Ⅰ patients improved by one or more functional class at the end of follow-up. Another retrospective review assessed BB tolerability in 16 patients with stage D HF on continuous milrinone infusion[35]. Twelve patients were started on metoprolol tartrate or carvedilol and the remaining four received only milrinone. After 6 mo, 92% of patients on milrinone were able to tolerate dual therapy with a BB. No significant changes in blood pressure and heart rate after were noted BB initiation. One patient in each group died, and rates of hospitalization for HF were similar (0.83/pt in combination group *vs* 0.5/pt in BB alone). While these studies suggest tolerability and symptomatic improvement with dual therapy, results cannot be unequivocally extrapolated due to the small sample sizes.

In a retrospective analysis, Zewail *et al*[36] reported hemodynamic and clinical outcomes of long-term combination therapy with intravenous milrinone and BB in 65 patients with severe HF (NYHA class IV and LVEF < 25%) refractory to oral medical therapy. Fifty-one patients (78%) successfully tolerated BB therapy while on intravenous milrinone, while 14 patients did not and thus received milrinone monotherapy. Functional class improved from NYHA class Ⅳ to Ⅱ-Ⅲ with combination therapy. While no patients in the milrinone-only arm could be weaned off, 47% patients (24/51) in the combination arm were successfully weaned off. The corrected QT interval was significantly prolonged in the monotherapy group (mean ± 436 ± 13 ms before *vs* 469 ± 28 ms after; $P = 0.002$), whereas the interval remained unchanged in the combination group. Most notably, survival at 3 years was 59% higher in the combination group *vs* the milrinone monotherapy group ($P < 0.001$). One died of sudden cardiac death on treatment day 116 in the combination group. Jiménez *et al*[10] carried out an observational study of 26 inotrope dependent patients (> 8 wk home inotrope support) with end stage HF, with 17 patients as bridge to transplantation and 9 patients as destination therapy. They reported an 85% survival at an average of 10 mo home inotropic therapy. The reported mortality rates in the above nonrandomized studies were consistent with randomized studies of similar HF patients[37].

Gattis *et al*[38] conducted a post-hoc analysis comparing patients receiving BB at the time of hospitalization to those who did not using the OPTIME-CHF study. The 949 patients with acute HF exacerbation were randomized to receive 48-72 h of intravenous milrinone *vs* placebo. In patients who were continued on BB on admission, there was no difference in the primary endpoint regardless of assignment to milrinone or placebo. Patients whose BB were withdrawn upon randomization to milrinone had worse outcomes (mortality 28.6% *vs* 7.7%, *P*-value not reported). Furthermore, patients who received both milrinone and BB during hospitalization had the lowest 60-d mortality (5.8%).

The findings of above studies suggest that combination therapy may reduce mortality and facilitate discontinuation of inotropic support in advanced HF. However, retrospective design and small sample sizes preclude firm conclusions on the impact of combination therapy on mortality, hospitalization, and symptomatic improvement. Further, as there is substantial evidence

Table 1 Clinical studies evaluating phosphodiesterase Ⅲ inhibitors in heart failure

Ref.	Aim of study	Background beta blocker therapy	Study size *n* (total)	HF symptoms	Trial duration	Major findings/conclusion	Impact of therapy on LVEF	Complications/adverse events	Inotrope weaning rate
Packer *et al*[29], 1991	Effect of oral milrinone on mortality of pts with symptomatic chronic HF on conventional therapy	No	1088	100% NYHA Ⅲ-Ⅳ 42% NYHA Ⅳ	Median F/U duration 6.1 mo (stopped early due to adverse effects)	28% increased mortality with milrinone (30% *vs* 24%)	Not reported	Syncope palpitations hypotension headache blurry vision	Not reported
Böhm *et al*[16], 1997	Metoprolol restores the reduction of the inotropic effect of the cAMP-phosphodiesterase inhibitor milrinone, independent of beta-adrenoceptor	Yes (100%)	15	NYHA Ⅱ or Ⅲ	6 mo	Treatment with metoprolol increased LVEF, fractional shortening and submaximal exercise tolerance and reduced heart rate, plasma norepinephrine concentrations After metoprolol treatment, milrinone increased fractional shortening but had no effect before beta-blocker treatment Effect of dobutamine was completely antagonized by treatment with metoprolol	Addition of metoprolol improved EF (%) from 24.6 ± 1.5 to 40.3 ± 3.6	Not reported	Not reported
Shakar *et al*[12], 1998	Clinical impact of combined therapy with enoximone and beta blocker	Yes (80%)	30	NYHA Ⅳ	Mean duration of combination therapy was 9.4 ± 1.8 mo; mean length of F/U was 20.9 ± 3.9 mo	Combination therapy with enoximone and beta blocker improved EF and functional status in severe HF	LVEF increased from 17.7 ± 1.6% to 27.6 ± 3.4% (P = 0.01) NYHA improved from 4 to 2.8 (P = 0.0001)	2 sudden deaths	48% were weaned off enoximone
Yamani *et al*[67], 2001	Clinical outcome and economic cost of dobutamine-based and milrinone-based therapy in patients with ADHF	Yes 20% (18% milrinone grp)	329 (60 milrinone grp)	100% NYHA Ⅳ	Retrospective review of ADHF admissions	No difference in the in-hospital mortality rate or clinical outcomes	Not reported	No difference in adverse effects between the grps (20% pts in milrinone grp with either NSVT or VT)	Not reported
Lowes *et al*[32], 2001	Efficacy of milrinone *vs* dobutamine in patients with decompensated heart failure on chronic carvedilol therapy	Yes (100%)	20	100% NYHA Ⅱ-Ⅳ	Acute therapy	Dobutamine has less favorable hemodynamic effects in patients treated chronically with carvedilol	Not reported	Not reported	Not reported
Kumar *et al*[33], 2001	Carvedilol titration in NYHA class Ⅲb/Ⅳ on milrinone therapy as compared to class Ⅱ/Ⅲa CHF without milrinone	Yes (90%)	32	Class Ⅱ-Ⅳ	Mean: 24 wk	Successful carvediolol uptitration in NYHA Ⅲ-b/Ⅳ can be achieved at similar rates as in NYHA Ⅱ/Ⅲa in the presence of stable chronic milrinone therapy	Not reported	No statistical difference in adverse events among the two grps	53% patients were weaned off milrinone infusions in a mean of 8.4 ± 8.4 wk

Metra *et al*[13], 2002	Hemodynamic effects of dobutamine and enoximone before and after 9-12 mo of beta-blocker therapy with metoprolol or carvedilol in chronic HF	Yes (100%)	34	NYHA Ⅱ-Ⅳ	9-12 mo	Beta blockers significantly inhibit the favorable hemodynamic response to dobutamine. No attenuation occurred with beta blockers and enoximone	Not reported	Not reported	Not reported
Cuffe *et al*[68], 2002	Short-term milrinone in addition to standard therapy to improve outcomes in pts with ADHF	Yes (22%)	949	93% NYHA Ⅲ-Ⅳ	Treatment for up to 72 h, 60 d F/U	Milrinone was associated with higher rate of treatment failure at 48 h due to AE (12.6% *vs* 2.1%)	Not reported	Hypotension, (SBP < 80 mmHg); 10.7% with milrinone Significant atrial arrhythmias during index hospitalization; 4.6%	Not reported
Felker *et al*[30], 2003	To assess the interaction between HF etiology and response to milrinone in ADHF	Yes (23%)	949	93% NYHA Ⅲ-Ⅳ	Treatment up to 72 h with 60 d F/U	In ischemic HF, milrinone was associated with worse outcomes: 60 d mortality or hospitalization: 42% *vs* 36% placebo; in-hospital mortality 5% *vs* 1.6% placebo In nonischemic HF, benefit was derived from milrinone: 60 d mortality or hospitalization: 28% *vs* 35% placebo; in-hospital mortality 2.6% *vs* 3.1% placebo	Not reported	No difference in atrial or ventricular arrhythmias and hypotension in both grps	Not reported
Aranda *et al*[23], 2003	Clinical outcomes and costs associated dobutamine *vs* milrinone in hospitalized pts awaiting cardiac transplantation	Yes (41% in dobutamine grp; 74% in milrinone grp)	36	Not reported presumably NYHA Ⅲ-Ⅳ	Enrollment 17 mo	No difference between milrinone and dobutamine with respect to clinical outcomes or hemodynamic measures Beta blocker use in dobutamine grp was associated with worsened pulmonary pressures and PCWP	Not reported	No difference in death of length of hospital stay	Not reported
Brozena *et al*[22], 2004	Feasibility and safety of continuous IV milrinone therapy administered at home in pts listed as status IB for heart transplant	Yes (73%)	60	NYHA Ⅱ-Ⅲ Peak VO_2 11.4 mL/kg per minute	43 mo F/U	88.3% of pts underwent OHT 3.2% died before transplant	Not reported	8% hospitalized for IV line infection	1 pt weaned off based on clinical improvement
Abraham *et al*[69], 2005	In-hospital mortality in ADHF pts receiving treatment with 1 of 4 vasoactive meds (NTG, nesiritide, milrinone, dobutamine)	Yes (56% milrinone grp)	2021 (milrinone)	100% NYHA Ⅳ	10/01-7/03	Worse inpatient mortality and longer LOS with IV inotropes	N/A	N/A	N/A
Feldman *et al*[70], 2007	Whether low-dose oral enoximone could wean pts with end-stage HF from IV inotropic support	Yes (40%)	201	100% NYHA Ⅲ-Ⅳ	26 wk	30 d after weaning, 51% of placebo pts and 61.40% enoximone pts were alive and free of IV inotropic therapy	Not reported	Dyspnea, 5% enoximone *vs* 0% placebo, $P < 0.05$	

						At 60 d, the wean rate was 30% in placebo grp and 46.5% in enoximone grp Kaplan-Meier curves demonstrated a trend towards decreased in time to death or reinitiation of IV inotropic therapy over the 182-d study period and a reduction at 60 d and 90 d after weaning in the enoximone grp			
Elkayam *et al*[71], 2007	Six month risks of all-cause mortality and all-cause mortality plus rehospitalization associated with the use of vasodilators, inotropes, and their combinations	Yes (62%)	433; 75 (vasodilator); 133 (IV inotrope); 47 (both); 178 (neither inotrope/ vasodilator)	Mean peak VO_2 10.0	N/A	Worse 6 mo mortality and either mortality/re-hospitalization with inotropes (whether alone or with vasodilator)	Not reported	N/A	N/A
Gorodeski *et al*[27], 2009	Relationship between choice of dobutamine or milrinone and mortality in inotrope dependent stage D HF pts	Yes [5% (dob) *vs* 34% (mil)]	112	Not reported presumably NYHA Ⅲ-Ⅳ	Median F/U of 130 d	Higher mortality in the dobutamine grp; No difference in mortality between inotrope type in propensity matched cohort	Not reported	Not reported	Not reported
Metra *et al*[37], 2009	Effects of low dose enoximone on symptoms, exercise capacity, and major clinical outcomes in pts with advanced HF who were also treated with beta blockers and other guideline recommended background therapy	ESSENTIAL Ⅰ Yes (83%) ESSENTIAL Ⅱ Yes (90%)	ESSENTIAL Ⅰ: 904 ESSENTIAL Ⅱ: 950	100% NYHA Ⅲ-Ⅳ	Median F/U duration 16.6 mo	No difference in first co-primary endpoints: All cause mortality, all-cause mortality and CV hospitalizations	Not reported	Palpitations 8% enoximone *vs* 5% placebo, $P = 0.01$	N/A

AE: Adverse event; dob: Dobutamine; F/U: Follow-up; grp: Group; HF: Heart failure; mil: Milrinone; NYHA: New York Heart Association; OPTIME-CHF: The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure study; OHT: Orthotopic heart transplant; PCWP: Pulmonary capillary wedge pressure; pts: Patients; SBP: Systolic blood pressure; IV: Intravenous; cAMP: Cyclic adenosine monophosphate; ADHF: Acute decompensated heart failure; CV: Cardiovascular; LVEF: Left ventricular ejection fraction; LOS: Length of stay; EF: Ejection fraction; NSVT: Non sustained ventricular tachyarrhythmia; NTG: Nitroglycerin; VT: Ventricular tachyarrhythmia; VO_2: Peak oxygen consumption; ADHERE: The Acute Decompensated Heart Failure National Registry; EMOTE: The EnoxiMone in intravenous inOTropE-dependent subjects study.

on BBs in mortality reduction, it would be unjustified to randomize BB *vs* placebo in milrinone treated patients with refractory HF. Larger observational studies would further elucidate the potential clinical benefits of combining BB with milrinone.

MOLECULAR PATHWAYS SUPPORTING COMBINATION THERAPY

Defective calcium (Ca^+) handling is thought to be a major contributor to mechanical and electrical dysfunction in HF (Figure 1)[39]. The increased mortality associated with PDEI therapy in HF is attributed to a proarrhythmic effect[29,40,41], contributing to increased sudden cardiac death and direct cardiomyocyte toxicity related to cyclic adenosine monophosphate (cAMP) mediated Ca^+ overload and sustained beta-1-receptor pathway signaling (Figure 2)[21]. Recent investigations suggest that modulation of

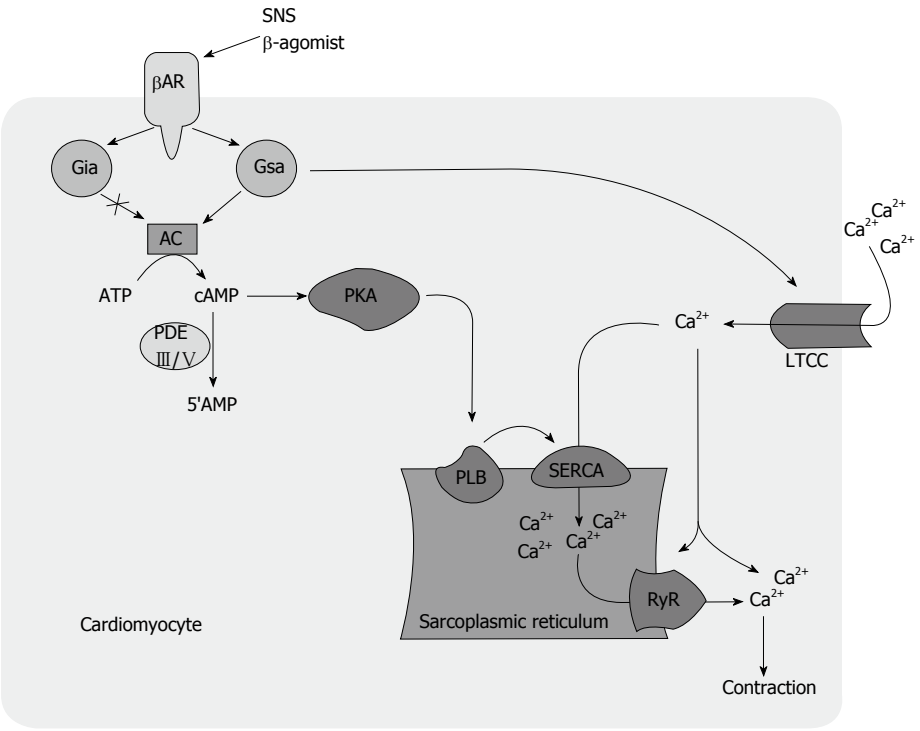

Figure 1 Beta-adrenoreceptor mediated signal transduction leads to the activation of both G stimulatory alpha protein and G inhibitory alpha protein. Activated Gαs activates adenylyl cyclase (AC) which converts ATP into cAMP while activated Gαi inhibits AC. Activated Gαs also leads to calcium (Ca^{2+}) mobilization into cardiomyocyte by activating L-type calcium channel (LTCC) independent of AC. This increase in intracellular Ca^{2+} concentration leads to activation of ryanodine receptor (RyR) which causes further release of Ca^{2+} from SR, a phenomenon known as calcium-induced calcium release. Elevated cAMP activates phosphokinase A (PKA) that inhibits phospholamban (PLB) by phosphorylating it. Phosphorylation of PLB increases uptake of Ca^{2+} from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This enhanced Ca^{2+} entry into SR has positive impact on both systolic and diastolic function. In diastole, decreased intracellular Ca^{2+} causes relaxation. In systole increased release of Ca^{2+} from SR store through RyR activation increases inotropy. In the failing myocardium, chronic stimulation of βAR results in ineffective activation of AC, persistent activation of L-type calcium channel that increases Ca^{2+} influx, and decreased Ca^{2+} uptake into the SR due to decreased SERCA activity. This translates into systolic and diastolic dysfunction and increased arrhythmogenicity. βAR: Beta-adrenoreceptor; ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; Gαi: G inhibitory alpha protein; Gαs: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system.

Ca^{+} handling may result in improvements in inotropy and lusitropy without increasing arrhythmogenesis and cardiotoxicity[39,42-44]. BBs have shown to attenuate these molecular responses[45-48] and may attenuate adverse effects associated with PDEIs (Figure 3)[49,50].

In the presence of BB, the harmful sustained B-receptor pathway signaling associated with HF, mediated through cAMP-independent G-a-stimulating protein coupling of Ca^{+} channels[51], is eliminated. The inotropic effect of PDEIs is still maintained through the phosphorylation of phopholamban on the sarcoplasmic reticulum (SR)[52-54]. Inotropic agents that act through inhibition of phospholamban are desirable and best tolerated[14,55]. Phospholamban phosphorylation causes decreased inhibition of SR calcium ATPase (SERCA) activity, resulting in its increased SR calcium uptake in diastole and subsequent increased release in cytosol in systole for augmented myocardial performance. This, in turn, results in increased diastolic and systolic functions[14]. Improvement in Ca^{+} handling, through targeted *SERCA* gene expression has shown to retard development of action potential duration alternans and hence decreased arrhythmogenesis[56]. This is further supported by an improved systolic and diastolic function without increase in heart rate in phospholamban knockout models, a maneuver that mimics phospholamban phosphorylation[57,58]. In addition, the delivery of pseudo-phosphorylated mutant of phopholamban into sheep heart using a viral vector reversed chronic pacing induced HF[59]. On the contrary, phosphorylation of L-type Ca^{+} channel leads to an increased Ca^{+} influx during the plateau phase of the action potential, resulting in increased intracellular Ca^{+} during both diastole and systole that causes a detrimental effect on diastolic function and arrhythmogenesis[14].

Using an extracorporeal circulation cardioplegia reperfusion model, Usta *et al*[60] showed evidence of decreased apoptosis with low dose milrinone on *ex vivo* human right auricle cardiomyocytes compared with controls. At lower concentrations, the most likely pharmacological target of PDEI is phopholamban as both are localized to SR[61,62]. A twelve-week treatment with lower dose of enoximone (≤ 50 mg three times daily) increased exercise capacity without increasing ventricular arrhythmias. This approach demonstrated favorable effects on degree of dyspnea and physician assessments of clinical status compared to placebo[61]. A contemporary observational study suggested better survival on low dose intravenous milrinone at 0.296 ± 0.092 mcg/kg per minute[28]. Although the short-term benefits have been documented, long-term efficacy and safety of low-dose PDEI remains to be demonstrated in controlled

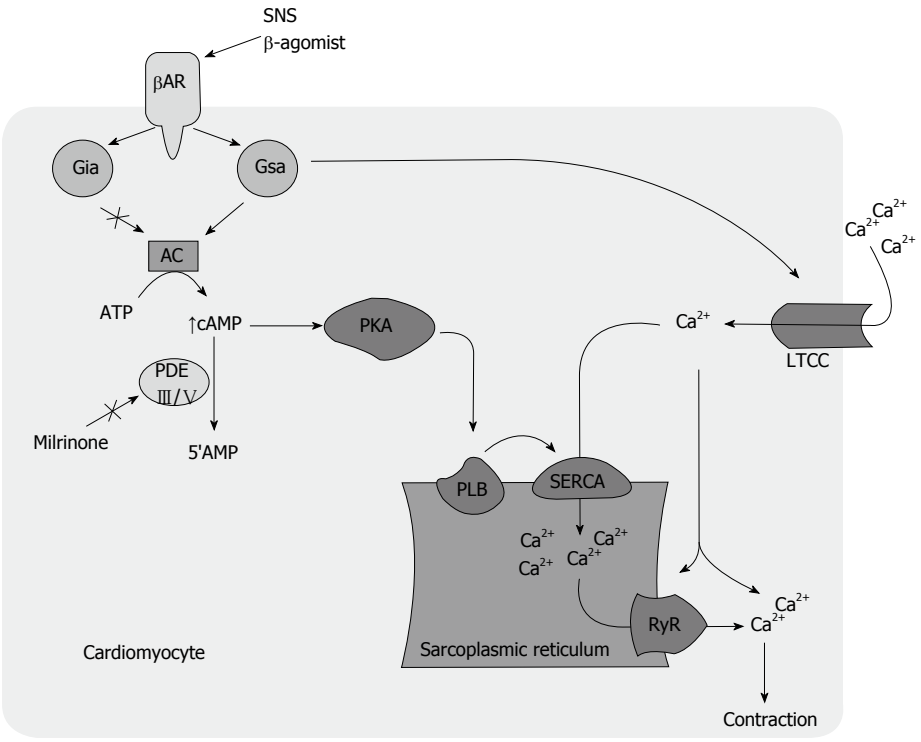

Figure 2 Milrinone causes inhibition of phosphodiesterase Ⅲ enzyme which decreases cyclic adenosine monophosphate concentration by converting later into inactive 5'adenosine monophosphate. Increased cyclic adenosine monophosphate (cAMP) activates phosphokinase A (PKA) that inhibits phospholamban (PLB) by phosphorylating it. Inhibition of PLB increases uptake of calcium (Ca^{2+}) from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This enhanced Ca^{2+} entry into SR has positive impact on both systolic and diastolic function. During diastole, decreased cytosolic Ca^{2+} causes relaxation. During systole increased release of Ca^{2+} from SR store through ryanodine receptor (RyR) activation increases inotropy. However, unchecked chronic stimulation of beta-adrenoreceptor (βAR) causes inhibition of AC through Gαi protein and increases intracellular Ca^{2+} influx by activation of L-type calcium channel (LTCC). Activated LTCC indirectly increases intracellular Ca^{2+} through activation of RyR mediated release of Ca^{2+} from SR. This increased intracellular influx of Ca^{2+} is associated with increased arrhythmogenicity. ATP: Adenosine triphosphate; Gαi: G inhibitory alpha protein; Gαs: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system.

trials. In patients with advanced HF who do not tolerate BB therapy, we choose intravenous milrinone continuous infusion at low dose (< 0.5 μg/kg per minute) as this strategy is shown to augment cardiac function to permit BB therapy[61].

In addition, when used in combination, BB may enhance hemodynamic effects related to PDEI therapy by decreasing activity of upregulated inhibitory G-alpha-inhibitory protein activity[12,63]. The choice of BB to use in combination with a PDEI is uncertain. The use of B1-selective agent is suggested to be preferable as its blockade leads to increased B2-receptor-mediated signal transduction through cross-regulatory mechanisms[64], which is less cardiomyopathic[65] and may even prevent apoptosis[66]. The vasodilator effect of carvedilol can be additive to that of milrinone. However, this combination may be not desirable in patients with marginal blood pressures. The vasodilator property is less pronounced and response to milrinone is not compromised by additional vasodilation once the patient becomes stable[17].

Clinical scenario

Case1: A 67-year-old man with chronic cardiomyopathy with severely reduced systolic function with LVEF < 15% without significant epicardial coronary artery disease was impaired by six hospitalizations in five months and New York Heart Association (NYHA) class Ⅳ functional status. Due to inability to tolerate HF medicines and inadequate diuretic response, invasive hemodynamic assessment was performed. Elevated biventricular filling pressures and decreased cardiac output were noted, both of which improved 20% after milrinone bolus (0.5 mcg/kg per minute over 10 min) (Table 2). Due to refractory cardiomyopathy and hemodynamic findings, he was started on long-term continuous home milrinone infusion. Consequently, the patient tolerated carvedilol initiation and up-titration on outpatient follow-up. His functional class improved to NYHA class Ⅱ-Ⅲ and HF hospitalizations decreased to three in the subsequent nine months. Defibrillator interrogation throughout did not reveal significant arrhythmias. Nine months into treatment, LVEF improved to 35%-40% and milrinone was discontinued (Video core tip). The patient continued to thrive independent of milrinone therapy.

Case 2: A 50-year-old man with chronic cardiomyopathy with severely reduced LVEF 10%-15% without significant epicardial coronary artery disease was admitted for decompensated HF with acute renal insufficiency and inadequate diuretic response. Invasive hemodynamics revealed elevated biventricular pressure with severely decreased cardiac output (Table 2). Intravenous mlri-

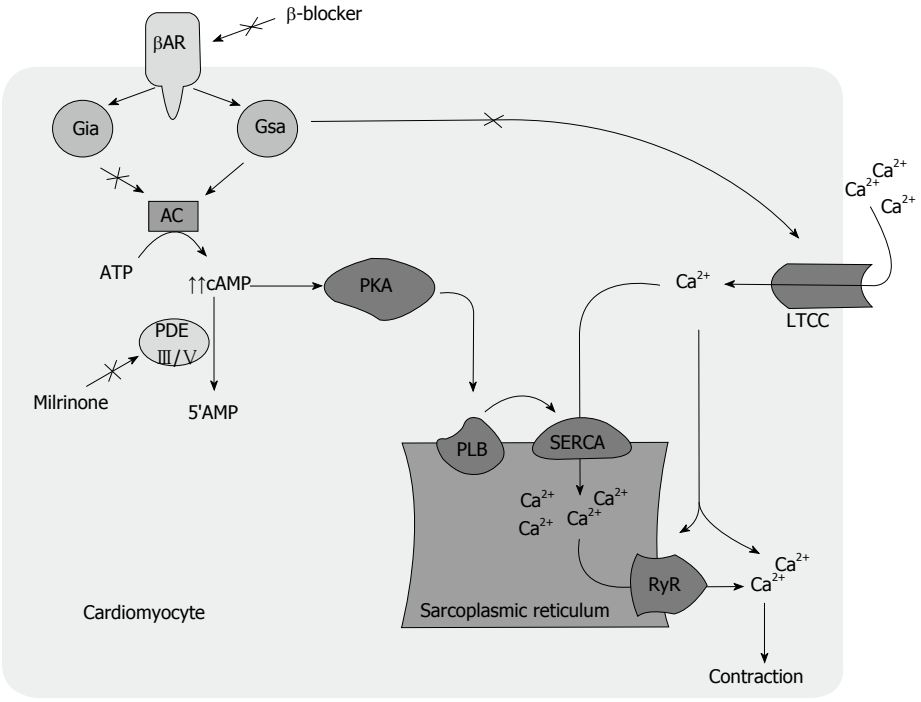

Figure 3 Concomitant use of beta blocker and milrinone causes inhibition of G inhibitory alpha protein which is an inhibitor of adenylyl cyclase and phosphodiesterase Ⅲ enzyme, both results in increased cyclic adenosine monophosphate concentration. Increased cAMP inhibits phospholamban (PLB) resulting in efficient movement of calcium (Ca^{2+}) from cytosol into the SR through sarcoplasmic reticulum calcium ATPase (SERCA). This PLB mediated Ca^{2+} handling results in improved systolic and diastolic function. In addition, BB inhibits beta-adrenoreceptor (βAR) mediated increased Ca^{2+} influx through L-type calcium channel (LTCC) that is associated with increased arrhythmogenicity. ATP: Adenosine triphosphate; cAMP: Cyclic adenosine monophosphate; Gαi: G inhibitory alpha protein; Gαs: G stimulatory alpha protein; PDE: Phosphodiesterase; SNS: Sympathetic nervous system; BB: Beta blocker; AC: Adenylyl cyclase.

Table 2 Hemodynamic parameters at baseline and after milrinone loading

Hemodynamic parameters	Patient 1		Patient 2		Reference values
	Baseline	Post-milrinone loading	Baseline	Post-milrinone loading	
RA (mmHg)	15		15		5-7
RV (mmHg)	54/15		Dec-58		15-30/1-5
PA (mmHg)	53/33 (40)	56/21 (34)	61/37 (45)		15-30/4-10; mean < 20
PA O_2 saturation	49.50%		57%		60%-80%
PCWP (mmHg)	29	15	30		< 12
Cardiac output (L/min)	5.1	7.1	3.3	6	4-8
Cardiac index (L/min per meter squared)	2.1	2.95	1.64	3.03	2.6-4.2
PVR (WU)	2.68	2.16	4.54		< 3 WU
Hemoglobin (g/dL)	10.2	10.2	11.7		13.5-17.5

PA: Pulmonary artery; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; RA: Right atrial; RV: Right ventricle; WU: Wood units.

none was initiated, permitting diuresis that led to a net 40-pound weight loss during the two-week hospitalization. The patient also underwent biventricular pacemaker implantation for cardiac resynchronization therapy. Over the ensuing year post-milrinone therapy, his ambulatory status improved from < 100 feet to > 6 city blocks. Defibrillator interrogation throughout the treatment duration did not reveal significant arrhythmias. Repeat LVEF after 10 mo improved to 20%-25% (Video core tip).

CONCLUSION

In patients with advanced HF, use of a combination therapy with low-dose intravenous milrinone infusion and BB offers an appealing strategy. In the treatment of advanced HF, we propose that chronic milrinone infusion be regarded as a "bridge to BB" in addition to the traditional bridge to advanced options or palliation strategy. Attempt at initiation and up-titration of BBs should be underscored in such patients. Milrinone provides hemodynamic support to initiate and up-titrate BB in the presence of BB-intolerance. Moreover, dual therapy improves symptoms and decreases hospitalization. Lastly, LVEF may improve with this approach without any ill-effects and significant arrhythmias, suggesting that this is a safe and effective therapeutic strategy in advanced refractory HF. Our experience with cases discussed above

shows improvement in LVEF after concomitant use of BB and intravenous continuous low-dose milrinone. It is possible that the cases might not have been adherent to prescribed HF medications prior to use of intravenous milrinone, and the increased LVEF is purely a reflection of medical compliance. Systematic exploration involving large cohorts is required for further understanding as the population with advanced HF continues to expand.

REFERENCES

1 **Bui AL**, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011; **8**: 30-41 [PMID: 21060326 DOI: 10.1038/nrcardio.2010.165]

2 **Heidenreich PA**, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogdon JG. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013; **6**: 606-619 [PMID: 23616602 DOI: 10.1161/hhf.0b013e318291329a]

3 **Chen-Scarabelli C**, Saravolatz L, Hirsh B, Agrawal P, Scarabelli TM. Dilemmas in end-stage heart failure. *J Geriatr Cardiol* 2015; **12**: 57-65 [PMID: 25678905 DOI: 10.11909/j.issn.1671-5411.2015.01.007]

4 **Krum H**, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, Medina N, Yushak M, Horn E, Katz SD. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation* 1995; **92**: 1499-1506 [PMID: 7664433 DOI: 10.1161/01.cir.92.6.1499]

5 **Cohn JN**, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, Krueger SK, Lejemtel T, Narahara KA, Packer M, Young ST, Holcslaw TL, Lukas MA. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J Card Fail* 1997; **3**: 173-179 [PMID: 9330125 DOI: 10.1016/S1071-9164(97)90013-0]

6 **Macdonald PS**, Keogh AM, Aboyoun CL, Lund M, Amor R, McCaffrey DJ. Tolerability and efficacy of carvedilol in patients with New York Heart Association class IV heart failure. *J Am Coll Cardiol* 1999; **33**: 924-931 [PMID: 10091817 DOI: 10.1016/s0735-1097(98)00680-9]

7 Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) *Lancet* 1999; **353**: 2001-2007 [PMID: 10376614 DOI: 10.1016/s0140-6736(99)04440-2]

8 **Francis GS**, Bartos JA, Adatya S. Inotropes. *J Am Coll Cardiol* 2014; **63**: 2069-2078 [PMID: 24530672 DOI: 10.1016/j.jacc.2014.01.016]

9 **Pinney SP**, Stevenson LW. Chronic Inotropic Therapy in the Current Era: Old Wines With New Pairings. *Circ Heart Fail* 2015; **8**: 843-846 [PMID: 26374915 DOI: 10.1161/circheartfailure.115.002481]

10 **Jiménez J**, Jara J, Bednar B, Bauerlein J, Mallon S. Long-term (& gt; 8 weeks) home inotropic therapy as destination therapy in patients with advanced heart failure or as bridge to heart transplantation. *Int J Cardiol* 2005; **99**: 47-50 [PMID: 15721498 DOI: 10.1016/j.ijcard.2003.11.064]

11 **Berger R**, Strecker K, Hülsmann M, Frey B, Pacher R, Stanek B. Experience with beta-blocker therapy in patients with advanced heart failure evaluated for HTx. *J Heart Lung Transplant* 2000; **19**: 1081-1088 [PMID: 11077226 DOI: 10.1016/s1053-2498(00)00201-1]

12 **Shakar SF**, Abraham WT, Gilbert EM, Robertson AD, Lowes BD, Zisman LS, Ferguson DA, Bristow MR. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol* 1998; **31**: 1336-1340 [PMID: 9581729 DOI: 10.1016/s0735-1097(98)00077-1]

13 **Metra M**, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, Dei Cas L. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol* 2002; **40**: 1248-1258 [PMID: 12383572 DOI: 10.1016/s0735-1097(02)02134-4]

14 **Shakar SF**, Bristow MR. Low-level inotropic stimulation with type III phosphodiesterase inhibitors in patients with advanced symptomatic chronic heart failure receiving beta-blocking agents. *Curr Cardiol Rep* 2001; **3**: 224-231 [PMID: 11305977 DOI: 10.1007/s11886-001-0027-8]

15 **Hauptman PJ**, Woods D, Prirzker MR. Novel use of a short-acting intravenous beta blocker in combination with inotropic therapy as a bridge to chronic oral beta blockade in patients with advanced heart failure. *Clin Cardiol* 2002; **25**: 247-249 [PMID: 12018885 DOI: 10.1002/clc.4950250512]

16 **Böhm M**, Deutsch HJ, Hartmann D, Rosée KL, Stäblein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. *J Am Coll Cardiol* 1997; **30**: 992-996 [PMID: 9316529 DOI: 10.1016/s0735-1097(97)00248-9]

17 **Lowes BD**, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. *Clin Cardiol* 2000; **23**: III11-III16 [PMID: 10754776 DOI: 10.1002/clc.4960231504]

18 **Yancy CW**, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62**: e147-e239 [PMID: 23747642 DOI: 10.1016/j.jacc.2013.05.019]

19 **Lindenfeld J**, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010; **16**: e1-194 [PMID: 20610207 DOI: 10.1016/j.cardfail.2010.04.004]

20 **Applefeld MM**, Newman KA, Sutton FJ, Reed WP, Roffman DS, Talesnick BS, Grove WR. Outpatient dobutamine and dopamine infusions in the management of chronic heart failure: clinical experience in 21 patients. *Am Heart J* 1987; **114**: 589-595 [PMID: 3630900 DOI: 10.1016/0002-8703(87)90757-5]

21 **Mehra MR**, Ventura HO, Kapoor C, Stapleton DD, Zimmerman D, Smart FW. Safety and clinical utility of long-term intravenous milrinone in advanced heart failure. *Am J Cardiol* 1997; **80**: 61-64 [PMID: 9205021 DOI: 10.1016/s0002-9149(97)00284-1]

22 **Brozena SC**, Twomey C, Goldberg LR, Desai SS, Drachman B, Kao A, Popjes E, Zimmer R, Jessup M. A prospective study of continuous intravenous milrinone therapy for status IB patients awaiting heart transplant at home. *J Heart Lung Transplant* 2004; **23**: 1082-1086 [PMID: 15454175 DOI: 10.1016/j.healun.2003.08.017]

23 **Aranda JM**, Schofield RS, Pauly DF, Cleeton TS, Walker TC, Monroe VS, Leach D, Lopez LM, Hill JA. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J* 2003; **145**: 324-329 [PMID: 12595851 DOI: 10.1067/mhj.2003.50]

24 **Harjai KJ**, Mehra MR, Ventura HO, Lapeyre YM, Murgo JP, Stapleton DD, Smart FW. Home inotropic therapy in advanced heart failure: cost analysis and clinical outcomes. *Chest* 1997; **112**: 1298-1303 [PMID: 9367472 DOI: 10.1378/chest.112.5.1298]

25 **Hershberger RE**, Nauman D, Walker TL, Dutton D, Burgess D. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. *J Card Fail* 2003; **9**: 180-187 [PMID: 12815567 DOI: 10.1054/jcaf.2003.24]

26 **Hauptman PJ**, Mikolajczak P, George A, Mohr CJ, Hoover R, Swindle J, Schnitzler MA. Chronic inotropic therapy in end-stage heart failure. *Am Heart J* 2006; **152**: 1096.e1-1096.e8 [PMID: 17161059 DOI: 10.1016/j.ahj.2006.08.003]

27 **Gorodeski EZ**, Chu EC, Reese JR, Shishehbor MH, Hsich E, Starling RC. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail* 2009; **2**: 320-324 [PMID: 19808355 DOI: 10.1161/circheartfailure.108.839076]

28 **Hashim T**, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, Loyaga-Rendon RY, George JF, Acharya D. Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure. *Circ Heart Fail* 2015; **8**: 880-886 [PMID: 26179184 DOI: 10.1161/circheartfailure.114.001778]

29 **Packer M**, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991; **325**: 1468-1475 [PMID: 1944425 DOI: 10.1056/nejm199111213252103]

30 **Felker GM**, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiade M, O'Connor CM. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003; **41**: 997-1003 [PMID: 12651048 DOI: 10.1016/s0735-1097(02)02968-6]

31 **Prins KW**, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of Beta-Blocker Withdrawal in Acute Decompensated Heart Failure: A Systematic Review and Meta-Analysis. *JACC Heart Fail* 2015; **3**: 647-653 [PMID: 26251094 DOI: 10.1016/j.jchf.2015.03.008]

32 **Lowes BD**, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol* 2001; **81**: 141-149 [PMID: 11744130 DOI: 10.1016/s0167-5273(01)00520-4]

33 **Kumar A**, Choudhary G, Antonio C, Just V, Jain A, Heaney L, Papp MA. Carvedilol titration in patients with congestive heart failure receiving inotropic therapy. *Am Heart J* 2001; **142**: 512-515 [PMID: 11526366 DOI: 10.1067/mhj.2001.117605]

34 **Constantinescu AA**, Caliskan K, Manintveld OC, van Domburg R, Jewbali L, Balk AH. Weaning from inotropic support and concomitant beta-blocker therapy in severely ill heart failure patients: take the time in order to improve prognosis. *Eur J Heart Fail* 2014; **16**: 435-443 [PMID: 24464574 DOI: 10.1002/ejhf.39]

35 **Earl GL**, Verbos-Kazanas MA, Fitzpatrick JM, Narula J. Tolerability of beta-blockers in outpatients with refractory heart failure who were receiving continuous milrinone. *Pharmacotherapy* 2007; **27**: 697-706 [PMID: 17461705 DOI: 10.1592/phco.27.5.697]

36 **Zewail AM**, Nawar M, Vrtovec B, Eastwood C, Kar MN, Delgado RM. Intravenous milrinone in treatment of advanced congestive heart failure. *Tex Heart Inst J* 2003; **30**: 109-113 [PMID: 12809251]

37 **Metra M**, Eichhorn E, Abraham WT, Linseman J, Böhm M, Corbalan R, DeMets D, De Marco T, Elkayam U, Gerber M, Komajda M, Liu P, Mareev V, Perrone SV, Poole-Wilson P, Roecker E, Stewart J, Swedberg K, Tendera M, Wiens B, Bristow MR. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J* 2009; **30**: 3015-3026 [PMID: 19700774 DOI: 10.1093/eurheartj/ehp338]

38 **Gattis WA**, O'Connor CM, Leimberger JD, Felker GM, Adams KF, Gheorghiade M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening chronic heart failure. *Am J Cardiol* 2003; **91**: 169-174 [PMID: 12521629 DOI: 10.1016/s0002-9149(02)03104-1]

39 **Lou Q**, Janardhan A, Efimov IR. Remodeling of calcium handling in human heart failure. *Adv Exp Med Biol* 2012; **740**: 1145-1174 [PMID: 22453987 DOI: 10.1007/978-94-007-2888-2_52]

40 **Cowley AJ**, Skene AM. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. Enoximone Investigators. *Br Heart J* 1994; **72**: 226-230 [PMID: 7946771 DOI: 10.1136/hrt.72.3.226]

41 **Uretsky BF**, Jessup M, Konstam MA, Dec GW, Leier CV, Benotti J, Murali S, Herrmann HC, Sandberg JA. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure. Lack of benefit compared with placebo. Enoximone Multicenter Trial Group. *Circulation* 1990; **82**: 774-780 [PMID: 2144216 DOI: 10.1161/01.cir.82.3.774]

42 **Marks AR**. Calcium cycling proteins and heart failure: mechanisms and therapeutics. *J Clin Invest* 2013; **123**: 46-52 [PMID: 23281409 DOI: 10.1172/JCI62834]

43 **Bristow MR**. Treatment of chronic heart failure with β-adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical cardiology. *Circ Res* 2011; **109**: 1176-1194 [PMID: 22034480 DOI: 10.1161/CIRCRESAHA.111.245092]

44 **Györke S**, Carnes C. Dysregulated sarcoplasmic reticulum calcium release: potential pharmacological target in cardiac disease. *Pharmacol Ther* 2008; **119**: 340-354 [PMID: 18675300 DOI: 10.1016/j.pharmthera.2008.06.002]

45 **Mann DL**, Kent RL, Parsons B, Cooper G. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation* 1992; **85**: 790-804 [PMID: 1370925 DOI: 10.1161/01.cir.85.2.790]

46 **Shivalkar B**, Van Loon J, Wieland W, Tjandra-Maga TB, Borgers M, Plets C, Flameng W. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. *Circulation* 1993; **87**: 230-239 [PMID: 8419012 DOI: 10.1161/01.cir.87.1.230]

47 **Kendall MJ**, Lynch KP, Hjalmarson A, Kjekshus J. Beta-blockers and sudden cardiac death. *Ann Intern Med* 1995; **123**: 358-367 [PMID: 7625625 DOI: 10.7326/0003-4819-123-5-199509010-00007]

48 **Mochizuki M**, Yano M, Oda T, Tateishi H, Kobayashi S, Yamamoto T, Ikeda Y, Ohkusa T, Ikemoto N, Matsuzaki M. Scavenging free radicals by low-dose carvedilol prevents redox-dependent Ca2+ leak via stabilization of ryanodine receptor in heart failure. *J Am Coll Cardiol* 2007; **49**: 1722-1732 [PMID: 17448375 DOI: 10.1016/j.jacc.2007.01.064]

49 **Gilbert EM**, Olsen SL, Renlund DG, Bristow MR. beta-adrenergic receptor regulation and left ventricular function in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; **71**: 23C-29C [PMID: 8096672 DOI: 10.1016/0002-9149(93)90083-o]

50 **Bristow MR**. Changes in myocardial and vascular receptors in heart failure. *J Am Coll Cardiol* 1993; **22**: 61A-71A [PMID: 8397233 DOI: 10.1016/0735-1097(93)90465-d]

51 **Lader AS**, Xiao YF, Ishikawa Y, Cui Y, Vatner DE, Vatner SF, Homcy CJ, Cantiello HF. Cardiac Gsalpha overexpression enhances L-type calcium channels through an adenylyl cyclase independent pathway. *Proc Natl Acad Sci USA* 1998; **95**: 9669-9674 [PMID: 9689139 DOI: 10.1073/pnas.95.16.9669]

52 **Hoeper MM**, Boeker KH. Overdose of metoprolol treated with enoximone. *N Engl J Med* 1996; **335**: 1538 [PMID: 8927102 DOI: 10.1056/nejm199611143352017]

53 **Travill CM**, Pugh S, Noble MI. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. *Clin Ther* 1994; **16**: 783-792 [PMID: 7859237]

54 **Galie N**, Branzi A, Magnani G, Melandri G, Caldarera I, Rapezzi C, Grattoni C, Magnani B. Effect of enoximone alone and in combination with metoprolol on myocardial function and energetics in severe congestive heart failure: improvement in hemodynamic and metabolic profile. *Cardiovasc Drugs Ther* 1993; **7**: 337-347 [PMID: 8364004 DOI: 10.1007/bf00880157]

55 **Bristow MR**, Shakar SF, Linseman JV, Lowes BD. Inotropes and beta-blockers: is there a need for new guidelines? *J Card Fail* 2001; **7**: 8-12 [PMID: 11605160 DOI: 10.1054/jcaf.2001.26655]

56 **Cutler MJ**, Wan X, Laurita KR, Hajjar RJ, Rosenbaum DS. Targeted SERCA2a gene expression identifies molecular mechanism and therapeutic target for arrhythmogenic cardiac alternans. *Circ Arrhythm Electrophysiol* 2009; **2**: 686-694 [PMID: 19948504 DOI: 10.1161/circep.109.863118]

57 **Luo W**, Grupp IL, Harrer J, Ponniah S, Grupp G, Duffy JJ, Doetschman T, Kranias EG. Targeted ablation of the phospholamban gene is associated with markedly enhanced myocardial contractility and loss of beta-agonist stimulation. *Circ Res* 1994; **75**: 401-409 [PMID: 8062415 DOI: 10.1161/01.res.75.3.401]

58 **del Monte F**, Harding SE, Dec GW, Gwathmey JK, Hajjar RJ. Targeting phospholamban by gene transfer in human heart failure.

Circulation 2002; **105**: 904-907 [PMID: 11864915 DOI: 10.1161/hc0802.105564]

59 **Kaye DM**, Preovolos A, Marshall T, Byrne M, Hoshijima M, Hajjar R, Mariani JA, Pepe S, Chien KR, Power JM. Percutaneous cardiac recirculation-mediated gene transfer of an inhibitory phospholamban peptide reverses advanced heart failure in large animals. *J Am Coll Cardiol* 2007; **50**: 253-260 [PMID: 17631218 DOI: 10.1016/j.jacc.2007.03.047]

60 **Usta E**, Mustafi M, Scheule AM, Ziemer G. Suppressing apoptosis with milrinone simulating extracorporeal circulation: a pilot study. *Thorac Cardiovasc Surg* 2010; **58**: 285-290 [PMID: 20680905 DOI: 10.1055/s-0030-1249925]

61 **Lowes BD**, Higginbotham M, Petrovich L, DeWood MA, Greenberg MA, Rahko PS, Dec GW, LeJemtel TH, Roden RL, Schleman MM, Robertson AD, Gorczynski RJ, Bristow MR. Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group. *J Am Coll Cardiol* 2000; **36**: 501-508 [PMID: 10933364 DOI: 10.1016/s0735-1097(00)00759-2]

62 **Dage RC**, Okerholm RA. Pharmacology and pharmacokinetics of enoximone. *Cardiology* 1990; **77** Suppl 3: 2-13; discussion 27-33 [PMID: 2148277 DOI: 10.1159/000174664]

63 **Sigmund M**, Jakob H, Becker H, Hanrath P, Schumacher C, Eschenhagen T, Schmitz W, Scholz H, Steinfath M. Effects of metoprolol on myocardial beta-adrenoceptors and Gi alpha-proteins in patients with congestive heart failure. *Eur J Clin Pharmacol* 1996; **51**: 127-132 [PMID: 8911876 DOI: 10.1007/s002280050172]

64 **Hall JA**, Ferro A, Dickerson JE, Brown MJ. Beta adrenoreceptor subtype cross regulation in the human heart. *Br Heart J* 1993; **69**: 332-337 [PMID: 8098220 DOI: 10.1136/hrt.69.4.332]

65 **Liggett SB**, Tepe NM, Lorenz JN, Canning AM, Jantz TD, Mitarai S, Yatani A, Dorn GW. Early and delayed consequences of beta(2)-adrenergic receptor overexpression in mouse hearts: critical role for expression level. *Circulation* 2000; **101**: 1707-1714 [PMID: 10758054 DOI: 10.1161/01.CIR.101.14.1707]

66 **Communal C**, Singh K, Sawyer DB, Colucci WS. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. *Circulation* 1999; **100**: 2210-2212 [PMID: 10577992 DOI: 10.1161/01.CIR.100.22.2210]

67 **Yamani MH**, Haji SA, Starling RC, Kelly L, Albert N, Knack DL, Young JB. Comparison of dobutamine-based and milrinone-based therapy for advanced decompensated congestive heart failure: Hemodynamic efficacy, clinical outcome, and economic impact. *Am Heart J* 2001; **142**: 998-1002 [PMID: 11717603 DOI: 10.1067/mhj.2001.119610]

68 **Cuffe MS**, Califf RM, Adams KF, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002; **287**: 1541-1547 [PMID: 11911756 DOI: 10.1001/jama.287.12.1541]

69 **Abraham WT**, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtel TH, Cheng ML, Wynne J. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; **46**: 57-64 [PMID: 15992636 DOI: 10.1016/j.jacc.2005.03.051]

70 **Feldman AM**, Oren RM, Abraham WT, Boehmer JP, Carson PE, Eichhorn E, Gilbert EM, Kao A, Leier CV, Lowes BD, Mathier MA, McGrew FA, Metra M, Zisman LS, Shakar SF, Krueger SK, Robertson AD, White BG, Gerber MJ, Wold GE, Bristow MR. Low-dose oral enoximone enhances the ability to wean patients with ultra-advanced heart failure from intravenous inotropic support: results of the oral enoximone in intravenous inotrope-dependent subjects trial. *Am Heart J* 2007; **154**: 861-869 [PMID: 17967591 DOI: 10.1016/j.ahj.2007.06.044]

71 **Elkayam U**, Tasissa G, Binanay C, Stevenson LW, Gheorghiade M, Warnica JW, Young JB, Rayburn BK, Rogers JG, DeMarco T, Leier CV. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J* 2007; **153**: 98-104 [PMID: 17174645 DOI: 10.1016/j.ahj.2006.09.005]

P- Reviewer: Bonanno C, den Uil CA, Landesberg G, Ueda H
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com