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

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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

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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-
Inotrope dependent advanced HF patients, combining milrinone infusion and BB therapy in advanced stage HF with severe functional limitation. 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. 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. Mehra et al. 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. 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. 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. 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 (< 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. 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. 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. 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. 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

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**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. Although the long-term benefit of beta-blocker (BB) in advanced HF is well established, many patients may be intolerant due to the negative hemodynamic impact of acute therapy and escape the benefits of HF therapy. 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.

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 enoxonime (an PDEI agent available in oral and intravenous formulations in Europe) have demonstrated a positive impact on hospitalization and functional status. Both milrinone and enoxonime have shown to improve left ventricular ejection fraction (LVEF) when used in combination with BBS. 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.

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...
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.[28]. 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[30]. The use of intravenous PDEI permits successful initiation and up titration of BBs in HF patients who are intolerant to BB therapy[13,23-34]. 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 inotropic 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 I-I-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[37] carried out an observational study of 26 inotrope dependent patients (> 8 wk home inotropic 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
| 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 nor epinephrine concentrations | 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) | Not reported | Not reported | Not reported |
| 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, 32%) | 320 (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 III b/IV on milrinone therapy as compared to class II / IIIa CHF without milrinone | Yes (90%)                       | 32                  | Class II-IV Mean: 24 wk           | Successful carvedilol up titration 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 | Not reported |

Table 1 Clinical studies evaluating phosphodiesterase III inhibitors in heart failure
| Reference            | Study Title                                                                 | Treatment/Outcome | NYHA Classification | Duration | Hemodynamic Changes | Other Observations                                                                 |
|----------------------|------------------------------------------------------------------------------|-------------------|---------------------|----------|---------------------|-----------------------------------------------------------------------------------|
| 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%)       | NYHA II-IIV         | 9-12 mo  | Beta blockers significantly inhibit the favorable hemodynamic response to dobutamine. No attenuation occurred with beta blockers and enoximone | Not reported                                                                      |
| Cuffe et al[68], 2002 | Short-term milrinone in addition to standard therapy to improve outcomes in pts with ADHF | Yes (22%)         | NYHA III-IIV        | 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                                                                      |
| Felker et al[30], 2003 | To assess the interaction between HF etiology and response to milrinone in ADHF | Yes (25%)         | NYHA III-IIV        | 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: 26% vs 35% placebo; in-hospital mortality 2.6% vs 3.1% placebo | 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) | Not reported | Enrollment 17 mo | No difference between milrinone and dobutamine with respect to clinical outcomes or hemodynamic measures | 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%)         | NYHA II-III         | Peak VO: 11.4 mL/kg per minute | 88.3% of pts underwent OHT; 3.2% died before transplant | Not reported |
| 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) | 100% NYHA IV        | 10/01-7/03 | Worse inpatient mortality and longer LOS with IV inotropes | 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%)         | NYHA III-IIV        | 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 |

**References:**
- Metra et al[13]
- Cuffe et al[68]
- Felker et al[30]
- Aranda et al[23]
- Brozena et al[22]
- Abraham et al[69]
- Feldman et al[70]
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 reintiation 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.

Worse 6 mo mortality and either mortality/rehospitalization with inotropes (whether alone or with vasodilator)

Not reported | N/A | N/A

Elkayam et al[7], 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 VO2 10.0 | N/A | N/A

Four month trends toward decreased in time to death or re-initation 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.

Gorodeski et al[9], 2009
Relationship between choice of dobutamine or milrinone and mortality in inotrope dependent stage D HF pts

| Yes [5% (dob) vs 34% (mil)] | 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 No difference in first co-primary end-points: All cause mortality, all-cause mortality and CV hospitalizations

Not reported | Not reported | Not reported

Metra et al[10], 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

| Yes (85%) | ESSENTIAL I: 904 | ESSENTIAL II: 950 | N/A | N/A

100% NYHA III-IV Median F/U duration 16.6 mo

Not reported | Palpitations 8% enoximone vs 5% placebo, P = 0.01

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Jaiswal A et al. Phosphodiesterase Inhibitors in end-stage heart failure

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.


daferol calcium (Ca²⁺) handling is thought to be a major contributor to mechanical and electrical dysfunction in HF (Figure 1)[29]. 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 Ca²⁺ overload and sustained beta-1-receptor pathway signaling (Figure 2)[21]. Recent investigations suggest that modulation of

MOLECULAR PATHWAYS SUPPORTING COMBINATION THERAPY
Defective Ca²⁺ handling is thought to be a major contributor to mechanical and electrical dysfunction in HF (Figure 1)[29]. 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 Ca²⁺ overload and sustained beta-1-receptor pathway signaling (Figure 2)[21]. Recent investigations suggest that modulation of

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)[46,50].

In the presence of BB, the harmful sustained B-receptor pathway signaling associated with HF, mediated through cAMP-independent G-α-stimulating protein coupling of Ca⁺ channels[51], is eliminated. The inotropic effect of PDEIs is still maintained through the phosphorylation of phospholamban 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 phospholamban 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 phospholamban 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
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. 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. 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, which is less cardiomyopathic and may even prevent apoptosis. 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.

Clinical scenario
Case 1: 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 milrinone...
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

| Hemodynamic parameters | Patient 1 | Patient 2 | Reference values |
|------------------------|-----------|-----------|------------------|
| RA (mmHg)              | Baseline  | 15        | 5-7              |
| RV (mmHg)              | 15        | 54/15     | 15-30/1-5        |
| PA (mmHg)              | 53/33 (40)| 56/21 (34)| 15-30/4-10; mean < 20 |
| PA O₂ saturation       | 49.50%    | 57%       | 60%-80%          |
| PCWP (mmHg)            | 29        | 15        | < 12             |
| Cardiac index (L/min per meter squared) | 5.1 | 7.1 | 3.3 | 6 |
| PVR (WU)               | 2.68      | 2.95      | 2.6-4.2          |
| Hemoglobin (g/dL)      | 10.2      | 10.2      | 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.
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.

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