

## Case Report

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Volume 4 : Issue 1

Article Ref. #: 1000HROJ4136

### Article History

Received: January 3<sup>rd</sup>, 2017

Accepted: January 24<sup>th</sup>, 2017

Published: January 24<sup>th</sup>, 2017

### Citation

Jaiswal A, Nguyen VQ, Carry B, Le Jemtel TH. Combination therapy with beta blocker and inotrope in decompensated heart failure: A clinical observation. *Heart Res Open J.* 2017; 4(1): 18-22. doi: [10.17140/HROJ-4-136](https://doi.org/10.17140/HROJ-4-136)

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# Combination Therapy With Beta Blocker and Inotrope in Decompensated Heart Failure: A Clinical Observation

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## INTRODUCTION

Inotropic support is contemplated in the presence of ongoing end-organ hypoperfusion or refractory symptoms in decompensated heart failure (DHF). However, inotropic agents may cause tachycardia leading to increased myocardial oxygen demand and arrhythmogenesis.<sup>1</sup> Introduction of beta blocker (BB) therapy in DHF patients requiring inotrope support is discouraged due to the negative hemodynamic impact of acute BB therapy.<sup>2-5</sup> On the other hand, reduction in heart rate by BB therapy results in decreased myocardial oxygen demand and increased ventricular diastolic filling.<sup>6,7</sup> Additionally, early introduction of BB therapy improves outcome in heart failure.<sup>2-5,8</sup>

We describe our clinical experience in two DHF patients with end-organ hypoperfusion while receiving intravenous milrinone who tolerated and derived benefit from addition of BB therapy. We discuss the molecular mechanisms that may support improvement in hemodynamics after addition of BB therapy to intravenous milrinone in DHF. When used together, BB may improve hemodynamics by enhancing inotropic effect of milrinone and mitigates cardiotoxic effects and the risk of arrhythmias associated with milrinone. Moreover, milrinone might counter negative hemodynamic effects of acute BB therapy. We propose that DHF patients receiving intravenous inotrope support with milrinone may benefit from addition of BB therapy in the absence of systemic hypotension.

## CASE PRESENTATIONS

### Case 1

A 69-year-old African-American man with long standing hypertension presented with worsening orthopnea and leg swelling, and was newly diagnosed with non-ischemic cardiomyopathy (normal myocardial perfusion imaging) with severely reduced left ventricular ejection fraction (LVEF) <15% and moderately decreased right ventricular systolic function. Intravenous diuresis led to symptomatic improvement. Once euvolemic he was started on carvedilol 3.125 mg twice daily but developed an acute drop in urine output, worsening of dyspnea, orthopnea, leg swelling and elevated serum lactic acid level. Carvedilol was then discontinued. Inotrope support was started with intravenous milrinone infusion at 0.25 mcg/kg/min. However, no clinical improvement was noted. Persistent sinus tachycardia (heart rate >140 beats per minute) prompted downtitration of milrinone to 0.125 mcg/kg/min. Refractory symptoms, worsened renal function and elevated lactate level despite continuous infusion of high dose loop diuretic and inotropic support prompted a bedside right heart catheterization that showed elevated pulmonary capillary wedge pressure of 22 mmHg and mixed venous oxygen saturation of 52%. Initiation of low dose metoprolol succinate (25 mg) next day decreased the heart rate and improved mixed venous saturation to 66%, and allowed for uptitration of milrinone back to 0.25 mcg/kg/min. This clinical strategy provided persistent diuresis, substantial improvement

in hemodynamic profile, gradual withdrawal of milrinone within 48 hours, and allowed the patient to be discharged on metoprolol succinate 50 mg. The patient did well during clinic visits for next 5 months and lost follow-up subsequently.

## Case 2

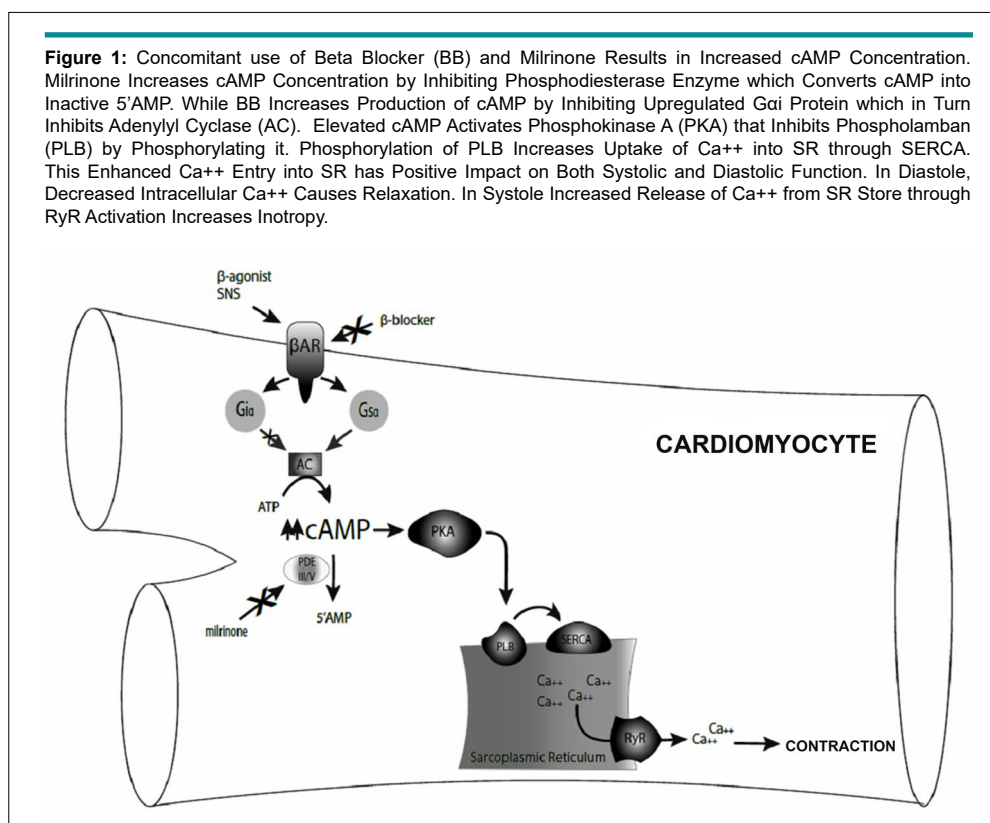
An 84 year-old African-American man with paroxysmal atrial fibrillation presented to emergency room with peripheral edema, decreased functional capacity and was found to be in atrial fibrillation with rapid ventricular response. Laboratory investigation showed elevated N-terminal brain natriuretic peptide (NT-pro BNP), serum lactic acid level and creatinine. A transthoracic echocardiogram revealed severely depressed biventricular systolic function and dilated inferior vena cava. The patient did not respond to escalated doses of intravenous loop diuretic. He declined right heart catheterization and was started on inotrope support with low dose milrinone infusion (0.25 mcg/kg/min). After 24 hours, improvement in fluid status was noted along with improvement in lactic acid and serum creatinine. He was started on metoprolol succinate 25 mg for persistent tachycardia which resulted in improved heart rate. The dose was subsequently increased to 100 mg in next three days and subsequently milrinone was weaned off. The patient was discharged to a nursing facility and after a month he died from aspiration pneumonia.

## DISCUSSION

Initiation of BB therapy in decompensated heart failure is

discouraged due to negative hemodynamic effect from decreased cardiac output.<sup>2-5</sup> Phosphodiesterase inhibitors (PDEI) directly increase cardiac contractility by elevating intracellular cyclic adenosine monophosphate (cAMP). However, it is noteworthy that in the failing myocardium the inotropic effects of type IIIA phosphodiesterase inhibitors (PDEI), which bypass beta adrenoceptors and inhibit cAMP, are also impaired due to post-receptor alterations.<sup>9-12</sup> Upregulation of G- $\alpha$ -inhibitory-protein activity decreases basal cAMP formation in failing myocardium.<sup>13-15</sup> Similarly, antagonism of cAMP-dependent signaling pathway can result in decreased cardiac contractility from acute use of BBs in DHF. The alterations  $\beta$ -adrenergic receptors and secondary messengers in HF have been reviewed in detail by Lymperopoulos et al.<sup>14,15</sup> However, when used in combination, BB may enhance hemodynamic effects related to PDEI therapy by decreasing activity of upregulated G- $\alpha$ -inhibitory-protein resulting in increased cAMP (Figure 1).<sup>9,16-18</sup>

In addition, BB therapy attenuates adverse effects associated with PDEI by modulation of intramyocardial calcium handling.<sup>19,20</sup> Improvement in calcium handling, through targeted SERCA gene expression has shown to retard development of action potential duration alternans and hence decrease arrhythmogenesis.<sup>21</sup> Moreover, these changes may result in improvements in inotropy and lusitropy without increasing arrhythmogenesis and cardiotoxicity.<sup>22-25</sup> Acute BB therapy inhibits  $Ca^{2+}$  leakage from failing *RyR2* even at a low dose, and addition to milrinone suppresses milrinone-induced  $Ca^{2+}$  leakage from failing *RyR2*, leading to greater improvement in cardiomyocyte function in dogs.<sup>26</sup> In the presence of BB,



the harmful sustained  $\beta$ -receptor pathway signaling associated with HF, mediated through cAMP-independent G- $\alpha$ -stimulating protein coupling of calcium channels,<sup>27</sup> is eliminated as well. The use of  $\beta$ 1-selective agent is preferable as its blockade leads to increased  $\beta$ 2-receptor-mediated signal transduction through cross-regulatory mechanisms,<sup>28</sup> which is less cardiomyopathic<sup>29</sup> and may even prevent apoptosis.<sup>30</sup>

Hauptman et al<sup>31</sup> successfully started an intravenous short acting BB agent (Esmolol) in three patients receiving milrinone with prior inability to tolerate BB therapy and transitioned them to oral BB agents. Kobayashi et al<sup>6</sup> reported improved cardiac function after addition of low dose ultra-short acting intravenous BB (Landiolol) in twenty DHF patients who had continued tachycardia on milrinone therapy. In both reports, patients receiving inotrope supports were hemodynamically stable (cardiac index of  $\geq 2.2$  L/minute/m<sup>2</sup>) and were bridged with short acting intravenous BB agents. In our cases, both patients had decreased cardiac output as clinically evident by elevated serum lactic acid and serum creatinine levels and diuretic resistance. In addition, above two reports used low dose BB while our patients tolerated rapid uptitration of the long acting oral BB therapy.

We administered intravenous milrinone for inotropic support as dobutamine comparatively increases myocardial oxygen demand. Additionally, dobutamine in combination with BB leads to increased heart rate and systemic vascular resistance without decrease in pulmonary wedge pressure.<sup>32,33</sup> At lower concentrations most likely pharmacological target of milrinone is phospholamban.<sup>34,35</sup> Inotropic agents that act through inhibition of phospholamban are desirable and best tolerated.<sup>36,37</sup>

Based on our clinical experience, we cannot determine whether increasing BB dose in DHF patients receiving chronic BB therapy will have similar hemodynamic improvement. A *post-hoc* analysis of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study reported worse mortality in patients whose BB were withdrawn upon randomization to milrinone (28.6% vs. 7.7%, *p*-value not reported).<sup>38</sup> Additionally, patients who received both milrinone and BB during hospitalization had the lowest 60-day mortality (5.8%).

## CONCLUSION

Down regulation of  $\beta$ 1-adrenoceptors along with desensitization of  $\beta$ -adrenoceptor-adenylyl cyclase signal transduction is recognized as an important mechanism contributing to impaired contractility in the failing human heart. Accordingly, it is likely that inotropic effect of milrinone may improve after addition of BB therapy. Coadministration of these drugs may offset and eliminate the deficit of each other. While milrinone might counter negative hemodynamic effect of acute BB therapy, the later decreases the risk of adverse arrhythmias associated

with milrinone. Further studies are required to assess whether coadministration of these drugs improves the outcome and becomes a beneficial strategy for the treatment of DHF.

## ESTABLISHED FACTS

- Parenteral inotropic agents are used in decompensated heart failure (DHF) patients with end-organ hypoperfusion or refractory symptoms.
- However, this approach may lead to tachycardia resulting in worsening of myocardial oxygen demand and proarrhythmia.

## NOVEL INSIGHTS

- Addition of beta blocker (BB) therapy to intravenous milrinone support in DHF may result in hemodynamic and clinical improvement.
- When used together, BB may improve hemodynamics by enhancing inotropic effect of milrinone and mitigates cardiotoxic effects and the risk of arrhythmias associated with milrinone. On the other hand, milrinone may counter negative hemodynamic effects of acute BB therapy and facilitate an early introduction of BB therapy.
- We discuss our clinical experience of hemodynamic improvement after addition of oral BB to milrinone in DHF with end-organ hypoperfusion.

## CONFLICTS OF INTEREST

Abhishek Jaiswal; Vinh Q. Nguyen; Brendan J. Carry and Thierry H. Le Jemtel declare no conflicts of interest.

**FUNDING:** None.

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