

Case Report

Corresponding author

Abhishek Jaiswal, MD

Tulane University Heart and
Vascular Institute

Tulane School of Medicine

1430 Tulane Avenue, SL#48

New Orleans

LA 70112, USA

Tel. 1-504-988-1612

Fax: 1-504-988-4237

E-mail: ajaiswal@tulane.edu

Volume 4 : Issue 1

Article Ref. #: 1000HROJ4136

Article History

Received: January 3rd, 2017

Accepted: January 24th, 2017

Published: January 24th, 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)

Copyright

©2017 Jaiswal A. This is an open access article distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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

Abhishek Jaiswal, MD^{*}; Vinh Q. Nguyen, MD; Brendan Carry, MD; Thierry H. Le Jemtel, MD

Tulane University Heart and Vascular Institute, Tulane School of Medicine, 1430 Tulane Avenue, SL#48, New Orleans, LA 70112, USA

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.¹ Introduction of beta blocker (BB) therapy in DHF patients requiring inotrope support is discouraged due to the negative hemodynamic impact of acute BB therapy.²⁻⁵ On the other hand, reduction in heart rate by BB therapy results in decreased myocardial oxygen demand and increased ventricular diastolic filling.^{6,7} Additionally, early introduction of BB therapy improves outcome in heart failure.^{2-5,8}

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

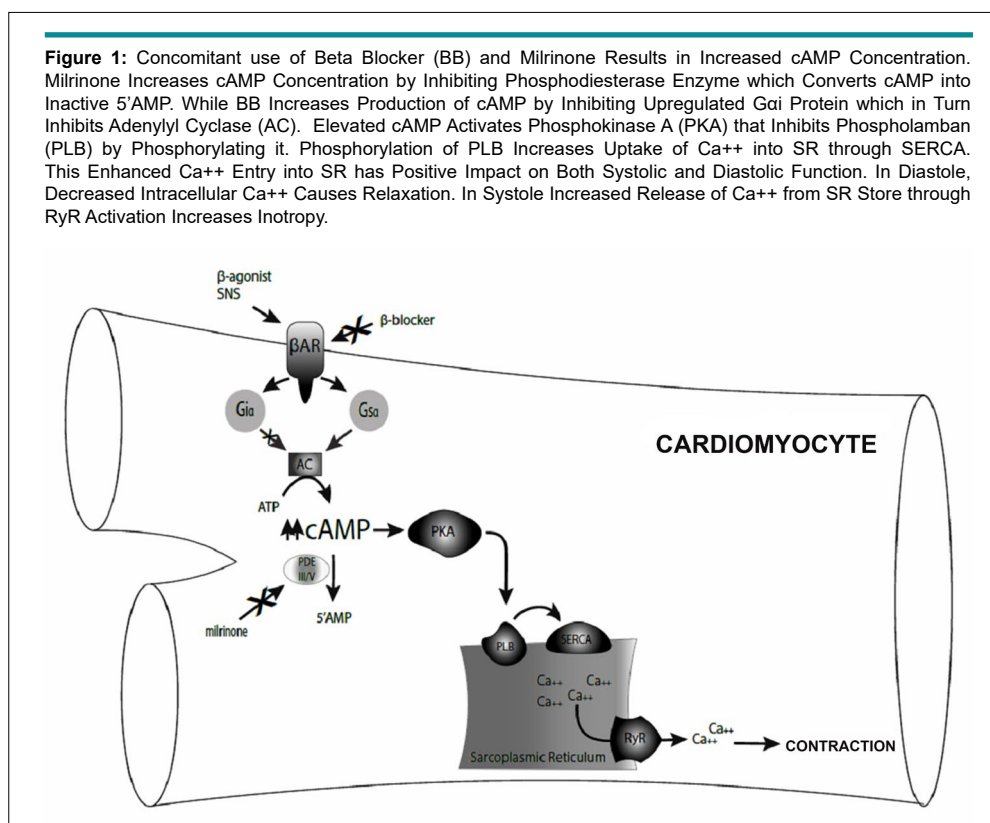
An 84 year-old African-American man with paroxysmal atrial fibrillation presented to emergency room with peripheral edema, decreased functional capacity and was found to be in atrial fibrillation with rapid ventricular response. Laboratory investigation showed elevated N-terminal brain natriuretic peptide (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.²⁻⁵ 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.⁹⁻¹² Upregulation of G- α -inhibitory-protein activity decreases basal cAMP formation in failing myocardium.¹³⁻¹⁵ Similarly, antagonism of cAMP-dependent signaling pathway can result in decreased cardiac contractility from acute use of BBs in DHF. The alterations β -adrenergic receptors and secondary messengers in HF have been reviewed in detail by Lymperopoulos et al.^{14,15} However, when used in combination, BB may enhance hemodynamic effects related to PDEI therapy by decreasing activity of upregulated G- α -inhibitory-protein resulting in increased cAMP (Figure 1).^{9,16-18}

In addition, BB therapy attenuates adverse effects associated with PDEI by modulation of intramyocardial calcium handling.^{19,20} Improvement in calcium handling, through targeted SERCA gene expression has shown to retard development of action potential duration alternans and hence decrease arrhythmogenesis.²¹ Moreover, these changes may result in improvements in inotropy and lusitropy without increasing arrhythmogenesis and cardiotoxicity.²²⁻²⁵ 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.²⁶ In the presence of BB,



the harmful sustained β -receptor pathway signaling associated with HF, mediated through cAMP-independent G- α -stimulating protein coupling of calcium channels,²⁷ is eliminated as well. The use of β 1-selective agent is preferable as its blockade leads to increased β 2-receptor-mediated signal transduction through cross-regulatory mechanisms,²⁸ which is less cardiomyopathic²⁹ and may even prevent apoptosis.³⁰

Hauptman et al³¹ 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 al⁶ 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 ≥ 2.2 L/minute/m²) 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.^{32,33} At lower concentrations most likely pharmacological target of milrinone is phospholamban.^{34,35} Inotropic agents that act through inhibition of phospholamban are desirable and best tolerated.^{36,37}

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).³⁸ Additionally, patients who received both milrinone and BB during hospitalization had the lowest 60-day mortality (5.8%).

CONCLUSION

Down regulation of β 1-adrenoceptors along with desensitization of β -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.

REFERENCES

1. Felker GM, O'Connor CM. Inotropic therapy for heart failure: An evidence based approach. *Am Heart J.* 2001; 142(3): 393-401. doi: [10.1067/mhj.2001.117606](https://doi.org/10.1067/mhj.2001.117606)
2. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation.* 1995; 92(6): 1499-1506. doi: [10.1161/01.CIR.92.6.1499](https://doi.org/10.1161/01.CIR.92.6.1499)
3. 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(4): 924-931.
4. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999; 353(9169): 2001-2007.

5. Cohn JN, Fowler MB, Bristow MR, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J Card Fail.* 1997; 3(3): 173-179.
6. Kobayashi S, Susa T, Tanaka T, et al. Low dose beta-blocker in combination with milrinone safely improves cardiac function and eliminates pulsus alternans in patients with acute decompensated heart failure. *Circ J.* 2012; 76(7): 1646-1653. doi: [10.1253/circj.CJ-12-0033](https://doi.org/10.1253/circj.CJ-12-0033)
7. Andersson B, Lomsky M, Waagstein F. The link between acute hemodynamic adrenergic beta-blockade and long-term effects in patients with heart failure: A study on diastolic function, heart rate and myocardial metabolism following intravenous metoprol. *Eur Heart J.* 1993; 14(10): 1375-1385. doi: [10.1093/eurheartj/14.10.1375](https://doi.org/10.1093/eurheartj/14.10.1375)
8. Packer M, Coats AJ, Fowler MB, et al. Carvedilol prospective randomized cumulative survival study group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med.* 2001; 344(22): 1651-1658. doi: [10.1161/01.CIR.0000035653.72855.BF](https://doi.org/10.1161/01.CIR.0000035653.72855.BF)
9. Bohm M, Deutsch HJ, Hartmann D, Rosee KL, Stablein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. *J Am Coll Cardiol.* 1997; 30(4): 992-996.
10. Eschenhagen T, Mende U, Nose M, et al. Increased messenger RNA level of the inhibitory G-protein α -subunits G_{i2} in human end-stage heart failure. *Circ Res.* 1992;70:688-696. doi: [10.1161/01.RES.70.4.688](https://doi.org/10.1161/01.RES.70.4.688)
11. Ungerer M, Böhm M, Elce JS, Erdmann E, Lohse MJ. Altered expression of β -adrenergic receptor kinase and β_1 -adrenergic receptors in the failing human heart. *Circulation.* 1993; 87(2): 454-463. doi: [10.1161/01.CIR.87.2.454](https://doi.org/10.1161/01.CIR.87.2.454)
12. Neumann J, Scholz H, Döring V, Schmitz W, von Meyerinck L, Kalmar P. Increase in myocardial Gi-proteins in heart failure. *Lancet.* 1988; 2(8617): 936-937. doi: [10.1016/S0140-6736\(88\)92601-3](https://doi.org/10.1016/S0140-6736(88)92601-3)
13. Danielsen W, v. der Leyen H, Meyer W, et al. Basal and isoprenaline stimulated cAMP content in failing versus nonfailing human cardiac preparations. *J Cardiovasc Pharmacol.* 1989; 14(1): 171-173. Web site: http://journals.lww.com/cardiovascularpharm/Abstract/1989/07000/Basal_and_Isoprenaline_Stimulated_cAMP_Content_in.26.aspx. Accessed January 2, 2017.
14. Lymperopoulos A, Rengo G, Koch WJ. Adrenergic system in heart failure: Pathophysiology and therapy. *Circ Res.* 2013; 113(6): 739-753. doi: [10.1161/CIRCRESAHA.113.300308](https://doi.org/10.1161/CIRCRESAHA.113.300308)
15. Capote LA, Perez RM, Lymperopoulos A. GPCR signaling and cardiac function. *Eur J Pharmacol.* 2015; 763: 143-148. doi: [10.1016/j.ejphar.2015.05.019](https://doi.org/10.1016/j.ejphar.2015.05.019)
16. Shakar SF, Abraham WT, Gilbert EM, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol.* 1998; 31(6): 1336-1340. doi: [10.1016/S0735-1097\(98\)00077-1](https://doi.org/10.1016/S0735-1097(98)00077-1)
17. Sigmund M, Jakob H, Becker H, et al. Effects of metoprolol on myocardial beta-adrenoceptors and Gi alpha-proteins in patients with congestive heart failure. *Eur J Clin Pharmacol.* 1996; 51(2): 127-132. doi: [10.1007/s002280050172](https://doi.org/10.1007/s002280050172)
18. Jaiswal A, Nguyen VQ, Le Jemtel TH, Ferdinand KC. Novel role of phosphodiesterase inhibitors in the management of end-stage heart failure. Novel role of phosphodiesterase inhibitors in the management of end-stage heart failure. *World J Cardiol.* 2016; 8(7): 401-412. doi: [10.4330/wjc.v8.i7.401](https://doi.org/10.4330/wjc.v8.i7.401)
19. 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(9): 23C-29C. doi: [10.1016/0002-9149\(93\)90083-O](https://doi.org/10.1016/0002-9149(93)90083-O)
20. Bristow MR. Changes in myocardial and vascular receptors in heart failure. *J Am Coll Cardiol.* 1993; 22(4 Suppl A): 61A-71A. doi: [10.1016/0735-1097\(93\)90465-D](https://doi.org/10.1016/0735-1097(93)90465-D)
21. 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(6): 686-694. doi: [10.1161/CIRCEP.109.863118](https://doi.org/10.1161/CIRCEP.109.863118)
22. Lou Q, Janardhan A, Efimov IR. Remodeling of calcium handling in human heart failure. *Adv Exp Med Biol.* 2012; 740: 1145-1174. doi: [10.1007/978-94-007-2888-2_52](https://doi.org/10.1007/978-94-007-2888-2_52)
23. Marks AR. Calcium cycling proteins and heart failure: Mechanisms and therapeutics. *J Clin Invest.* 2013; 123(1): 46-52. doi: [10.1172/JCI62834](https://doi.org/10.1172/JCI62834)
24. Bristow MR. Treatment of chronic heart failure with β -adrenergic receptor antagonists: A convergence of receptor pharmacology and clinical cardiology. *Circ Res.* 2011; 109(10): 1176-1194. doi: [10.1161/CIRCRESAHA.111.245092](https://doi.org/10.1161/CIRCRESAHA.111.245092)
25. Györke S, Carnes C. Dysregulated sarcoplasmic reticulum calcium release: Potential pharmacological target in cardiac disease. *Pharmacol Ther.* 2008; 119(3): 340-354. doi: [10.1016/j.pharmthera.2008.06.002](https://doi.org/10.1016/j.pharmthera.2008.06.002)
26. Kobayashi S, Susa T, Ishiguchi H, et al. A low-dose β_1 -blocker in combination with milrinone improves intracellular Ca^{2+} handling in failing cardiomyocytes by inhibition of milrinone-induced diastolic Ca^{2+} leakage from the sarcoplasmic

- reticulum. *PLoS ONE*. 2015; 10(1): e0114314. doi: [10.1371/journal.pone.0114314](https://doi.org/10.1371/journal.pone.0114314)
27. Lader AS, Xiao YF, Ishikawa Y, et al. Cardiac G α overexpression enhances L-type calcium channels through an adenylyl cyclase independent pathway. *Proc Natl Acad Sci U S A*. 1998; 95(16): 9669-9674. Web site. <http://www.pnas.org/content/95/16/9669.short>. Accessed January 2, 2017.
28. Hall JA, Ferro A, Dickerson JE, Brown MJ. Beta adrenoreceptor subtype cross regulation in the human heart. *Br Heart J*. 1993; 69(4): 332-337. doi: [10.1136/hrt.69.4.332](https://doi.org/10.1136/hrt.69.4.332)
29. Liggett SB, Tepe NM, Lorenz JN, et al. Early and delayed consequences of beta (2)-adrenergic receptor overexpression in mouse hearts: Critical role for expression level. *Circulation*. 2000; 101(14): 1707-1714. doi: [10.1161/01.CIR.101.14.1707](https://doi.org/10.1161/01.CIR.101.14.1707)
30. 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(22): 2210-2212. doi: [10.1161/01.CIR.100.22.2210](https://doi.org/10.1161/01.CIR.100.22.2210)
31. Hauptman PJ, Woods D, Pritzker 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(5): 247-249. doi: [10.1002/clc.4950250512](https://doi.org/10.1002/clc.4950250512)
32. Metra M, Nodari S, D'Aloia A, et al. 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(7): 1248-1258. doi: [10.1016/S0735-1097\(02\)02134-4](https://doi.org/10.1016/S0735-1097(02)02134-4)
33. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: Differing hemodynamic effects and individual patient responsiveness. *Circulation*. 1986; 73: III175-III183. Web site. <http://europepmc.org/abstract/med/3510774>. Accessed January 2, 2017.
34. Lowes BD, Higginbotham M, Petrovich L, et al. Low-dose enoximone improves exercise capacity in chronic heart failure. Enoximone Study Group. *J Am Coll Cardiol*. 2000; 36(2): 501-508. Web site. <http://www.pubfacts.com/detail/10933364/Low-dose-enoximone-improves-exercise-capacity-in-chronic-heart-failure-Enoximone-Study-Group>. Accessed January 2, 2017.
35. Dage RC, Okerholm RA. Pharmacology and pharmacokinetics of enoximone. *Cardiology*. 1990; 77(Suppl 3): 27-33. doi: [10.1159/000174664](https://doi.org/10.1159/000174664)
36. 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(3): 224-231. doi: [10.1007/s11886-001-0027-8](https://doi.org/10.1007/s11886-001-0027-8)
37. Bristow MR, Shakar SF, Linseman JV, Lowes BD. Inotropes and beta-blockers: Is there a need for new guidelines? *J Card Fail*. 2001; 7(2 Suppl 1): 8-12.
38. Gattis WA, O'Conner CM, Leimberger JD, Felker GM, Adams KF, Gheorghide M. Clinical outcomes in patients on beta-blocker therapy admitted with worsening heart failure. *Am J Cardiol*. 2003; 91(2): 169-174. doi: [10.1016/S0002-9149\(02\)03104-1](https://doi.org/10.1016/S0002-9149(02)03104-1)