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Review Article

Inotropes in Chronic Beta-Blocker Therapy

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ABSTRACT

The increasing rate of cardiovascular disorders contributes to rising hospitalized patients receive chronic oral beta-blocker therapy. Beta-blockers remain one of the fundamental therapy for chronic heart failure. Still, their role in decompensated heart failure and severe sepsis during hospitalization is often debated and inconsistent in clinical practice. In recent years, evidence of the efficacy and clinical outcomes of beta-blockers in acute heart failure (AHF) have accumulated. Clinical research indicates that chronic beta-blockade withdrawals should be prevented, or as soon as hemodynamic stabilization and euvolemic condition are reached, it should be reinstituted. As a subset of AHF patients with low cardiac output required inotropes, the choice of proper agent is fundamental. Different inotropic agents such as inhibitors of the phosphodiesterase, levosimendan, and dobutamine also their associations with beta-blockers are discussed.

Key words: Inotropes, Beta-blocker, Decompensated heart failure, Severe sepsis.

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INTRODUCTION

Beta-blockers (BB), across all heart failure spectrums (HF), play a critical role in decreasing the mortality rate and improving functional class.[1,2] On the contrary to chronic heart failure (HF), data on the tolerance to beta-blockers are minimal in patients that are highly symptomatic due to decompensation or acute HF in hospitalization. The therapeutic dilemma after an HF exacerbation is the issue of reducing or halting long-term beta-blocker treatment with negative inotropic activity.[3-5] Co-administering inotropes and beta-blockers will attenuate the desirable hemodynamic effects on the inotropic agent.[6]

Prolonged elevated levels of catecholamines correlate well with a poor prognosis. By the fact that beta-blocker in chronic heart failure have a definite survival benefit, one might assume that beta-adrenergic activation also leads to detrimental long-term effects.[7] Though many patients treated with beta-blocking agents improved, a small percentage of patients may exacerbate or deteriorate and require hospitalization after the initiation. Therefore, in advanced HF patients and patients who have already received beta-blocker maintenance therapy who do not tolerate beta-blocker initiation, concomitant treatment of the inotropic and beta-blocker agent may be required.[8,9]

Increasing long-term mortality has always been a problem considering the inotropic agent, despite the short-term improvement in hemodynamic and symptoms. Indeed, according to the latest published heart failure guidelines from the European Society of Cardiology, inotrope should be reserved for patients with a severe reduction in cardiac output resulting in impaired vital organ perfusion, which occurs most often in hypotensive AHF (Class IIb recommendation, level of evidence C).[10] If beta-blockade is presumed to contribute to hypotension upon hypoperfusion, levosimendan or a PDE III inhibitor may be considered to counter the effects of beta-blockade (Class IIb recommendation, level of evidence C).[10] The dosage and the corresponding recommendation class and level of evidence of each inotrope in acute heart failure are also outlined in Table 1.

Dobutamine in patients treated with beta-blockers

Dobutamine has the capability to stimulate beta-1, beta-2, and alpha-1 receptors, enhancing myocardial contractility, and therefore cardiac output with a slight reduction in systemic vascular resistance.[11] Thus, the inotropic effects of dobutamine are based on the extent of occupancy of the beta-adrenergic receptors and its signal transduction pathway.[12] High doses of beta-blockers will counteract the dobutamine pharmacologic actions. The inhibition and simultaneous stimulation of the same receptors (β1, β2, and α) appear logical to be inefficient. Nevertheless, the selectivity of the beta-blocker may play a major role in determining the dobutamine response to the beta-blocker. Dobutamine was evidently unable to improve cardiac index and heart rate when combined with non-selective beta-adrenoreceptor blockers (carvedilol) and only to a limited extent with β-1 selective blockers (metoprolol).[13,14] This observation may be explained by the fact that (1) metoprolol has a 75-fold selectivity for β1 over β2 receptor[15], while the affinity of dobutamine is considerably high for β2 receptor[16,17], which have significant inotropic and chronotropic activity and are left unoccupied, (2) long term therapy with metoprolol may induce upregulation of the β1 adrenoreceptor, which in turn may preserve or even enhance dobutamine response[15,18], where carvedilol does not.[8,19] Inotropic drugs with different cellular pathways clearly might serve as an alternative in this situation.

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Table 1: Positive inotropes in acute heart failure with recommendation classes and levels of evidence.

Inotrope	Intravenous bolus dose	Intravenous maintenance dose	Recommendation class	Level of evidence
Dobutamine	No	2–20 µg/kg/min	IIb	C
Dopamine	No	3–5 µg/kg/min; inotropic (inotropic effect) >5 µg/kg/min: inotropic and vasoconstriction effect	IIb	C
Milrinone	25–75 µg/kg over 10–20 min	0.375–0.75 µg/kg/min	IIb	C
Enoximone	0.5–1.0 mg/kg over 5–10 min	5–20 µg/kg/min	IIb	C
Levosimendan	6 to 12 µg/kg over 10 min	0.05 to 0.2 µg/kg/minute	IIb	C

(modified from Ponikowski *et al.*[10])

When is it safe to initiate beta-blocker in those patients with beta-adrenergic inotropic agents?

There is a lack of evidence regarding this issue. Based on its duration of action that is generally short (T½= 2 minutes), dobutamine is rapidly metabolized by catechol-0-methyltransferase.[20] It could be safely assumed to initiate a beta-blocker soon after successful weaning of dobutamine.

The importance of initiating beta-blocker on predischarge hospitalized HF patients was evaluated in the IMPACT-HF trial, where predischarge initiation of carvedilol was associated with better compliance of beta-blocker until 60 days after hospitalization (91% vs. 73%, P < 0.0001) without increasing side effects or duration of hospital stay. Thus, beta-blockers should be initiated once hemodynamic stability and euvolemic state are obtained, ideally before the patient leaves the hospital.[16,17]

Phosphodiesterase III inhibitors in patients treated with beta-blockers

Milrinone and enoximone have important differences from dobutamine. The type III PDE inhibitors worked downstream to the β-1 by blocking the breakdown of cyclic adenosine monophosphate in the myocardium and vascular smooth muscle, leading to increased intracellular calcium, producing positive inotropic and lusitropic effects. [8] The rationale behind the combination of PDE III inhibitors with beta-blocker is that, owing to their site of action that beyond the beta-adrenergic receptor, PDE III inhibitors could maintain their hemodynamic effects in the presence of beta-blockade.[21]

A study by Lowes *et al.*[22] evaluated the efficacy of milrinone and dobutamine in patients chronic carvedilol-treated patients. Milrinone administration during concomitant carvedilol therapy significantly increased cardiac index and decreased mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), and mean arterial blood pressure (MAP) without altering heart rate. In contrast, dobutamine only improved cardiac index at high doses, which is not usually used for heart failure treatment (15–20 µ/kg/min). At these doses, dobutamine also increased heart rate, MAP, and mPAP. These data are in accordance with a study by Metra *et al.*[14], which compared the hemodynamic effects of dobutamine and enoximone before and after long-term administration of metoprolol or carvedilol in chronic HF patients. As previously mentioned, carvedilol, and to lesser extent metoprolol, significantly inhibited the desirable hemodynamic effect of dobutamine. At the same time, in the face of beta-blockade, enoximone could maintain or even enhanced its hemodynamic effects. Besides, beta-blockers can minimize the negative effects of PDE III inhibitors by reducing the heart rate along with their pro-arrhythmic effects.[23] This evidence generally supports the combination of PDE III inhibitors with a beta-blocker, especially carvedilol, when inotropes therapy is necessary. The recommendation from the 2016 ESC HF guidelines supports the use of PDE III inhibitors to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequent hypoperfusion (Class IIb recommendation, level of evidence C).[10] An important drawback from milrinone would be from the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial[24], with an ischemic etiology, milrinone showed a trend towards higher rates of adverse clinical outcomes.

Levosimendan in patients treated with beta-blockers

In acute decompensated HF states, levosimendan is increasingly used as a short term treatment when inotropic support is required. It enhances myocardial contractility by binding to troponin C, increasing the sensitivity to calcium, thus depending on intracellular calcium concentrations.[25] By opening the ATP-sensitive potassium channels, levosimendan exerts its vasodilation effect[26], and at higher doses, it also inhibits cardiac PDE, predominately PDE III.[27] Levosimendan acts beyond the beta-adrenergic receptor and thus preserve its hemodynamic effects in concomitant with beta-blocker use. This distinction also contributes to the 2016 ESC HF guidance that levosimendan is the preferred agent for HF patients pretreated with beta-blocker when an inotropic agent is needed (Class IIb recommendation, level of evidence C).[10] Combining treatment with beta-blocker and levosimendan is also potentially favorable.

The hemodynamic effects of levosimendan were compared with dobutamine in low output HF in Levosimendan Infusion versus Dobutamine (LIDO) trial.[28] In the sub-group analysis, the concomitant administration of beta-blockers with levosimendan had significant effects on the increase in cardiac output and the decrease in PCWP (p=0.01 and p=0.03, respectively). In contrast, the effect of dobutamine on cardiac output and PCWP was mitigated by beta-blockade. The hemodynamic superiority of levosimendan over dobutamine appears to have been enhanced in the face of beta-blockade (Figure 1).[28]

Subgroup analysis of the SURVIVE trial[29] produced interesting insights. Randomization with levosimendan in patients treated with concomitant beta-blocker treatment has been linked to markedly lower mortality at day 5 than dobutamine arm (1.5 vs. 5.1% deaths; HR, 0.29; CI 0.11-0.78, P = 0.01). It should be noted that only half of the patients in the SURVIVE trial received beta-blocker, quite a smaller number than current randomized clinical trials, with much higher usage of beta-blocker. Therefore, it is likely now that the clinical scenario favoring levosimendan use is more popular than at the time of SURVIVE.

In patients with acute decompensated heart failure, Bergh *et al.*[30] compare the effects of a 24-h intravenous infusion of levosimendan and

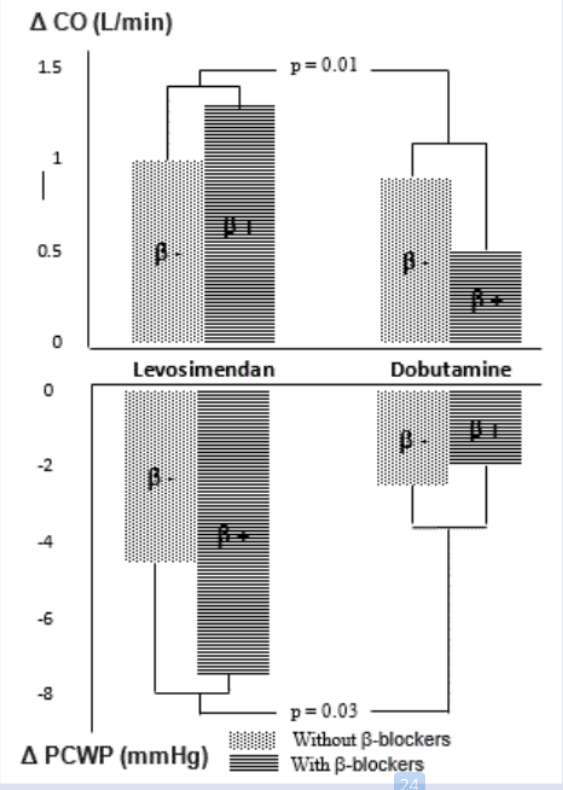

Figure 1: The synergistic effects of beta-blockers on cardiac output (L/min) and pulmonary capillary wedge pressure (mmHg) in heart failure patients (Modified from Follath *et al.*[28]).

a 48-h infusion of dobutamine. The optimal oral treatment, including a beta-blocker for all patients, was given. The cardiac index was improved by both agents, and PCWP decreased. Similar hemodynamic progress was seen over 24-h, while hemodynamic improvement (increased cardiac index and PCWP decrease) and neuro-hormonal improvement (decline in BNP levels) were substantially greater with levosimendan at 48 hours than with dobutamine.

Beta-blocker in severe sepsis and septic shock, which inotropes to use?

Sepsis-induced myocardial depression is related to high sympathetic tone.[31] Septic patients often remain tachycardia even though common factors such as hypovolemia, anemia, agitation, and medication effects are eliminated.[32] The latest and growing evidence suggests that treatment with beta-blockers will improve cardiovascular parameters and, possibly, the survival rate of severe sepsis or septic shock.[33,34] Beta-blockade will limit sympathetic over-stimulation and its related adverse events.[32]

In septic shock patients who were given oral metoprolol to maintained heart rates of less than 95 beats/min, a good safety profile was documented. Morelli *et al.* investigated the effect of continuous infusion of short-acting β-blocker, esmolol in 154 septic shock patients. In this randomized controlled study, esmolol that was titrated to maintain heart rate between 80/min to 94/min was correlated with a reduction in norepinephrine and fluid requirements and a decrease in mortality (28-day mortality of 80.5% in the control group vs. 49.4% in the esmolol group).[35] Furthermore, in a study conducted in 2017 by Fuch *et al.*, from a total of 296 patients with severe sepsis on chronic therapy of beta-blocker, the continuation of beta-blocker was significantly associated with a decreased rate of hospitalization, 28-day (P=0.04) and 90-day mortality rates. [36]

Cardiac depression is reported in up to 60% of septic shock patients, which manifest as global left ventricular hypokinesia[37], which is the major reason for inotropes use during septic shock. Candidates for vasopressor or inotropes to preserve hemodynamic parameters are patients that may not respond to intensive fluid resuscitation. When it is desired to give beta-blocker to such patients, it is important to choose the right inotropes.

The latest Surviving Sepsis Campaign recommendations support the use of dobutamine, up to 20μg/kg/min, as a first choice agent in patients with (a) myocardial dysfunction, as suggested by increased cardiac filling pressures and low cardiac output, (b) persistent hypoperfusion in the presence of (b) adequate intravascular volume and adequate MAP using vasopressor agents. Inotropes dose should be titrated based on perfusion as an endpoint.[37] However, these guideline suggestions are based on a scarcity of evidence on outcomes from randomized controlled trials.

The preference of dobutamine is based mainly on the early goal-directed therapy randomized controlled trial, in which dobutamine was received in only 14 percent of patients.[37]

The utmost importance to notice about dobutamine in septic patients receiving beta-blocker is the dependency of dobutamine on beta-adrenergic receptor occupancy. Although few trials have been conducted, alternative inotropic agents may be used to increase cardiac output in specific scenarios, especially when beta-blocker therapy will be instituted. Every PDE-3 inhibitor has vasodilatory consequences, which may intensify sepsis hypotension, which would theoretically cause harm to its usage throughout this scenario.[41]

Since calcium desensitization plays a significant role in the pathophysiology of septic myocardial depression[38], the use of levosimendan has also been suggested in septic shock. The latest data regarding levosimendan use in these patients have been promising.[39,40] It has been documented that levosimendan could reduce serum lactate levels, offer a reno-protective effect, and restores the cardiac index without increasing demand for myocardial oxygen, contributing to better short-term outcomes.[40,41]

CONCLUSION

In this review, we presented a context for inotropes prescription on patients with chronic beta-blocker therapy, including a summary of possible risks and benefits in the light of more contemporary evidence. Beta-blocker initiation should be pursued once hemodynamic stabilization is established, optimally, before leaving the hospital. Data indicates that persistent beta-blockade elimination during hospitalization should be avoided if possible. The PDE inhibitor or levosimendan that does not interfere specifically with beta-adrenergic receptors can preferably be used for those undergoing beta-blockers and require inotropic therapy.

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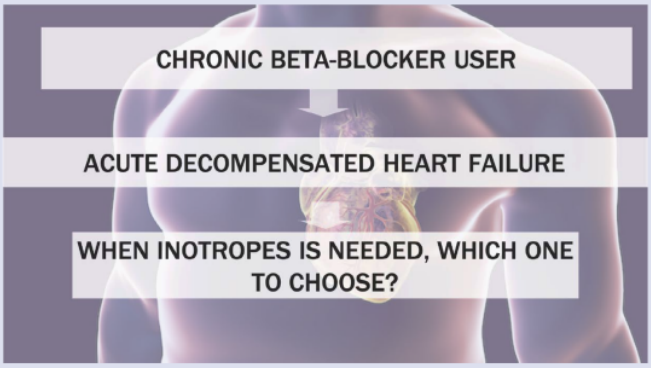

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