Inotropes in the Beta-Blocker Era

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Summary: Beta-adrenergic blocking agents are now standard treatment for mild to moderate chronic heart failure (CHF). However, although many subjects improve on beta blockade, others do not, and some may even deteriorate. Even when subjects improve on beta blockade, they may subsequently decompensate and need acute treatment with a positive inotropic agent. In the presence of full beta blockade, a beta agonist such as dobutamine may have to be administered at very high ($> 10 \mu\text{g/kg/min}$) doses to increase cardiac output, and these doses may increase afterload. In contrast, phosphodiesterase inhibitors (PDEIs) such as milrinone or enoximone retain their full hemodynamic effects in the face of beta blockade. This is because the site of PDEI action is beyond the beta-adrenergic receptor, and because beta blockade reverses receptor pathway desensitization changes, which are detrimental to PDEI response. Moreover, when the combination of a PDEI and a beta-blocking agent is administered long term in CHF, their respective efficacies are additive and their adverse effects subtractive. The PDEI is administered first to increase the tolerability of beta-blocker initiation by counteracting the myocardial depressant effect of adrenergic withdrawal. With this combination, the signature effects of beta blockade (a substantial decrease in heart rate and an increase in left ventricular ejection fraction) are observed, the hemodynamic support conferred by the PDEI appears to be sustained, and clinical results are promising. However, large-scale placebo-controlled studies with PDEIs and beta blockers are needed to confirm these results.

Key words: beta blockers, phosphodiesterase inhibitors, heart failure, milrinone, enoximone

Introduction

Beta-adrenergic blocking agents are standard treatment for patients with mild to moderate chronic heart failure (CHF).^{1,2} The benefits of beta blockade include time-dependent improvements in myocardial function and remodeling, and a decrease in hospitalizations and mortality.^{1,2} The U.S. Carvedilol Trials reported a composite 65% reduction in mortality and a reduction in cardiovascular hospitalizations.³ The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)⁴ recently reported a 32% reduction in all-cause mortality when a beta blocker was added to standard therapy. The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) demonstrated a 34% reduction in all-cause mortality as well as significant improvements in cardiovascular mortality, sudden death, and worsening heart failure.⁵ These findings have led to the recommended use of beta blockers in patients with CHF with a primary or secondary dilated cardiomyopathy phenotype and New York Heart Association Class II or III symptoms.^{1,2}

However, because of the degree to which the failing heart is dependent on adrenergic support,⁶ there is also the potential for adverse effects of antiadrenergic agents in the subset of patients with advanced or severe CHF. The Moxonidine in Congestive Heart Failure (MOXCON)⁷ trial was recently stopped early due to higher mortality in the active arm⁸ moxonidine is a centrally acting inhibitor of sympathetic outflow that reduces systemic and cardiac norepinephrine.⁹ In MOXCON, a marked reduction in cardiac adrenergic support to heart rate, contractility, and/or blood pressure may have been deleterious to patients with more advanced CHF leading to an early increase in mortality.¹⁰

As with moxonidine, there is also potential for adverse effects of beta-blocking agents in subjects with more advanced heart failure. Some patients do not tolerate initiation and up-titration of beta blockade, others exhibit a decrease in left ventricular (LV) function, which has been associated with increased mortality,¹¹ and some subjects who improve go on to decompensate. In these decompensated patients who develop a clinically significant low cardiac output state, inotropic support is often necessary to improve hemodynamics. Thus, for optimal therapeutic management of CHF it is important to un-

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derstand the interaction between positive inotropes and beta blockers. This paper reviews the pharmacologic, hemodynamic, and clinical effects of beta blockers and positive inotropes acting within the beta-receptor pathways, and discusses how the interactions between these two classes of agents may be used to improve clinical outcomes of patients in advanced CHF.

Myocardial Beta-Receptor Signal Transduction in Congestive Heart Failure

The general schema for beta-adrenergic receptor coupled signal transduction is given in Figure 1. Agonist occupancy of both β_1 - and β_2 -adrenergic receptors stimulates adenylyl cyclase (AC), which leads to increased intracellular concentration of second messenger cyclic adenosine monophosphate (cAMP). Increases in intracellular cAMP activate protein kinase A (PKA), which, through phosphorylation of molecular targets such as phospholamban and calcium channels, increases contractile function. The coupling of β_1 and β_2 receptors to AC stimulation and to subsequent changes in systolic and diastolic function is mediated via G proteins that either stimulate (G_s) or inhibit (G_i) AC activity. In model systems, the β_1 -adrenergic receptor is predominantly coupled to G_s , whereas the β_2 receptor is uniquely coupled to both G_s and G_i .¹² In addition, the β_1 receptor may be coupled to ion channel activation by cAMP independent mechanisms,¹³ and may also have exclusive coupling to apoptotic pathways.¹⁴ This heterogeneity of signal transduction pathway coupling creates the po-

tential for the β_1 receptor being selectively coupled to more adverse biological effects than the β_2 receptor.¹

Congestive heart failure is characterized by desensitization of the beta-receptor pathways due, at least in part, to sustained increased cardiac adrenergic stimulation. In this setting, beta-receptor pathways undergo several alterations, which result in reduced response to adrenergic stimulation (Table I). Normal, nonfailing ventricular myocardium contains 75 to 80% β_1 receptors and 20 to 25% β_2 receptors.^{15, 16} In failing myocardium, the percentage of β_1 receptors is reduced to 60 to 70% and the β_2 -receptor population is proportionately increased to 30 to 40%.^{15, 16} This redistribution is a result of a selective downregulation of β_1 -adrenergic receptors in the failing heart, with little or no change in β_2 -receptor numbers.^{15, 16} Downregulation of β_1 receptors is marked in right ventricles failing in the setting of primary pulmonary hypertension,¹⁶ moderate in both ventricles with idiopathic dilated cardiomyopathy,^{15, 17} and mild in ischemic dilated cardiomyopathy.¹⁷ In failing ventricular myocardium, levels of β_1 -receptor protein are reduced in all cellular compartments, including the cell membrane.¹⁶ In addition, a partial uncoupling of β_2 -^{17, 18} and β_1 -adrenergic receptors¹⁷ from functional response occurs secondary to at least two regulatory changes, upregulation in G_{ai} ¹⁹⁻²¹ and receptor phosphorylation.²²

As a result of these signal transduction changes the response to both beta agonists and phosphodiesterase inhibitors (PDEIs) is decreased in the failing heart.²³⁻²⁵ This can be observed in Figure 2, which gives the responses of several PDEIs, including enoximone and milrinone, as well as the beta agonist isoproterenol, in isolated tissue preparations of nonfailing versus failing human hearts. As can be observed in Figure 2, the response to PDEIs and isoproterenol is attenuated in failing right ventricular trabeculae, while the response to the Na channel agonist BDF-9148 is not decreased. The reason for the decreased response of PDEIs is upregulation in G_{ai} .^{17, 19-21}

FIG. 1 Beta-adrenergic signal transduction in human cardiac myocytes. β_1 AR = β_1 -adrenergic receptor; β_2 AR = β_2 -adrenergic receptor; AC = adenylyl cyclase; G_s = stimulatory G protein with α , β , and γ subunits; G_i = inhibitory G protein with α , β , and γ subunits; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; PDE_c = cytosolic phosphodiesterases; PDE_p = particulate, SR-associated PDE III; SR = sarcoplasmic reticulum; PHLMBN = phospholamban; PKA = cAMP-dependent protein kinase A; CAMK = calmodulin-activated kinase; AMP = adenosine monophosphate.

TABLE I Summary of beta-adrenergic pathway abnormalities in various kinds of dilated cardiomyopathy

Abnormality	IDC (LV, RV)	ISCDC (LV, RV)	PPH (RV only)
Downregulation of β_1 -adrenergic receptors	++	+	+++
Uncoupling of β_2 -adrenergic receptors	+	+	+
Uncoupling of β_1 -adrenergic receptors	—	++	—
Upregulation of β ARK-1	++	++	?
Increased activity of G_i	+	+	—
Decreased adenylyl cyclase catalytic activity	+ (RV only)	—	++

Abbreviations: IDC = idiopathic dilated cardiomyopathy, ISCDC = ischemic dilated cardiomyopathy, LV = left ventricular, RV = right ventricular, PPH = primary pulmonary hypertension.

FIG. 2 Effects of various inotropic agents on systolic tension response in nonfailing and failing human right ventricular trabeculae, mean $\pm$ standard error of the mean. OPC-8212 = vesnarinone, FLSQ = flosequinan, ENOX = enoximone, MIL = milrinone, ISO = isoproterenol.

Sites of Action of Myocardial Inotropes

The target of action of positive inotropic agents and their interaction with beta-blocking agents differs depending on the class of drug and pharmacologic mechanism of action. As shown in Figure 1, beta agonists exert their effects through β_1 - and β_2 -receptor occupancy on the surface of cardiac myocytes, with subsequent signal transduction resulting in stimulation of adenylyl cyclase and in activation of cAMP dependent and independent pathways. As shown in Figure 2, preparations of human failing hearts given isoproterenol demonstrate an attenuated systolic tension response when compared with nonfailing controls.^{15–17, 24} In the intact failing heart, the response to the partial beta agonist dobutamine is likewise altered.²⁵ As discussed above, the attenuation of beta-agonist responses in the failing human heart is due to changes in beta-adrenergic receptors and $G_{\alpha i}$. Although beta-blocker therapy may reverse some of the desensitization changes, when a beta agonist is administered in the presence of full-dose beta blockade, no effect of the beta agonist will be realized until the antagonist has been displaced from the receptor via mass action.

Phosphodiesterase type III, which milrinone and enoximone selectively inhibit, is a particulate fraction-associated enzyme, which is anchored to the sarcoplasmic reticulum^{26, 27} and is unaltered in the failing human heart.²⁷ The PDEI-based inotropes are selective, competitive inhibitors of PDE-III and exhibit positive inotropic and vasodilatory effects by inhibiting intracellular degradation of cAMP. In cardiovascular tissues, the increases in cAMP activate myocardial protein kinase A (PKA)²⁷ and in vascular smooth muscle cGMP-dependent protein kinase (PKG).²⁸ In myocardial cells sarcoplasmic reticulum (SR)-associated PDE inhibition leads to PKA-mediated phosphorylation of phospholamban, resulting in increased reuptake of calcium and subsequently increased sarcoplasmic reticulum Ca^{2+} release. In vascular smooth muscle, activation of PKG results in vasodilation.²⁸ Thus, these agents can stimulate cardiac function and produce vasodilation in the absence of beta-adrenergic receptor activation. Because PDE-

III is SR associated and PKA is compartmentalized close to the SR via A-kinase anchoring proteins (AKAPs),²⁹ a selective PDEI-III inhibitor has a relatively specific effect on the SR. Compared with beta agonists, this leads to a preferential effect on systolic and diastolic function versus heart rate.^{30, 31} Because the site of action is beyond beta-adrenergic receptors, beta blockade will not attenuate the favorable hemodynamic actions of PDEIs.

Concomitant Use of Inotropes and Beta Blockers in Advanced Heart Failure: Theoretical Considerations

The concomitant use of a beta agonist and a beta-blocking agent is not rational, since agonist action is blocked by the antagonist. On the other hand, there are theoretical advantages to the concomitant use of PDEIs and beta blockers in advanced CHF. Based on their site of action, the overall response to PDEIs in patients on beta blockade is preserved or even enhanced.^{32, 33} This is, at least in part, because beta blockers can reduce the upregulation of the inhibitory $G_{\alpha i}$ protein.³⁴ Table II compares the positive and negative properties of beta blockers and PDEIs. The profile for beta blockers includes eventual biologic improvement of intrinsic systolic function, a biologically based reversal of remodeling, lowering of heart rate, favorable metabolic effects, antiarrhythmic properties, and anti-ischemic effects.³⁵ However, as noted earlier, the use of beta blockers can present difficulties in patients with advanced heart failure (HF) due to myocardial depression and worsening of heart failure. Moreover, in some patients on high-dose beta blockers, there is impairment in exercise tolerance and other adverse effects, which may preclude their use.

On the other hand, the pharmacologic action of PDEIs produces favorable hemodynamic effects^{36, 37} and an improvement in exercise performance attributable to hemodynamic improvement.^{38, 39} However, at higher doses, PDEIs may increase heart rate and myocardial metabolic requirements and exacerbate ischemia. In addition, the proarrhythmic effects of PDEIs have led to an increase in mortality in multiple randomized studies.^{40–42} As shown in Table II, when given in combination, the potential adverse effects of PDEIs or beta-blocking agents are "cancelled" by the beneficial effects of the other class. Moreover, the pharmacologically based favorable hemodynamic effects of PDEIs and the salutary biologic effects of beta blockers on left ventricular (LV) function are theoretically (Table II) and operationally additive.⁴³

Hemodynamic Effects of Dobutamine versus Phosphodiesterase Inhibitors in Patients Treated with Beta Blockade

Several studies^{32, 44} have described the concomitant use of the partial beta agonist dobutamine and beta-blocking agents in subjects with heart failure. In one study, nine patients with HF treated chronically with the β_1 -, β_2 -, and α -receptor-blocking agent carvedilol were given a graded dobutamine infusion (5, 10, 15, and 20 $\mu\text{g/kg/min}$) and were eval-

TABLE II Cardiovascular effects of beta-adrenergic blocking agents, phosphodiesterase inhibitors, or their combination in subjects with heart failure

Effect	Beta blocker	PDEI	Beta blocker + PDEI
Heart rate	↓	↔ or ↑	↓
Systolic function	↓ then ↑	↑	↑↑
Diastolic function	↔	↑	↑
Arterial vasodilation	↑, ↔ or ↓	↑	↑
Venodilation	↑, ↔ or ↓	↑	↑
LV filling pressure	↔ or ↑, then ↓	↓	↓
MVO ₂	↓	↔ or ↑	↓
Exercise capacity	↔ or ↓	↑	↑
Proarrhythmia	↓	↔ or ↑	↔ or ↓

Abbreviations: PDEI = phosphodiesterase inhibitor, LV = left ventricular, MVO₂ = maximal venous oxygen (consumption).

uated by right heart catheterization and blood pressure monitoring. Dobutamine produced a significant increase in cardiac index, from 2.4 to 3.3 l/min/m.⁴⁴ However, this improvement was observed at doses that are not typically used to treat decompensated CHF (15 to 20 µg/kg/min). At these doses, dobutamine significantly increased heart rate (from 68 to 82 beats/min), mean systemic pressure (from 90 to 117 mmHg), and mean pulmonary artery pressure (from 21 to 30 mmHg). Dobutamine did not significantly alter pulmonary capillary wedge pressure. Thus, dobutamine did produce dose-related increases in cardiac output in patients with CHF treated with carvedilol, but large doses of dobutamine were required to overcome beta blockade.⁴⁴ In another study, it was shown that chronic treatment with carvedilol resulted in more complete blockade of beta receptors than alpha receptors, resulting in increases in blood pressure when high-dose dobutamine was administered.³²

Because dobutamine is a relatively nonselective agonist, chronic treatment with metoprolol (a beta₁-selective-blocking agent) does not produce as complete an inhibition of dobutamine response as does carvedilol.⁴⁴ Moreover, as metoprolol displaces the administered agonist from the beta₁ receptor, the contractile response may even be enhanced compared with pre-beta-blocker treatment.⁴⁵ However, in metoprolol-treated patients, the response to a PDEI is still superior to dobutamine (M. Metra, oral communication).^{32, 44} Thus, beta agonists are not the inotropic agents of choice in treating decompensated patients who are taking beta-blocking agents.

In contrast, as stated earlier, the effects of PDEIs are actively enhanced in subjects treated with beta-blocking agents. This can be seen in Figure 3, which compares the dose responses of dobutamine versus milrinone in two groups of heart failure subjects treated with 50–100 mg/day of carvedilol who were case-matched for baseline LV filling pressures and for a comparable increase in cardiac index. As can be observed in Figure 3, the favorable hemodynamic response to milrinone occurred at a relatively low dose, 25 µg/kg given over 10 min. In con-

trast, dobutamine increased cardiac index only at a relatively high dose (15 µg/kg/min) that was accompanied by an increase in systemic afterload and no decrease in pulmonary artery pressures. Similar results in subjects treated chronically with carvedilol or metoprolol have been obtained with the PDEI enoximone versus dobutamine (M. Metra, oral communication).

Limitations of Beta-Blocking Agents in Chronic Heart Failure

As noted earlier, beta-blocking agents favorably alter the natural history of heart failure in subjects with a dilated cardiomyopathy (primary or secondary) phenotype, and mild to moderate CHF.^{1–5} However, based on results of MERIT-HF⁴⁶ and Beta-Blocker Evaluation Survival Trial (BEST),^{47, 48} beta-blocking agents appear to be much less effective in more advanced HF; that is, subjects in New York Heart Association (NYHA) Class IV in both MERIT-HF⁴⁶ and BEST⁴⁸ derived no benefit from beta blockade in terms of reduction in mortality or hospitalizations. The most likely explanation for the lack of effect of beta blockers in more advanced heart failure is that withdrawal of adrenergic support to the severely failing heart is not helpful or can even harm a substantial group of these subjects.

Long-Term Treatment with Phosphodiesterase Inhibitors and Beta Blockers in Advanced Heart Failure

As discussed above and as outlined in Table II, combination therapy using a PDEI and a beta blocker might attenuate the adverse effects of each while preserving or enhancing each agent's beneficial properties. In a recent study,⁴³ 30 patients with severe CHF (left ventricular ejection fraction = 17.2 ± 1.2%, cardiac index = 1.6 ± 0.1 l/min/m², pulmonary capillary

FIG. 3 Comparison of the hemodynamic effects of milrinone and dobutamine at doses that produce similar responses in cardiac index. CI = confidence index, HR = heart rate, MAP = mean arterial pressure, PCWP = pulmonary capillary wedge pressure, MPAP = mean pulmonary arterial pressure, LVSWI = left ventricular stroke work index, LVSVI = left ventricular stroke volume index.

wedge pressure = 25.2 ± 1.5 mmHg) were treated with a combination of oral enoximone and oral metoprolol. Enoximone was administered at a dosage of 0.5–1.0 mg/kg three times per day. After clinical stabilization, metoprolol was administered at 6.25 mg twice per day and titrated up to a target dosage of 100–150 mg per day. The purpose of this protocol was to attempt to use the PDEI as a bridge to beta blockade in subjects intolerant to the latter or who had CHF too advanced to attempt introduction of beta-blocker treatment.⁴³ Twenty-nine (97%) patients tolerated enoximone and 80% of patients tolerated the addition of metoprolol. The protocol required patients to remain on enoximone for 6 months, whereupon it was withdrawn. However, enoximone therapy had to be reinstated in 52% of patients as a result of deterioration following withdrawal of the PDEI. This finding suggests that the combination therapy had a beneficial effect beyond that produced by beta blockade. Results from this study demonstrated significant improvement in mean LV ejection fraction, from $17.7 \pm 1.6\%$ to $27.6 \pm 3.4\%$; mean heart rate decreased from 101 ± 4.0 to 80.0 ± 4.0 beats/min and NYHA functional class improved from 4.0 ± 0 to 2.8 ± 0.1 . Hospitalizations were reduced, and limited data on survival in this group of patients were promising.⁴³ These data support the idea that the combination of a PDEI and a beta-blocking agent is additive for efficacy and subtractive for adverse effects. Because of these findings, a large placebo-controlled trial of enoximone and metoprolol versus placebo (the “EMPOWER” trial) is underway. In addition, the “PROBE” study—involving the use of milrinone to facilitate the initiation of oral carvedilol therapy in patients hospitalized with NYHA functional class III/IV CHF—will begin soon.

Conclusions

Beta-adrenergic receptor blocker treatment has become an important therapy for subjects with mild to moderate CHF. For decompensated patients with CHF in need of inotropic support, it is important to understand the interaction of inotropic and beta-blocker therapy. The beta-adrenergic agonists and PDEIs used as inotropes have different interactions with beta-adrenergic systems due to their different sites and mechanisms of action. For short-term inotropic support in subjects receiving beta-blocking agents, PDEIs have obvious advantages to beta agonists. Moreover, the combination of PDEI and a beta blocker is promising in the long-term treatment of advanced CHF. However, additional studies are required before definite conclusions can be reached about the safety and efficacy of this combination.

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