Chronic heart failure (CHF) is a leading cause of morbidity and mortality throughout the world. The pathogenesis of CHF is complex but β1-adrenoceptors are critical in the process, because β1-adrenoceptor blockers have been shown to significantly reduce the mortality and hospitalization rates in patients with CHF. Recent animal and human studies have demonstrated that there is an over expression of β3-adrenoceptors in the failing heart, and stimulation of these receptors leads to further depression in ventricular function. We hypothesize that β3-adrenoceptors and their over activities are one of the critical mechanisms of CHF, and addition to conventional heart failure therapies, β3-adrenoceptor antagonism would further improve cardiac function and clinical outcomes.
β3-adrenoceptor antagonism improves clinical outcomes of chronic heart failure

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ABSTRACT

Chronic heart failure (CHF) is a leading cause of morbidity and mortality throughout the world. The pathogenesis of CHF is complex but β₁-adrenoceptors are critical in the process, because β₁-adrenoceptor blockers have been shown to significantly reduce the mortality and hospitalization rates in patients with CHF. Recent animal and human studies have demonstrated that there is an over expression of β₃-adrenoceptors in the failing heart, and stimulation of these receptors leads to further depression in ventricular function. We hypothesize that β₃-adrenoceptors and their over activities are one of the critical mechanisms of CHF, and addition to conventional heart failure therapies, β₃-adrenoceptor antagonism would further improve cardiac function and clinical outcomes.

Key words: Chronic heart failure, β₃-adrenoceptor, left ventricular function, β-blockers.
INTRODUCTION

Chronic heart failure (CHF) is common cardiovascular disease where the heart is unable to supply the body and the heart muscle itself with adequate circulatory volume and pressure. The prevalence of heart failure is approximately 2% in the adult population but it can be as high as 10% in the elderly (1). CHF is associated with significant debilitating symptoms such as fatigue, shortness of breath and edema (1). The annual mortality of CHF can be as high as 40% in severe cases (2).

The sympathetic system has been recognized several decades ago to play a critical role in the pathogenesis and progress of CHF. The failing heart is adrenergically activated, which helps to maintain cardiac performance over the short term by increasing contractility and heart rate (3). However, the continuously increased adrenergic drive present in the failing heart delivers adverse biological signals to the cardiac myocyte via β1-, β2- and α1-adrenergic receptors. This detrimental adrenergic pathway has become the fundamental basis for the use of antiadrenergic agents in the treatment of CHF (4).

A third β-adrenoceptor subtype, the β3-adrenoceptor, has been identified a little more than 10 years ago in human hearts (5). Unlike β1 or β2-adrenoceptors, the function of β3-adrenoceptor is to suppress the contraction and relaxation of the non-failing heart (6). Recent studies have shown a significant upregulation of β3-adrenoceptors in the failing hearts of animal models (7) or patients (8). Although the causal relationship between the upregulation of β3-adrenoceptor and left ventricular dysfunction is still under investigation, given the negative inotropic effects associated with β3-adrenoceptor stimulation, we hypothesize that this subtype of adrenoceptor
plays a critical role in the pathogenesis and progression of CHF. We also hypothesize that in addition to conventional treatments of CHF, β3-adrenoceptor blockers will provide further clinical benefits in terms of mortality and hospitalization.

**Adrenergic signaling in the failing heart**

In the failing human heart, there are 3 adrenergic receptors (β₁, β₂, and α₁) in cardiac myocytes coupled to a positive inotropic response and cell growth (4, 9). β-Adrenergic receptors convert the substrate MgATP to cAMP via a stimulatory Gₛ protein, which activates an effector enzyme adenylyl cyclase (4). cAMP is a positively inotropic and chronotropic second messenger and promotes cell growth (4). α₁-receptors are coupled via a G_q protein phospholipase C. Through the second messenger diacyl glycerol, α₁-receptors, which are also upregulated in the failing heart, activate the growth-promoting protein kinase C family (4). At a later stage of CHF, β₁-adrenoceptors are downregulation but β₂-adrenoceptors are primarily unchanged (8).

During CHF, there is a significant increase in overall and cardiorenal sympathetic nervous activity. Patients with CHF have a 4-fold increase in cardiac norepinephrine spillover (10). Norepinephrine is an exceptionally cardiotoxic substance that produces cardiac myocyte injury in concentrations found in the failing heart (11). Cytotoxicity of norepinephrine appears to be mediated through β- rather than α-adrenergic receptors (11). Animal studies have demonstrated that overexpression of β- receptors produces an overtly cardiomyopathic phenotype and ultimately chamber dilatation and systolic dysfunction (4). Cardiac expression of a constitutively activated α₁-receptor produces concentric hypertrophy (4). These data...
indicate that chronic adrenergic activation observed in CHF is a rather harmful compensatory mechanism and therefore should be counteracted by anti-adrenergic therapies.

**Effect of β₃-adrenoceptors on ventricular contractility and function**

Recent evidence shows that β₃-adrenoceptors are also upregulated in animal or human failing hearts (7,8,12). In a canine heart failure model, β₃ mRNA and protein levels are increased by 73% and 147%, respectively (7). A selective β₃ agonist, BRL-37344, induces dose-dependent depressions of myocyte contraction and relaxation, to a much greater extent in heart failure myocytes than in normal myocytes (7). BRL-induced inhibitions of myocyte contraction and relaxation are not changed by pretreatment with β₁- and β₁-/β₂-adrenoceptor antagonists, but β₃-antagonists completely prevent the BRL-induced contractile dysfunction (7). These data indicate that the negative inotropic action of BRL is coupled to β₃-adrenoceptors.

In the failing human hearts, the expression of β₃-adrenoceptor is increased by 2-3 times, and the positive inotropic effect of isoprenaline is reduced by 75% compared with that observed in nonfailing hearts (8). However, the negative inotropic effect of β₃-adrenoceptor agonists BRL-37344 was only mildly reduced in these failing hearts, which is somewhat different from those observed from animal hearts (7).

The intracellular pathways of β₃-adrenoceptor stimulation are not understood, but some studies suggest that they are through Nitric oxide-cGMP pathways (13).
**Effect of β-blockers on CHF**

Large-scale clinical trials have demonstrated that long-term treatment with β-blockers improves survival, reduces sudden death and hospital admission for worsening heart failure in patients with CHF. Although β₁-selective and nonselective blockers have been used to treat CHF, a recent study has shown that carvedilol, a nonselective β-and α₁-receptor blocker, is superior to metoprolol, a selective β₁-blocker, in improving clinical outcomes of CHF (14).

Most currently used β-blockers for heart failure management bind to β₃-adrenoceptors but at different concentrations, β-blockers exhibit distinct patterns of selectivity and activity at β₁-adrenoceptors (15). The effects of conventional doses of β-blockers on β₃-adrenoceptors of failing cardiomyocytes are not yet thoroughly characterized. The effect of selective β₃-adrenoceptor antagonists on left ventricular function has recently been investigated in a canine model of pacing-induced CHF. In the nonfailing heart, L-748,337, a specific β₃-adrenoceptor antagonist, produces a mild increase in left ventricular contractile performance (16). However, in the beating failing heart and in isolated myocytes from the failing heart, L-748,337 is associated with a significant improvement in left ventricular contraction and relaxation (16). These data suggest selective β₃-adrenoceptor antagonism may offer significant clinical benefits.

**Summary**

In CHF, there is a marked increase in sympathetic tone and cardiac norepinephrine release which downregulates β₁-adrenoceptor system. There is also a significant increase in the

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β₃-adrenoceptor abundance in the ventricles. The upregulated β₃-adrenoceptor pathway exhibits a negative inotropic effect which may contribute to progressive cardiac dysfunction. β-blockers are able to suppress the over activities of sympathetic system and improve the clinical outcomes of patients with CHF. β₃-selective blockers may offer additional clinical benefits by inhibiting the detrimental β₃-adrenoceptor pathway that is over expressed in CHF.
References


