How Do β-Blockers Improve Ventricular Function in Patients With Congestive Heart Failure?

William H. Barry, MD; E. Michael Gilbert, MD

The binding of β-adrenergic agonists such as norepinephrine and isoproterenol to the β-1 adrenergic receptor (AR) in the sarcolemma of the ventricular myocyte increases intracellular levels of cAMP via G, protein-induced stimulation of adenyl cyclase. cAMP activates protein kinase A (PKA), which causes phosphorylation of proteins involved in Ca²⁺ homeostasis, such as phospholamban and the L-type Ca²⁺ channel, increasing the intracellular calcium ion concentration ([Ca²⁺]) transient, and thus causing a positive inotropic effect. It is now very well established that patients with congestive heart failure due to ischemic or idiopathic dilated cardiomyopathy are in a hyperadrenergic state. Treatment of these patients with β-adrenergic receptor-blocking drugs reduces morbidity and mortality, improves ventricular function, and reverses pathological remodeling. Clinical and experimental animal studies have suggested a number of mechanisms by which chronic exposure to this class of drugs, which have a negative inotropic effect in normal myocardium, could have an apparently paradoxical beneficial effect in failing myocardium.

See p 2459

Seminal work by Bristow and associates showed that β-1 AR density is reduced in the failing myocardium, and receptor density is increased by treatment with some β-AR blockers. An increase in β-receptor density may restore toward normal an available positive inotropic reserve in patients with heart failure. In isolated myocytes, a cytotoxic effect of prolonged adrenergic stimulation can be demonstrated, suggesting that β-blockade may reduce a deleterious effect of the chronic hyperadrenergic state on myocyte survival. Treatment with β-blockers also slows the heart rate. Because failing myocardium displays a decrease in contractility with increasing rate of stimulation, this may improve ventricular function. At slow rates of stimulation, the myocyte action potential is prolonged, allowing for more Ca²⁺ influx via Na/Ca exchange, and permitting more complete relaxation and reloading of the sarcoplasmic reticulum (SR) with Ca²⁺, despite a reduced expression of SR Ca²⁺ ATPase SERCA2a, which is present in the myocardium of many patients with heart failure. Finally, the reduced expression of SERCA2a and α-myosin heavy chains may be restored toward normal by changes in gene expression induced by β-blocking drugs. This could improve systolic and diastolic function.

In this issue of Circulation, Reiken et al describe another possible mechanism by which β-blockers may improve SR function and thus calcium homeostasis and contractility in failing myocardium: A reduction in PKA-mediated hyperphosphorylation of the SR calcium release channel. The cardiac calcium release channel, or ryanodine receptor 2 (RyR2), is a macromolecular complex comprised of homotetramers, with each of the 4 subunits containing a PKA phosphorylation site and capable of binding 1 molecule of FK506-binding protein (FKBP12.6). The channel complex, which is opened by exposure to Ca²⁺ entering the myocyte via the L-type Ca²⁺ channel during excitation-contraction coupling, also includes phosphatases, which can induce dephosphorylation. As Reiken et al discuss, work from their group has shown that FKBP12.6 is dissociated from RyR2 by exposure to FK506, or by hyperphosphorylation, and this causes the RyR2 calcium release channel to display an increased sensitivity to Ca²⁺, a greater open probability resulting in a “leaky” channel that could cause SR Ca²⁺ depletion, and impaired cooperativity between RyR subunits. Reiken et al studied myocardium obtained from hearts of 9 patients with heart failure not treated with β-blockers, from 10 patients with heart failure treated with β-blockers, and from 5 normal patients. In patients with heart failure, there was a reduced binding of FKBP12.6 to RyR2 associated with hyperphosphorylation of RyR2 detected by a back phosphorylation technique and abnormal RyR2 channel function in planar lipid bilayers characterized by an increased opening probability and greater prevalence of subconductance states. All these abnormalities were reversed toward normal in myocardium from patients with heart failure who had been treated with β-blockers. Reiken et al suggest that RyR2 hyperphosphorylation due to increased activation of PKA (and reduced phosphatase activity) results in dissociation of FKBP12.6 from RyR2, thus inducing a SR Ca²⁺ leak with SR Ca²⁺ depletion and hence a negative inotropic effect. Treatment with β-blockers is proposed to improve myocardial function by decreasing the degree of phosphorylation of RyR2, thus decreasing the degree of dissociation of FKBP12.6 and enhancing SR function.

It is somewhat surprising that hyperphosphorylation of RyR2 is present in heart failure, in which there is downregulation of β-ARs. Indeed, some studies have shown that phosphorylation of phospholamban, another substrate for PKA-mediated phosphorylation, is actually reduced in myo-
inconsistent with the idea that heart failure is associated with a decreased 
[Ca\(^{2+}\)] transient. This would cause an acute increase in contractility, along with PKA-induced increases in the SR 
[Ca\(^{2+}\)] uptake induced by phospholamban phosphorylation, and the increase in the L-type 
[Ca\(^{2+}\)] current induced by phosphorylation of the Ca\(^{2+}\) channel. This is plausible, but one might question why a positive inotropic effect, rather than a negative inotropic effect resulting from depletion of SR 
[Ca\(^{2+}\)] due to 
[Ca\(^{2+}\)] release channel leakiness, would predominate in the presence of hyperphosphorylation-induced dissociation of 
FKBP12.6 from RyR2. The reason may relate to the degree to which SR 
[Ca\(^{2+}\)] stores can be maintained in the face of an increased SR 
[Ca\(^{2+}\)] leak. For example, FK506 induces depletion of SR 
[Ca\(^{2+}\)] in rabbit myocytes and decreases the [Ca\(^{2+}\)] transient, whereas in mouse SR 
[Ca\(^{2+}\)] stores are not depleted and FK506 increases the transient.15 Thus, in normal myocardium, during sympathetic stimulation with activation of β-adrenergic receptors, stimulation of SR 
[Ca\(^{2+}\)] uptake by phosphorylation of phospholamban might be sufficient to maintain SR 
[Ca\(^{2+}\)] stores despite a SR 
[Ca\(^{2+}\)] release channel leak with a resulting positive inotropic effect due to increased sensitivity of RyR2 to 
[Ca\(^{2+}\)]. In failing myocardium, because of downregulation of SERCA2a and possibly reduced phosphorylation of phospholamban,12 this compensatory increase in SR 
[Ca\(^{2+}\)] uptake might be inadequate to maintain SR 
[Ca\(^{2+}\)] stores.

The immunosuppressive actions of FK506 (tacrolimus) are well known and result from the ability of a complex of FK506 and FKBP to bind to calcineurin and inhibit its phosphatase activity, resulting in the inhibition of T-lymphocyte activation.19 Use of FK506 in pediatric transplant recipients has been reported to be associated with the development of hypertrophic cardiomyopathy.20 Long-term exposure to ryanodine, which impairs SR 
[Ca\(^{2+}\)] release channel function, has been reported to induce hypertrophy in rats.21 Therefore, FK506 could possibly induce hypertrophy in young patients because of its ability to cause dissociation of 
FKBP12.6 from RyR2, thus inducing SR dysfunction. No significant myocardial effects of the use of tacrolimus in adult patients have been recognized, but could theoretically occur. Further study of the clinical significance of modulation of RyR2 function by drugs, intracellular signaling pathways, and other RyR2-associated proteins such as sorcin22 in heart failure and other conditions is clearly warranted.

References


**KEY WORDS:** Editorials heartbeat failure, heart failure, heart failure, ventricles, receptors, adrenergic, beta