One of the most effective means of increasing cardiac output is by activating cardiomyocyte β-adrenergic receptors (βARs). βARs couple primarily to the stimulatory G-protein Gs, which activates adenylyl cyclase; increasing intracellular cAMP levels activate protein kinase A to phosphorylate its substrates troponin I, the L-type Ca2⁺-channels, and phospholamban (PLB), thus enhancing contractility. In the case of PLB, phosphorylation relieves its inhibition of the sarcoplasmic reticulum Ca2⁺-ATPase, thereby altering Ca2⁺ cycling (1). βAR agonists, such as dobutamine, that rapidly increase contractility of the heart have become a mainstay in the acute treatment of decompensated heart failure.

This pathway has also been investigated for potential therapies to treat chronic heart failure, but here paradox abounds. In chronic human heart failure and in many animal models of the syndrome, βAR function is, unexpectedly, limited by several molecular mechanisms. These include a decrease in the expression and coupling of the β1AR subtype, a decrease in the coupling of the β2AR subtype, an increase in expression of the inhibitory G protein Gi, an increase in the expression of the βAR kinase (which phosphorylates and desensitizes βARs), and a decrease in expression or function of adenyl cyclase. Because the consequent decrease in βAR signaling limits energy expenditures in a heart that has little metabolic reserve, this response is generally thought to be adaptive. Indeed, judicious administration of βAR antagonists (β blockers) in chronic heart failure can improve cardiac performance (2). However, because these changes each alter βAR function in different ways, it would be naive to assume that they are all beneficial; some may well be adaptive — acting to oppose the progression of failure — while others are maladaptive. Delineating the mechanisms that uncouple βAR activity from contractility in models of failing ventricular function should provide insight into the critical lesions for adaptive and maladaptive regulation and help identify the most appropriate targets for therapeutic intervention.

Toward this end, a number of transgenic and gene ablation mice have been created, in which various components of the pathway are amplified or missing. These studies have yielded some intriguing results. For example, a low level of β2AR overexpression in the hearts of transgenic mice is well tolerated, with persistent enhancement of ejection fraction and absence of histopathological findings (3, 4). In contrast, low-level overexpression of the β1AR subtype results in cardiomyopathy with depressed contractile function (5, 6). Such results indicate that although β1AR and β2AR each couple to Gi, these receptor subtypes must engage distinct signaling pathways. Thus, it appears that β1AR, but not the β2AR, can couple to the inhibitory G-protein, Gi, which may lead to an attenuated cAMP response (7) or to the activation of other, less-well-defined pathways (8). β2AR can also affect ion flow through the type III Na⁺/H⁺ exchanger by binding the Na⁺/H⁺ exchanger regulatory factor (9). Recent studies (10) also indicate that the two subtypes have different distributions within membrane microdomains of the myocyte, which may be another critical distinction. Interestingly, overexpression of adenyl cyclase types V and VI in transgenic mouse hearts results in enhanced ventricular performance without apparent deleterious effects (11, 12), suggesting that cAMP alone may not be the only second messenger that is necessary for adrenergic mediated toxic effects.

As the characterization of these genetically altered mice unfolds, various cross-breeding experiments are being carried out between mouse models of cardiomyopathy and other transgenic or knockout lines, in hopes of correcting specific aspects of the deranged signaling seen in the various models. In this issue of the JCI, Freeman et al. (13) report on the outcomes of altering three components of the signal transduction pathway in a mouse model of hypertrophic cardiomyopathy (HCM). HCM mice overexpress a modified myosin heavy chain, which results in hypertrophy followed by ventricular dilatation, depressed fractional shortening and exercise intolerance (14, 15). Freeman et al. (13) crossed these mice, which show evidence of βAR dysfunction, with other strains that either overexpress the β2AR in the heart, express a βAR kinase inhibitor (βARKet) in the heart, or are genetically ablated for PLB (PLB-null). Previous studies, confirmed here, showed that these perturbations each lead to enhanced contractility (16–18). However, their effects on the course of ventricular failure in the HCM mice were quite different. The HCM/β2AR mice initially show enhanced systolic function over that of nontransgenics, but by 8 months, the fractional shortening of their cardiac muscles is reduced, and half of the mice are dead. In contrast, HCM/PLB-null mice and HCM/βARKet mice show normal fractional shortening throughout the 12-month study period. Furthermore, hypertrophy occurs in the HCM/β2AR and HCM/PLB-null mice but not the HCM/βARKet mice. The expression profiles of three hypertrophy related genes, β-myosin heavy chain, atrial natriuretic factor, and α-skeletal actin also differ in the groups. Normal expression of these genes is not found in any of the crossbred mice, but PLB-null–crossed mice showed the greatest improvement.
in β-myosin heavy chain expression, whereas the most favorable response for atrial natriuretic factor and α-skeletal actin was with the βARKct-crossed mice. Given that the βARKct mice also show no evidence of myocardial hypertrophy, as assessed by heart-to-body weight ratios, it appears that expression of this peptide had the most favorable chronic effects of the crosses, within the context of the HCM phenotype.

A consistent finding in these types of crossbreeding experiments with the βARKct animal is that beneficial effects are only found when βARK levels or activities are increased. Thus, in the muscle-specific LIM knockout (19), the HCM mouse, and the calasequinrin overexpression (20) models, βARK is increased, and in each case, transgenic overexpression of the inhibitor peptide substantially improves function. In contrast, the G01 overexpressing model of cardiomyopathy, which also displays βAR desensitization, hypertrophy, and marked ventricular dysfunction (21), does not have elevated βARK levels, and in these cases, ventricular function and βAR responsiveness are not rescued with the βARK inhibitor (22, 23). Instead, restoration of other dysfunctional components of βAR signaling improves function in vitro or in vivo (23–25).

The βARKct peptide acts by binding the βγ subunits that are released from G-protein heterotrimers. βγ is required for βARK translocation and thus its ability to phosphorylate βARs. Since its beneficial effects are seen only in systems that feature elevated kinase activity, it appears that the inhibitory βARKct peptide acts specifically on this aspect of the pathogenesis. However, other physiologic and biochemical indices of hypertrophy are also improved by βARKct, and it is intriguing to consider whether blocking βγ may have effects other than inhibiting βARK. Indeed, βγ stimulates tyrosine kinase signaling and phospholipase C activation, which could accelerate hypertrophy. Another consideration is that as cardiac function improves when βγ signaling is attenuated, βAR function returns as a secondary response. This appears to be the case during β-blocker treatment, as βAR function has been reported to improve during successful therapy (2). Finally, βARK phosphorylates multiple G protein–coupled receptors, so the phenotypic improvement in animals expressing the inhibitory peptide may be explained in part by the ability of βARK to desensitize other receptors. It should be noted that βAR overexpression (23) and PLB ablation (26, 27) have improved a number of phenotypic characteristics of other models of cardiomyopathy. A coherent picture of how interdiction at these various points in the pathway can sometimes afford qualitatively similar rescue is still lacking.

Looking ahead to human therapy, because the strategy employed will surely depend on the etiology of the failure and the need for acute or chronic therapy, crossbreeding experiments like those of Freeman et al. (13) are crucial to identify strategies to pursue (or avoid) for the clinical modification of heart failure. However, understanding how these approaches achieve their effects will ultimately provide the greatest impetus for developing new genetic or pharmacologic therapies for human heart failure.