What Is the Role of β-Adrenergic Signaling in Heart Failure?

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Abstract—This review addresses open questions about the role of β-adrenergic receptors in cardiac function and failure. Cardiomyocytes express all three β-adrenergic receptor subtypes—β1, β2, and, at least in some species, β3. The β1 subtype is the most prominent one and is mainly responsible for positive chronotropic and inotropic effects of catecholamines. The β2 subtype also increases cardiac function, but its ability to activate nonclassical signaling pathways suggests a function distinct from the β1 subtype. In heart failure, the sympathetic system is activated, cardiac β-receptor number and function are decreased, and downstream mechanisms are altered. However, in spite of a wealth of data, we still do not know whether and to what extent these alterations are adaptive/protective or detrimental, or both. Clinically, β-adrenergic antagonists represent the most important advance in heart failure therapy, but it is still debated whether they act by blocking or by resensitizing the β-adrenergic receptor system. Newer experimental therapeutic strategies aim at the receptor desensitization machinery and at downstream signaling steps. (Circ Res. 2003;93:896-906.)

Key Words: β-adrenergic receptors ■ G proteins ■ transgenic mice ■ cardiac hypertrophy ■ apoptosis
heart failure? This review will attempt to elucidate open questions in understanding myocardial β-adrenergic signaling with respect to its role in cardiac hypertrophy and failure.

β-Adrenergic Receptor Subtypes and Their Signaling

β-Adrenergic Receptors in the Heart
The classical subdivision of β-receptors defines the β₁ subtype as the one that stimulates cardiac muscle, and the β₂ subtype that relaxes smooth muscle.20 Both receptors couple to Gs and thereby elevate cAMP, but distinct downstream signaling decreases contractility in smooth muscle cells and increases it in cardiomyocytes. However, the β₁-receptor contributes to relaxation of blood vessels21 and the β₂-receptor to cardiac contractility.2 Even though the predominant cardiac β₁ subtype (70% to 80% depending on species) is the strongest stimulus for cardiac function, the expression levels are quite small: no more than 50 to 70 fmol/mg membrane protein in most species. Therefore, there is little receptor reserve.

Expression of the β₂ subtype is essentially limited to adipose tissue,22 but several groups have reported β₁-receptor effects and mRNA in human, guinea pig, and canine heart and cardiomyocytes.3 However, in contrast to its Gs-mediated signaling in adipose tissue, these reports suggest coupling to a nonclassical G α/nitric oxide pathway mediating negative inotropic effects. In mice, cardiac-specific overexpression of β₁-receptors enhanced cardiac contractility,23 and experiments with β₁/β₂ knockout mice have provided no or very modest β₁-receptor effects.4,26,27 Thus, the importance of this subtype remains to be defined.

A fourth receptor subtype, β₃, had been postulated to mediate cardiostimulatory effects of the antagonist CGP12177. However, studies with β₁- and β₂-receptor knockout mice have led to the conclusion that the β₁ effects are mediated by the β₁-receptor.28,29

β-Adrenergic Receptor Signaling
Why should the heart express several different subtypes of β-adrenergic receptors? Evidence has been accumulating that subtype differences are important for cardiac function and failure.

First, the three receptor subtypes have different affinities for their ligands (Figure 1). Second, there is increasing evidence for specific subcellular localizations and distinct signaling pathways. The basic hypothesis is that spatial segregation of receptors allows their association with other—equally segregated—proteins to form “signalosomes” that mediate subtype-specific responses.

Signaling by cardiac β-receptors has been studied in great detail (Figures 1 and 2). The classical common pathway is activation of adenylyl cyclases via Gs, resulting in increased cAMP levels. The primary target for cAMP is protein kinase A (PKA). PKA phosphorylates several proteins that are essential for cardiac function: L-type calcium channels,30,31 phospholamban,32 troponin I,33 ryanodine receptors,34 myosin binding protein-C (MyBP-C),35 and protein phosphatase inhibitor-1.36 This affects cardiomyocyte contractility behavior by increasing Ca²⁺ influx (L-type channel), increasing Ca²⁺ reuptake into the sarcoplasmic reticulum (phospholamban/SERCA), and modulating myofilament Ca²⁺ sensitivity (troponin I, MyBP-C). Another target of cAMP are cAMP-gated HCN pacemaker channels.37

Figure 1. Agonist activation and coupling/signaling properties of β-adrenergic receptor subtypes. GRK indicates G protein–coupled receptor kinase; βArr, β-arrestin; PDE, phosphodiesterase; PI3K, phosphatidylinositol 3-kinase; and AC, adenylyl cyclase. Data from Hoffmann et al.184

Figure 2. Calcium cycling in cardiac myocytes and regulation by PKA. AC indicates adenylyl cyclase; RyR, ryanodine receptor; PLB, phospholamban; SERCA, sarcoplasmic reticulum calcium ATPase; CaM, calmodulin; CaMK, calmodulin-dependent kinase; CaN, calcineurin; GRK, G protein–coupled receptor kinase; NCX, sodium-calcium exchanger; NHE, sodium-proton exchanger; and PP, protein phosphatase.
Most studies agree that in cardiomyocytes the cAMP pathway is stimulated through β_{1}- as well as β_{2}-receptors. However, even though the β_{2} subtype causes greater adenylly cyclase stimulation than the β_{1} subtype in transfected cells^{38,39} and in cardiomyocytes,^{40-41} the β_{1} subtype confers greater functional effects in cardiomyocytes.^{2} One explanation for this difference is that cAMP generated by β_{2}-receptor stimulation is not equivalent to cAMP-generated via β_{1}-receptors. Another explanation is the existence of additional signaling pathways that modify the G_{i}/adenyl cyclase/PKA pathway.

Such additional nonclassical signaling is particularly important for the β_{1} (and perhaps the β_{2}) subtype, but less for the β_{2}-receptor. Many coupling proteins have been identified for the three β-receptor subtypes,^{42} but only a few of them have been demonstrated in the heart (Figure 1). Nonclassical signaling for the β_{3}-adrenergic receptor—studied less—may include a calcium signal not inhibitable by inactive cAMP analogues.^{43} It will be a major task to elucidate the physiological role(s) of these nonclassical signaling pathways.

**Compartmentation of β-Adrenergic Signaling**

Receptor-generated signals are usually measured as global changes in second messenger concentrations, which are implicitly assumed to change in a uniform manner. This simplistic view would mean that intracellular signaling uses neither spatial nor temporal information. However, evidence is accumulating that this is not the case, and that compartmentation of intracellular signaling may be more than an excuse for results that are difficult to interpret.

Studies on intact hearts and isolated cardiomyocytes helped to establish this concept. Work in the 1970s suggested that PKA activation by prostaglandin E and isoprorenaline exerted differential effects on glycogen phosphorylase phosphorylation in rat heart.^{46} Similarly, cAMP accumulation via the glucagon-like peptide receptor was recently found to be completely uncoupled from inotropic effects in cardiomyocytes.^{47} Different “efficacies” of cAMP generated via β-receptor activation or via direct adenyl cyclase stimulation with forskolin further suggested spatial compartmentation of cAMP in cardiomyocytes.^{48} Recent electrophysiological studies showed that localized stimulation of β-receptors on frog cardiomyocytes activated L-type Ca^{2+} channels in the vicinity of the receptors, whereas forskolin activated also distant Ca^{2+} channels.^{49} Inhibition of isoprenaline effects by acetylcholine^{50} and NO were also locally restricted.^{51} Imaging of cAMP in neonatal cardiomyocytes showed that the noradrenaline-induced cAMP signal diffused only ≈1 μm, but phosphodiesterase inhibition led to generalized cAMP elevation.^{52} Thus, cAMP degradation by phosphodiesterases may spatially limit cAMP signals.

Several pieces of evidence point toward differences in compartmentation between β_{1}- and β_{2}-receptors. First, β_{2}-receptors can couple, in addition to G_{i}, also to G_{s}, whereas β_{1}-receptors couple only to G_{i}.^{53} G_{i} coupling is enhanced by PKA-mediated β_{2}-receptor phosphorylation. Second, the PKA phosphorylation pattern induced by β_{1}- and β_{2}-receptor stimulation seems different, at least in some species. Two groups found only β_{1}-induced troponin I phosphorylation in rats,^{54,55} whereas others described phosphorylation via both subtypes in human heart.^{56} Phospholamban phosphorylation has been reported after β_{1}- but not β_{2}-receptor activation in canine and human cardiomyocytes,^{54,57} while in other studies, particularly in human heart, both subtypes caused phosphorylation.^{55,56} β_{2}-Receptor stimulation increased PKA activity in the particulate fraction of cardiomyocytes, whereas after β_{1}-receptor stimulation this increase was limited to the soluble fraction. In adult rat cardiomyocytes, the complete absence of a cAMP signal after β_{2}-receptor stimulation has been reported.^{58}

Which mechanisms permit spatial compartmentation of cardiomyocyte β-adrenergic signaling? First, receptors might have different cell surface localizations. In one study, the β_{1} subtype was copurified with cardiomyocyte caveolae, while the β_{2} subtype was more evenly distributed.^{59} In another study, the β_{1} subtype was preferentially localized in caveolae on rat neonatal cardiomyocytes, and this was taken as a reason for efficient adenyl cyclase coupling.^{60} Second, the receptors are probably embedded into large signalosomes, which might differ between the β_{1} and the β_{2} subtype. β_{2}-Receptor signalosomes containing an entire signalosome chain have recently been demonstrated in neurons.^{60} And third, postreceptor signaling may also be spatially organized.^{61} cAMP signals might be spatially regulated via their site of generation (receptor localization) and via localized destruction (phosphodiesterases). Several experiments show loss of spatial localization after phosphodiesterase inhibition.^{58,52,62} β_{2}-Receptors can actively recruit phosphodiesterase-4 to the plasma membrane.^{63} Downstream signaling proteins also have specific localizations. In particular, PKA is spatially localized via binding to A-kinase anchoring proteins^{64} and the same applies for protein phosphatases^{65} and possibly their inhibitors.

In addition to spatial compartmentation, β-receptor coupling is also temporally regulated. First, β-receptors desensitize. This is most prominent for the β_{1} subtype and small for the β_{2} subtype.^{66,67} Desensitization occurs via receptor phosphorylation either by PKA or by G protein–coupled receptor kinases, GRKs,^{68,69} plus β-arrestins.^{70} Both mechanisms uncouple receptors from G proteins.^{71} In addition, the receptor/β-arrestin complex recruits several proteins that initiate nonclassical signaling pathways. Since the GRK/β-arrestin mechanism is most prominent for the β_{2} subtype, this explains why nonclassical signaling pathways are most prominent for this subtype. Furthermore, PKA-induced phosphorylation of β_{2}-receptors promotes switching from G_{i} to G_{s}^{71,72} And finally, prolonged stimulation results in receptor down-regulation, ie, a reduction in receptor number. In summary, β-receptor signaling is a multifaceted process, and our current understanding seems still incomplete.

**Alterations of the β-Adrenergic System in Heart Failure**

Numerous studies show alterations of the cardiac β-receptor system in failing hearts. They include a reduction of the β_{1} subtype and its mRNA by up to ~50%, correlated to disease severity,^{75,76} while the β_{2}-receptor levels remained unchanged in most studies. It is still not clear why downregu-
lation in heart failure is specific for the \( \beta_1 \) subtype. The remaining \( \beta \)-receptors are desensitized, presumably mostly via GRKs (see below). In addition, up to 2-fold increases of \( \text{Go}_i \)—particularly \( \text{Go}_{\alpha_2} \)—and its mRNA occur early in heart failure\(^\text{12–14,77} \) and may cause reduced responsiveness of many \( G_i \)-coupled receptor systems.\(^\text{78–81} \) In addition, canine heart failure models show downregulation of \( \text{Go}_i \)\(^\text{82} \) and of adenyl cyclases V and VI,\(^\text{83} \) which are rate-limiting in the \( \beta \)-receptor system.\(^\text{84} \) Heart failure–induced elevated catecholamine levels most likely cause all these alterations that functionally limit the contractile reserve.

Even though these changes have been confirmed repeatedly, their interpretation is uncertain. They can be interpreted either as a beneficial mechanism that protects the heart from the detrimental effects of chronic \( \beta \)-receptor stimulation, including arrhythmias, energy dysbalance, hypertrophy, and apoptosis—even though they deprive the heart from the benefits of short-term \( \beta \)-adrenergic responsiveness. Alternatively, they may lead to further deterioration of heart failure, since they disable the heart to meet its demands. Depending on these interpretations, therapeutic strategies might attempt either to inhibit the \( \beta \)-receptor system even further or to restore its sensitivity. Both apparently contrasting strategies are currently being pursued.

**Role of GRKs in Heart Failure**

Increased GRK activity appears to be a major factor contributing to \( \beta \)-receptor desensitization in failing hearts.\(^\text{85,86} \) Numerous studies have demonstrated upregulation of GRK activity and GRK2 mRNA in patients and animal models of heart failure and hypertrophy.\(^\text{11,87,88} \) This has led to the hypothesis that cardiac function might be restored by inhibiting GRKs.\(^\text{86} \) No GRK inhibitors have so far been described that would allow a testing of this hypothesis, but several studies with the C-terminus of GRK2 ("\( \beta \)ARKct") appear to support it. This 184 amino acid C-terminus inhibits GRK-mediated receptor phosphorylation,\(^\text{89} \) and its overexpression has led to reduction of heart failure in several heart failure models.\(^\text{86,90,91} \)

However, again the alternative hypothesis is that increased GRK activity is part of a protective adaptation. This hypothesis would be compatible with the long-term damage caused by chronic stimulation or transgenic \( \beta_2 \)-receptor overexpression,\(^\text{92,93} \) and with the beneficial effects of \( \beta \)-blockers in heart failure patients.\(^\text{16} \) In this case, the beneficial effects of \( \beta \)ARKct might be mediated by mechanisms distinct from GRK2 inhibition.

In fact, \( \beta \)ARKct impairs many \( G\beta\gamma \) pathways, and several lines of evidence suggest that \( G\beta\gamma \) inhibition ("scavenging") is important for its effects. First, the detrimental \( \beta \)-receptor–mediated effects appear to be due more to the cAMP than to nonclassical signaling since (1) transgenic overexpression of the \( \beta_1 \) subtype is more detrimental than that of the \( \beta_2 \) subtype\(^\text{93,94} \) even though the \( \beta_1 \) subtype activates essentially only the cAMP pathway and does not internalize well,\(^\text{6,95} \) and (2) the detrimental effects of \( \beta_1 \)-receptor overexpression are very similar to those of overexpression of \( \text{Go}_i \) or PKA.\(^\text{96–98} \) Second, GRK2 transgenic mice show no overt cardiac pathology,\(^\text{99} \) arguing against a detrimental role of GRK activity per se. Third, in a transgenic mouse model of heart failure, \( \beta \)-blockers conferred a benefit in addition to \( \beta \)ARKct, suggesting an unrelated mechanism of action for the two principles.\(^\text{91} \) And fourth, the protective effects of \( \beta \)ARKct on heart failure progression have been reproduced with N-terminally truncated phosducin,\(^\text{100} \) a supposedly "pure" \( G\beta\gamma \)-binding protein\(^\text{101} \) that did not restore the cAMP signal.

Thus, \( \beta \)-receptor blockade and \( \beta \)ARKct might be regarded as independent and complementary therapeutic principles in heart failure. The usefulness and the mechanisms of \( \beta \)ARKct and of "pure" \( G\beta\gamma \) inhibitors will be questions for future investigations.

**Cardiac \( \beta \)-Adrenergic Receptor Transgenic Mice**

Transgenic cardiac overexpression of \( \beta_1 \)-receptors in mice at 20 to 30 pmol/mg protein led to marked enhancement of basal contractility\(^\text{94} \) but caused no overt cardiac pathology.\(^\text{102} \) Adenovirus-mediated \( \beta_2 \)-receptor overexpression enhanced myocardial contractility in a rabbit heart failure model.\(^\text{103} \) However, later studies showed that 50-fold overexpression of \( \beta_2 \)-receptors was well tolerated, whereas 350-fold overexpression induced cardiac pathology.\(^\text{104} \) High-density \( \beta_2 \)-receptor overexpression rescued left ventricular contractility after myocardial infarction\(^\text{105} \) but worsened cardiac function after aortic banding\(^\text{106} \) and negatively affected several genetic heart failure models,\(^\text{86} \) including \( \text{Go}_i \) overexpression.\(^\text{107} \) Lower levels (30-fold overexpression) had beneficial effects in the same model,\(^\text{107} \) suggesting an expression optimum for enhancing cardiac function via \( \beta_1 \)-receptors.

Cardiac overexpression of \( \beta_1 \)-receptors in transgenic mice caused cardiomyocyte hypertrophy, followed by fibrosis and heart failure.\(^\text{93,108} \) Calcium transients were prolonged, and expression of the sarcoplasmic reticulum (SR) protein junction was reduced.\(^\text{109} \) Interestingly, \( \beta_1 \)-receptor transgenic mice develop marked cardiomyocyte hypertrophy without a major increase in heart weight,\(^\text{93} \) indicating a dramatic loss of ventricular cardiomyocytes, perhaps via apoptosis,\(^\text{108} \) \( \beta_1 \) as well as \( \alpha \) agonists have long been known to cause hypertrophy.\(^\text{110} \) These data indicate that the \( \beta_1 \)-receptor system is ideally suited for short-term increases in cardiac function but causes marked damage after prolonged activation.

The differences reported between \( \beta_1 \)- versus \( \beta_2 \)-receptor overexpression are remarkable. Since both subtypes activate cAMP signaling, they must be due to nonclassical, receptor-specific pathways such as \( \beta_1 \)-receptor coupling to \( G_i \) and mitogen-activated protein (MAP) kinases.\(^\text{72,111,112} \) In addition, compartmentation of cAMP signals might cause differences between \( \beta_1 \) and \( \beta_2 \)-receptor–generated cAMP.\(^\text{98} \) The potential clinical implications of these differences are obvious. For example, \( \beta_1 \)-selective antagonists might be superior to nonselective blockers in heart failure, because they would leave the \( \beta_2 \)-receptor operational. And increasing \( \beta_2 \)-receptors to an optimum level might also be beneficial.\(^\text{103} \)

**Which Mechanisms Mediate Detrimental \( \beta_1 \)-Receptor Effects?**

**Candidate Downstream Targets**

The potentially \( \beta_1 \)-selective damage must be mediated via \( \beta_1 \)-initiated signals. Since the major \( \beta_1 \) signal in cardiomyo-
cytes is the cAMP/PKA pathway, the prime suspects are the targets of PKA-mediated phosphorylation. Identifying the relevant targets is difficult since our knowledge is mostly derived from acute β-receptor stimulation, while in heart failure β-adrenergic activation lasts for years. Adaptive changes and transcriptional/translational alterations may dominate long-term responses. A striking example of opposite effects of short- versus long-term β-adrenergic stimulation is the sodium proton exchanger NHE1.

**Phospholamban**
The most prominent cardiac target of PKA is phospholamban (PLB), a 52 amino acid phosphoprotein that controls SR Ca\(^{2+}\) uptake by inhibiting SERCA.\(^{52}\) PKA-mediated phosphorylation of PLB relieves this inhibition. Experiments with PLB knockout mice indicate that PLB mediates the positive inotropic and part of the positive inotropic β-receptor effects.\(^{113,114}\) Even though phospholamban is a major PKA target in cardiomyocytes, it is probably not responsible for the detrimental β1-receptor effects. First, PLB knockout rescued several (but not all)\(^{115,116}\) heart failure models including β1-receptor transgenic mice,\(^{117}\) suggesting that phospholamban inhibition by PKA is not detrimental. Second, gene therapy approaches inhibiting phospholamban\(^{118,119}\) or augmenting SERCA\(^{120,121}\) ameliorated several heart failure models. However, there may be important differences between mice and humans, since two inactivating mutations of phospholamban have recently been reported to cause heart failure in patients.\(^{122,123}\) At present, it is unclear how these findings can be integrated.

**Other Calcium Regulatory Proteins**
Ryanodine receptor (RyR) hyperphosphorylation by PKA leading to increased open probability has been implicated in the pathogenesis of heart failure.\(^{34}\) Others have disputed this observation\(^{124}\) or attributed the PKA-induced increase in SR Ca\(^{2+}\) release to an indirect mechanism involving phospholamban.\(^{125}\) Thus, the role of RyR phosphorylation in heart failure awaits clarification.\(^{126}\)

PKA-mediated phosphorylation opens L-type Ca\(^{2+}\) channels triggering SR Ca\(^{2+}\) release through the RyR.\(^{114}\) Basal L-type currents are maintained\(^{127}\) in heart failure, but single-channel recordings show an increased open probability.\(^{128}\) Further PKA targets are MyBP-C and troponin I, which may disinhibit myosin actin interaction\(^{13}\) and reduce Ca\(^{2+}\) sensitivity of myofilaments,\(^{129}\) respectively. It is not clear whether these effects contribute to heart failure.

A functional imbalance between pathways in or decreasing diastolic Ca\(^{2+}\) might lead to elevated cytosolic Ca\(^{2+}\) levels as a common final pathway in failing cardiomyocytes.\(^{130}\) The downstream mechanisms exerting possible detrimental Ca\(^{2+}\) effects and the roles of Ca\(^{2+}\)-dependent proteins such as calcineurin and CaM kinase remain to be elucidated.\(^{131}\)

**Protein Phosphatases and Protein Phosphatase Inhibitor-1**
Recent evidence indicates a regulatory role for phosphatases in cardiomyocytes.\(^{132}\) Phosphatase 2A occurs in β2-receptor signalosomes in neurons\(^{60}\) and colocalizes with the RyR.\(^{34}\) Heart failure is accompanied by increased global protein phosphatase (PP) activity.\(^{132}\) The protein phosphatase inhibitor-1, PPI-1, inhibits PP1 only in its PKA-phosphorylated form and seems to amplify β-adrenergic signaling in cardiomyocytes.\(^{133,134}\) PPI-1 mRNA, protein, and phosphorylation are reduced by 2- to 5-fold in failing human hearts,\(^{134,135}\) leading to reduced PP1 inhibition.\(^{132}\) Expression of constitutively active PPI-1 rescued the function of failing cardiomyocytes.\(^{133}\) In order to delineate a role of PPI-1 in heart failure, the proteins regulated by PPI-1–sensitive dephosphorylation need to be identified.

**Sodium Proton Exchanger NHE1**
A remarkable example of how fundamentally short- and long-term effects can differ is the involvement of the cardiac sodium proton exchanger NHE1 in the detrimental effects of chronic β-receptor stimulation. Acute β-receptor stimulation may inhibit NHE1.\(^{136}\) However, in β1-receptor transgenic mice NHE1 is upregulated, and pharmacological NHE1 inhibition prevented the development of hypertrophy, fibrosis, and heart failure.\(^{137}\) The mechanisms of the protective effects of NHE1 inhibition, the roles of intracellular sodium and calcium, and NHE1 regulation remain to be investigated.\(^{137,138}\)

**Apoptosis**
β-Receptor stimulation causes apoptosis of isolated rat cardiomyocytes. Different approaches demonstrate proapoptotic effects of β1 and antiapoptotic effects of β2-receptors.\(^{139-141}\) These in vitro studies are paralleled by findings in transgenic mice where β1-receptor and Go, overexpression markedly increased cardiomyocyte apoptosis.\(^{130,132,145}\) However, the studies differ as to the responsible intracellular signaling pathways. β1–Receptor–mediated stimulation of p38 MAP kinase\(^{111}\) and activation of Akt kinase via G\(^141\) have been proposed as antiapoptotic mediators. The proapoptotic effect of β1-receptors has been found to be dependent on reactive oxygen species,\(^{143}\) while others imply PKA-independent activation of CaMK.\(^{43}\) Thus, the mechanistic links for the opposing effects of β1 versus β2-receptor stimulation on cardiomyocyte apoptosis remain uncertain. Nor is it clear how much β2-receptor–mediated apoptosis contributes to heart failure.\(^{144}\)

**Impact on Clinical Medicine**

**β-Adrenergic Receptor Polymorphisms**
Genes for all three β-receptor subtypes contain single nucleotide polymorphisms. Eighteen β1-receptor variants\(^{145}\) and 13 β2-receptor variants have been described,\(^{146}\) but only two β1 and three β2 variant genes are common and have been extensively studied with respect to cardiovascular function (Table). Two attractive hypotheses arise from these studies.

First, the β1-receptor Gly\(^389\) variant (allele frequency 25% in whites, 42% in blacks) shows reduced cAMP signals\(^{147}\) and may represent an impaired variant of the potentially harmful β1-receptor. Clinical studies have given mixed results (Table), suggesting that the more active Arg\(^389\) variant may be detrimental in some contexts. For example, the risk for heart failure in blacks was increased for the Arg\(^389\) variant only when combined with the α2c–receptor deletion polymorphism.
Cardiovascular Role of $\beta_1$-Receptor Arg$^{385}$Gly and $\beta_2$-Receptor Thr$^{164}$Ile Polymorphisms

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<td>Case/control and sibling pair analysis</td>
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<td>10 + 247</td>
<td>Thr$^{164}$Thr &gt; Thr$^{164}$Ile</td>
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(allele frequency 4% in whites, 38% in blacks), which is a risk factor by itself. Large cohort studies investigating more complete sets of such polymorphisms including complete haplotypes will be needed for an answer.

Second, the $\beta_2$-receptor Ile$^{164}$ variant is a rare variant of the potentially protective $\beta_2$-receptor displaying reduced agonist-binding and activity when expressed in fibroblasts or transgenic mice. Healthy volunteers or patients heterogeneous for the Ile$^{164}$ variant exhibited lower chronotropic and inotropic response to the $\beta_2$ agonist terbutaline, reduced exercise capacity, and decreased survival in heart failure (Table). These findings support the hypothesis that an impaired $\beta_2$-receptor represents a risk factor for cardiovascular disease and particularly heart failure.

The Gly$^{16}$ and the Gln$^{27}$ variants of the $\beta_2$-receptor may exhibit altered agonist-induced downregulation and have been associated with decreased exercise capacity. These data are inconsistent and have been discussed elsewhere.

**$\beta$-Blockade in Heart Failure**

Since the pioneering work in the 1970s, it took two decades until $\beta$-blockers turned from contraindication to standard treatment in heart failure. Blocking $\beta$-receptors when cardiac function depends on sympathoadrenergic drive long appeared counterintuitive. Today, three large studies with bisoprolol, metoprolol, and carvedilol show a similar reduction in the risk of death by a third or more, a benefit greater than of any other drug used in heart failure.

**Why Do $\beta$-Blockers Work in Heart Failure?**

How can long-term application of negative inotropic compounds increase cardiac index, exercise capacity, and survival? Two basic mechanisms might explain this paradox: a block of the detrimental consequences of sustained $\beta_1$-receptor stimulation or resensitization of the cardiac $\beta$-receptor system. We are not aware of studies that would prove the energy balance in failing hearts, which show energy...
starvation and high-energy phosphate depletion, since they reduce heart rate and improve diastolic filling and blood flow. β-Blockers apparently induce a partial switch from fatty acid to glucose metabolism by inhibiting carnitine palmitoyl transferase. Finally, β-blockers reverse failure-specific alterations in cardiac gene expression, which may be involved in progression of the disease.

The resensitization hypothesis is supported by the fact that β-blockers upregulate β-receptor levels and normalize elevated GRK and Gαi levels. While these receptors are partially available even in the continued presence of β-blockers, it is doubtful whether their increase is functionally relevant. However, resensitization of downstream elements does result in enhanced responses to phosphodiesterase inhibitors.

Differences Between β-Blockers

Bisoprolol, carvedilol, and metoprolol have been shown to be beneficial in heart failure, and others may follow. Metoprolol and bisoprolol are β1-selective and have modest inverse activity (ie, they decrease the spontaneous activity of the receptor in the absence of agonist), whereas carvedilol is nonselective, shows no inverse activity, dissociates slowly from the receptor, and is a radical scavenger and α1-receptor antagonist. All three compounds led to similar clinical results, but carvedilol was superior to metoprolol in the recent COMET trial. Methodological criticism aside, this trial does not answer the questions of possibly protective β-receptors and whether the additional properties of carvedilol are important. A role for intrinsic activity is supported by the observations that the strong partial agonist xamoterol was detrimental in heart failure, and the weak partial agonist bucindol was ineffective in the BEST trial. The beneficial β-blockers are neutral (carvedilol) or inverse agonistic (bisoprolol, metoprolol). However, because of the low constitutive activity of the β2-receptor, it is uncertain how important inverse agonism is. Taken together, the question is still open which pharmacological properties of β-blockers make them effective in heart failure.

Conclusions

Overwhelming evidence supports a major role for the β-adrenergic system in heart failure. While this system is ideally suited for short-term increases in cardiac performance, its long-term activation is apparently detrimental. These damaging effects appear to be mainly due to stimulation of the β1 subtype, but the responsible signaling pathways need to be identified. Relevant beneficial effects of the β2 subtype remain to be confirmed, again together with the elucidation of the responsible—presumably nonclassical—signaling pathways. And the role of the β2-receptor in the heart is still unclear.

The many changes in the β-adrenergic system in heart failure are most likely a protective adaptation. β-Blockers presumably act by (further) inhibiting the detrimental effects of β1-receptor stimulation, but perhaps also by resensitizing downstream signaling elements. Future questions include the role of resensitization, the essential properties of clinically effective β-blockers, and the importance of the many downstream signaling steps in finding new strategies for the treatment of heart failure.

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