Cardiac adrenergic receptor effects of carvedilol

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Carvedilol is an adrenoceptor antagonist which modulates the activity not only of $\beta_1$ and $\beta_2$ but also of $\alpha_1$ adrenergic receptors present on the cell surface membrane of the human cardiac myocyte. In the heart, carvedilol has approximately 7 times higher potency for $\beta_1$ and $\beta_2$ adrenoceptors, but in the doses 50–100 mg day$^{-1}$ used in clinical practice, it is essentially non-selective. In human myocardial preparations and in cultured heart cells, carvedilol has no intrinsic sympathomimetic activity but is able to identify high affinity agonist-binding receptors whose pharmacological signature is reduction in binding by incubation with guanine nucleotides (guanine nucleotide-modulatable binding). This property is more prominent for the human $\beta_2$ than for the $\beta_1$ adrenoceptor. The property of guanine nucleotide-modulatable binding for carvedilol and structurally related bucindolol correlates with their ability to directly down-regulate $\beta_1$-like receptors present in cultured chick myocytes, and with a lack of reversal of down-regulation of cardiac $\beta$-receptors in patients with heart failure. Carvedilol does not exhibit high levels of inverse agonist activity, which may contribute to its good tolerability in subjects with heart failure.

These data indicate that carvedilol produces a high degree of adrenergic receptor blockade in the failing human heart, and does not re-sensitize the $\beta$-receptor pathway to stimulation by adrenergic agonists. (Eur Heart J (1996) 17 (Suppl B): 8–16)

Key Words: Cardiac adrenoceptors, $\beta$-blockade, $\alpha$-blockade, carvedilol, heart failure.

Introduction

The contractile function of human cardiac myocytes is dependent on two mechanisms (Fig. 1). Intrinsic contractile function, expressed by the Frank-Starling relationship, accounts for the ability of the cardiac myocyte to respond to increased stretch by increased power of contraction and is utilized in the normal heart to maintain pump performance at rest. In addition, the heart possesses the ability to increase or decrease its function substantially and rapidly. In the normal heart, cardiac output can be increased by 2–10 fold within seconds to meet the circulatory demands of increased activity$^{[1]}$. These changes in function are accomplished by mechanisms which may be categorized as those subserving modulated cardiac function$^{[2]}$. Under normal physiological conditions the role of these supportive mechanisms is to allow cardiac pumping performance to meet the circulatory demands of increased activity.

When the heart begins to fail, the modulated function mechanisms are utilized to increase output both by increasing heart rate and contractility. The most important of these mechanisms responsible for the stimulation of cardiac function are the adrenergic pathways. There are two $\beta$-adrenergic receptor subtypes — $\beta_1$ and $\beta_2$ — coupled by the stimulatory guanine nucleotide-binding protein ($G_s$) to the effector
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Figure 2: Schematic representation of four seven-membrane spanning G-protein coupled receptors and their relationship to adrenergic neurons.

Enzyme adenylyl cyclase (AC) on the cell surface membrane of human myocardial cells (Fig. 2). When an agonist binds to β₁ or β₂-receptors, the α subunit of Gα (Gα) increases its binding affinity for GTP, which then binds GTP preferentially to GDP. Liganded αG (αG • GTP) is a powerful stimulus for the activation of AC, which generates cyclic AMP from ATP. Cyclic AMP exerts positive inotropic and chronotropic activity by increasing the flux of calcium through sarcoplasmic granules and increasing Ca²⁺ uptake and release by the cytoplasmic reticulum. In addition, β₁-adrenergic receptors are coupled through Gα to slow Ca²⁺ channel influx by cyclic AMP-independent pathways. When the heart begins to fail, these mechanisms are stimulated by increased cardiac adrenergic activity. This occurs as a consequence of increased sympathetic nerve activity, presynaptic facilitation of norepinephrine release and later by decreased neuronal norepinephrine reuptake. Increased circulating epinephrine also participates in stimulation of cardiac β-adrenergic receptors, particularly in the initial phases of heart failure.

Norepinephrine is 60 times more selective for human cardiac β₁ than β₂ adrenoceptors, but epinephrine is nonselective. This and other observations have led to the concept that the β₁ adrenoceptor subtype is the neurotransmitter (norepinephrine) receptor, while the β₂ subtype is the hormone (epinephrine) receptor.

Immediate stimulation of pump performance by β-adrenergic mechanisms is subsequently aided by two additional means of stabilizing or increasing cardiac function, namely increased plasma volume producing an increase in preload, and hypertrophy of the cardiac myocyte resulting in more contractile elements. Plasma volume expansion results from endocrine and intrarenal mechanisms. Cardiac hypertrophy is produced by a combination of increased myocyte stretch, increased neurotransmitter release, and a variety of autocrine, paracrine and hormonal activities which together enhance cardiac myocyte growth. The specialized subcellular mechanisms mediating the induction and maintenance of hypertrophy belong to the modulated mechanistic influences shown in Fig. 1 and are the means by which the myocyte can increase its contractile state. These specialized growth-promoting mechanisms include but are not confined to the α₁ and β-adrenergic receptor pathways, the angiotensin II (AT₁) receptor pathway and the endothelin 1 (ET₁) receptor pathway. The α₁, AT₁ and ET₁ receptors are all coupled through the effector enzyme phospholipase C (PLC), as well as through other effector enzymes. The second messengers for hypertrophy include diacyl glycerol-protein kinase C, cyclic AMP-protein kinase A, Ca²⁺ and a variety of kinase cascades which terminate in the production of transcription factors.

Signalling of the three major means of increasing cardiac contractile function (β-adrenergic stimulation, increased preload, and cardiac myocyte hypertrophy) is largely accomplished by simultaneous and co-regulated activation or induction of the adrenergic and renin-angiotensin systems (Fig. 3). The β₁, β₂ and α₁ adrenergic and the angiotensin II AT₁ receptors are all 7 membrane-spanning proteins which form binding pockets to trap agonists on the cell surface, and have intra-membrane and intracellular portions to interact with G proteins and various regulatory kinases. The densities of the four receptors varies greatly in human cardiac membranes, ranging in non-failing myocytes from 50–80 fmol mg⁻¹ for the β₁-adrenergic to 3–6 fmol mg⁻¹ for the angiotensin II AT₁ receptor, in a rank order of β₁ > β₂ > α₁ > AT₁ (Fig. 4). The adenylyl cyclase coupled receptors are relatively high density while phospholipase C-coupled receptors are low density, so that their detection in high yield, crude membrane fractions is technically difficult. Each of these modulated function receptors (MFRs) undergoes regulatory changes in chronic myocardial failure, changes that are indicative of exposure to elevated levels of cognate agonist.

Adrenergic • • Renin-angiotensin

Direct cardiotoxicity

Increased heart rate and contractility

Volume overloaded

Increased MVO₂

Increased wall stress

Myocyte damage

Hypertrophy

Decreased contractility

Figure 3 Critical role of the co-activated/induced adrenergic and renin-angiotensin systems in producing myocardial damage and decreased intrinsic myocardial function in chronic heart failure.

Figure 4 Receptor densities for four key seven-membrane spanning G-protein coupled receptors in crude membrane preparations from non-failing (■) and failing (□) human left ventricles. Failing left ventricles were taken from Class III–IV heart failure patients with idiopathic dilated cardiomyopathy who were not being supported by intravenous inotropes or mechanical assist devices. The mean age in non-failing hearts was 36±5 ± 3-2 years, and in failing hearts 37±1 ± 2-5 years (P=NS). P<0-05 vs non-failing.

Regulatory changes in modulated function receptors in failing human ventricular myocardium

In the failing ventricular myocardium, the β₁-adrenergic[8,9] and angiotensin II AT₁ receptors[10] both exhibit down-regulation or loss of receptor protein from all identifiable cellular pools (Fig. 4; Table 1). For both the β₁ and angiotensin II AT₁ receptors, this appears to be due to a reduction in the steady-state abundance of mRNA[12]. In ischaemic cardiomyopathy, β₁ receptors may also be partially uncoupled from pharmacological response. β₂ receptors are not down-regulated in the failing human heart but are weakly uncoupled from pharmacological response[14]. In the failing ventricle, α₁ adrenergic receptors are only slightly up-regulated[6,15,16], and are partially uncoupled from pharmacological response[17].

The variety of additional changes have been described in G proteins, regulatory kinases and adenylyl
Table 1  Adrenergic and angiotensin II signal transduction changes in failing human ventricular myocardium

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Degree of change 0-3+</th>
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<tbody>
<tr>
<td></td>
<td>IDC (LV, RV)</td>
</tr>
<tr>
<td>1. β₁ AR density</td>
<td>↓</td>
</tr>
<tr>
<td>2. β₂ AR coupling</td>
<td>↓</td>
</tr>
<tr>
<td>3. β₁ AR coupling</td>
<td>NSC</td>
</tr>
<tr>
<td>4. G, function</td>
<td>↑</td>
</tr>
<tr>
<td>5. AC catalytic unit</td>
<td>LV, NSC</td>
</tr>
<tr>
<td>6. βARK,</td>
<td>↑</td>
</tr>
<tr>
<td>7. Ang II AT₁ R density</td>
<td>↓</td>
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</table>

cyclase. Several laboratories have identified an up-regulation in the functional activity\[18-20\] or amount\[21,22\] of the inhibitory protein G, which transduces the signals of the M₂ muscarinic, A₁ adenosine or somatostatin receptor pathways for inhibition of adenylyl cyclase activity. No changes have been identified in the α subunit of G, in the failing heart, although its activity is decreased by age\[23\]. The activity and amount of βARK, an agonist-activated receptor kinase, is increased in the failing heart\[11\]. Finally, the activity and the amount of adenylyl cyclase is decreased in pressure overload failure, but not in the volume overloaded left ventricle\[20,24\].

These changes in MFR withdraw the cardiac myocyte from chronic stimulation by the adrenergic and renin-angiotensin systems and are the equivalent of producing incomplete adrenergic blockade with a partial agonist. Since regulatory changes only account for loss of 50-60% of total β-receptor pathway activity in advanced heart failure, the cardiac myocyte remains exposed to some adrenergic stimulation. Chronic stimulation continues through these same pathways due to increased agonist exposure so that these regulatory changes result in the compromise of modulated/stimulated function of the same systems. Thus the prime functional activity of these systems is compromised, while the adverse effects remain.

An important point to emphasize is the difference in adrenergic receptor distribution in failing as compared to that in non-failing myocardium. This may be demonstrated by comparing the relative subtype percentages of β₁, β₂ and α₁ receptors in non-failing and failing ventricular myocardium taken from subjects with idiopathic dilated cardiomyopathy compared to non-failing organ donors. The non-failing myocardium is dominated by the β₁ receptor subtype, whereas failing myocardium exhibits a mixture of receptor subtypes with the β₂ and α₁ receptor comprising approximately 50% of the total population (Fig. 5). In the failing heart, the β₂ receptor represents 35%-40% of the total β-receptor population (Fig. 6). These data would suggest that β₁-selective blocking agents may have inherent limitations in their ability to inhibit the adverse biological effects of elevated cardiac adrenergic drive in the failing human heart.

Figure 5 Adrenergic receptor percentages in non-failing (■) and failing (□) human heart, same subjects as in Fig. 4. *P<0.05 vs non-failing.

Figure 6 β-adrenergic receptor percentages in non-failing (■) and failing (□) human heart, same subjects as in Fig. 4. *P<0.001 vs non-failing.

Pharmacology of carvedilol in human cardiac and model systems

Examination of adrenergic receptor subtype selectivity

Previous studies in human ventricular myocardial and lymphocyte membranes have suggested that carvedilol has a relatively small degree of β₁ selectivity. Computer modelling of [\(^{125}\)I]-ICYP-CGP20712A competition curves generated in mixed receptor populations in
human ventricular myocardium indicates a $\beta_1/\beta_2$ selectivity ratio of approximately 3000-fold. However, the interpretation of these findings is complicated by the agonist binding properties of carvedilol which leads to complex binding curves (Fig. 7). There is also a lack of precision of computer modelling when binding sites are relatively similar in affinity. However, assuming that the binding in the presence of guanine nucleotides ($3 \times 10^{-5}$ M Gpp(NH)p) represents the true antagonist binding affinity, a comparison of the binding properties of carvedilol in multiple human systems indicates that the racemic compound does possess some relative $\beta_1$ receptor selectivity (Table 2). The degree of selectivity varies from 11-fold using membranes from non-failing ventricles, containing >80% $\beta_1$ receptors compared to lymphocyte membranes containing 100% $\beta_2$ receptors, to 2-fold using recombinant human systems. Averaging the dissociation constants across all types of assays

Table 2 Selectivity for human $\beta_1$ vs. $\beta_2$ receptors ($K_i$ or $K_p$, nM ± SEM), in presence of Gpp(NH)p

<table>
<thead>
<tr>
<th>Compound</th>
<th>ICYP competition, curves, nonfailing Ht vs lymph.</th>
<th>Cardiac function assays</th>
<th>ICYP competition, curves, failing heart</th>
<th>Recombinant systems</th>
<th>Average values</th>
<th>Selectivity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$\beta_1$</td>
<td>$\beta_2$</td>
<td>$\beta_1$</td>
<td>$\beta_2$</td>
<td>$\beta_1$</td>
<td>$\beta_2$</td>
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<tr>
<td>Carvedilol (n=5-8)</td>
<td>4.5 ± 1.2</td>
<td>49 ± 16</td>
<td>6.2 ± 2.2</td>
<td>36 ± 24</td>
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<tr>
<td>Bucindolol (n=3-10)</td>
<td>2.7 ± 1.1</td>
<td>9.7 ± 1.7</td>
<td>4.6 ± 3.5</td>
<td>4.3 ± 1.0</td>
<td>5.2 ± 2.0</td>
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<tr>
<td>Metoprolol (n=3)</td>
<td>--</td>
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<td>--</td>
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<td>48 ± 22</td>
<td>3777 ± 1709</td>
</tr>
<tr>
<td>Bisoprolol (n=3)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>70 ± 38</td>
<td>7135 ± 3383</td>
</tr>
<tr>
<td>Propranolol (n=1-6)</td>
<td>3.8 ± 1.9</td>
<td>12.6</td>
<td>--</td>
<td>--</td>
<td>4.4 ± 1.5</td>
<td>4.4 ± 1.5</td>
</tr>
<tr>
<td>Xamoterol (n=5)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>64 ± 32</td>
<td>4412 ± 1816</td>
</tr>
<tr>
<td>CGP 20712A (n=2-21)</td>
<td>2.2 ± 0.6</td>
<td>1398 ± 236</td>
<td>2.0</td>
<td>3333</td>
<td>2.1</td>
<td>2366</td>
</tr>
</tbody>
</table>

*Competition curve data unreliable with <10-fold selectivity.
Table 3  β/β2-receptor binding profile of carvedilol

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Species/tissue</th>
<th>β1KD, nM</th>
<th>β2KD, nM</th>
<th>β1/β2</th>
<th>α1KD, nM</th>
<th>β1/α1</th>
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<tr>
<td>Sponer</td>
<td>Guinea pig heart,</td>
<td>5.7</td>
<td>37.1</td>
<td>6.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>trachea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monopoli</td>
<td>Human LV, IMA</td>
<td>1.6</td>
<td>—</td>
<td>—</td>
<td>2.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Bristol</td>
<td>Human LV</td>
<td>4.0</td>
<td>29.1</td>
<td>7.3</td>
<td>9.4</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Figure 8  Competition binding between [125I]ICYP (ICYP) and the S and R isomers of carvedilol in human recombinant β1 and β2 receptors. × = S isomer, β2 receptors; ○ = R isomer, β2 receptor, + = S isomer, β1 receptor; * = R isomer, β1 receptor. The respective K1 (nm) values are 1.1, 15.3, 0.40, and 26.1.

yields a 7-fold selectivity of carvedilol for β1 compared to β2 receptors, indicating that the drug can be expected to be non-selective in standard pharmacological doses (Table 2). This agrees with data generated in animal model systems, which indicate a 6.5-fold β1/β2 selectivity [22] (Table 3). This compares with bucindolol and propranolol which are non-selective and metoprolol and bisoprolol which are highly β1 selective (Table 3).

Other studies [26-28] indicate that carvedilol is a potent antagonist of human α1 receptors, with a β1/α1 blocking ratio of approximately two (Table 3). This indicates that carvedilol is a high (nm) affinity competitive blocking agent for β1, β2 and α1 receptors, with a descending rank order of potency of 1:2:7 for β1, α1 and β2 adrenergic receptors respectively.

Guanine nucleotide modulatable binding

β-adrenergic receptor antagonists are capable of identifying a higher affinity binding state that is converted to lower affinity by incubation with high concentrations of non-hydrolyzable guanine nucleotides such as Gpp(NH)p [29,30]. Initially, it was thought that antagonists were not capable of identifying higher affinity agonist binding sites, namely that binding could not be altered by incubation with guanine nucleotides [29,30], but it is now clear that bucindolol and carvedilol do possess 'guanine nucleotide modulatable binding' [27,28,31]. This may be observed in competition curves for [125I]ICYP; carvedilol, bucindolol and the partial agonist xamoterol are displaced to the right by incubation with Gpp(NH)p, compared to the absence of shift with metoprolol (Fig. 7).

Previous studies in myocardial membranes prepared from human left and right ventricles have indicated that carvedilol possesses guanine nucleotide-modulatable binding (GNMB), so that the addition of non-hydrolyzable guanine nucleotides such as Gpp(NH)p results in a reduction in its binding affinity. However, human myocardial membranes contain both β1 and β2 receptors and carvedilol possesses a slight amount of β1 selectivity. Therefore, the resolution of carvedilol competition curves in human myocardial membranes is complicated by two classes of receptors, either of which may exhibit GNMB. A further compli-
cations is the racemic nature of carvedilol, where the S isomer has higher affinity for both \( \beta_1 \) and \( \beta_2 \) receptors than the R isomer. To clarify these issues, the GNMB properties in cells expressing human recombinant \( \beta_1 \) and \( \beta_2 \) receptors have been studied.

Experiments have been performed with both isomers of carvedilol using hamster kidney tsAF8 cells stably transfected with human \( \beta_1 \) and \( \beta_2 \) cDNAs. These transfections result in high-density expression of receptors, 0.5-2 pmol mg\(^{-1}\) in the transfected cells compared to <50 fmol mg\(^{-1}\) in wild-type cells. Representative competition curves between \([\text{I}^{125}]\)-ICYP and the highly selective \( \beta_1 \)-agonist CGP20712A give simple (1 site fit) binding curves indicating they are homogeneously \( \beta_1 \) and \( \beta_2 \).

In these recombinant systems competition curves between ICYP and the S and R isomers of carvedilol performed in the presence of Gpp(NH)p demonstrate differences in \( \beta \)-adrenergic receptor binding affinities (Fig. 8). The binding curve for the \( \beta_1 \) receptor and the S isomer is to the left of the \( \beta_2 \)-S isomer curve. In contrast, the R isomer of carvedilol demonstrates slight selectivity for \( \beta_2 \) receptors. As a result of these different affinities for \( \beta_1 \) and \( \beta_2 \) receptors, the stereospecificity of the S vs R isomers of carvedilol is greater for \( \beta_1 \) vs \( \beta_2 \) receptors, 65-fold vs 14-fold. Additionally, in these recombinant systems agonist binding of carvedilol is found only for the \( \beta_2 \) receptor and only with the S isomer.

Lack of intrinsic sympathomimetic activity

Despite the presence of GNMB no intrinsic sympathomimetic activity (ISA) has been found for carvedilol in chick heart cell membranes, human myocardium or in the intact human heart. However, a small amount of ISA responsible for receptor down-regulation and GNMB may still be possible, even though previous studies have been conducted in the presence of conditions which augment signal transduction, e.g. simultaneous incubation with forskolin. A further screen for minute amounts of ISA will involve measuring cyclic AMP levels in intact cells using stably transfected CHO cells which contain a high signal-to-noise ratio and which generate large amounts of cyclic AMP in response to \( \beta \)-agonist.

Inverse agonist properties of carvedilol, bucindolol, metoprolol, propranolol and xamoterol

Unoccupied adrenergic receptors may possess intrinsic activity (Fig. 9). Agonists may, therefore, function by stimulating inactivated receptors, and antagonists by inactivating receptors which are in the active state, so-called 'inverse agonism'\(^{32,33}\). Just as agonists differ in their ability to activate inactivated receptors, ranging from partial to full agonists, antagonists also differ in their abilities to inactivate active state receptors. The SF9 cell transfected with a baculovirus expression system, which exposes human \( \beta_1 \) or \( \beta_2 \) receptors at ultra-high density (\( \sim 10 \) pmol . mg\(^{-1}\)) furnishes a useful method of screening for inverse agonism as well as for small amounts of intrinsic activity. The inhibition of cAMP generation in this system is a measure of inverse agonism, and this system has been utilized to compare the inverse agonist properties of carvedilol, bucindolol, metoprolol, propranolol and xamoterol (Fig. 10a).

Using the maximum degree of inhibition, propranolol and metoprolol have relatively large amounts of inverse agonist activity, compared to carvedilol, bucindolol and the partial agonist xamoterol. Using a concentration \( 10 \times K_i \) for the \( \beta_2 \) receptor, the rank order of inverse agonist was metoprolol > propranolol > carvedilol > xamoterol > bucindolol (10b). Thus it is to be expected that the degree of inverse agonism of a \( \beta \)-blocking drug will correlate with its negative inotropic and chronotropic properties when sympathetic activity is low or when receptors are unoccupied\(^{34}\).

Effects of carvedilol on \( \beta \)-adrenergic receptor density and mRNA abundance in cultured ventricular myocytes

The comparative effects of various \( \beta \)-blocking drugs on \( \beta \)-receptor density in the chick heart cell membrane have been studied (Fig. 11). Carvedilol markedly down-regulated the chick heart cell \( \beta_1 \)-like receptors, which raises the question of whether carvedilol destabilizes receptor mRNA, as do \( \beta \)-agonists\(^{33}\). However, there was no reduction and possibly a slight increase in \( \beta_1 \)-receptor mRNA abundance after exposure to carvedilol.

Clinical pharmacologic relevance of the adrenergic receptor properties of carvedilol

The increased adrenergic drive in heart failure may mediate adverse myocardial effects through three separate signal transduction systems, the \( \beta_1 \), \( \beta_2 \) and \( \alpha_1 \) adrenergic receptor pathways and, in commonly used doses, carvedilol blocks all three receptors. This is in contrast to metoprolol and bisoprolol, which are highly
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Figure 10 'Inverse agonist' activity of four β receptor antagonists and the partial agonist xamoterol in a baculovirus (BV) expression system. Data are expressed as the percent reduction in adenylyl cyclase (AC) activity as either the maximal reduction (a) or the degree of reduction referenced against concentrations that are approximately $10 \times K_I$ for human β2 adrenergic receptors (AR) (b). In (a) GNMB=guanine nucleotide modulatable binding. □ = metoprolol; ■ = propranolol; ■ = carvedilol; ● = bucindolol; □ = xamoterol; ∗ P ≤ 0.05 vs metoprolol.

β1-selective and bucindolol, which is non-selective for β receptors and has no significant α1-blocking activity. In addition, carvedilol does not up-regulate down-regulated β1 receptors36. This is in contrast to metoprolol and bisoprolol, and in model systems the effect is similar to that seen with bucindolol. The moderate amount of inverse agonism of carvedilol means that the drug may give rise to bradycardia and attendant side effects38, although the number of patients in clinical trials withdrawn for these symptoms or requiring a pacemaker is relatively low (2%-4%, unpublished observations). The lack of a marked degree of inverse agonism indicates that carvedilol will not produce excessive myocardial depression; myocardial depression which may be present before the drug is given, can be expected to be compensated for by its vasodilator activity.

In summary, carvedilol produces total adrenergic receptor blockade in the failing human heart. Unlike with metoprolol, β1 and β2 adrenergic receptor pathways are not up-regulated or recoupled. In addition, unlike metoprolol, carvedilol significantly lowers cardiac adrenergic activity, due to β2 receptor blockade37. As an anti-adrenergic drug, carvedilol is superior to metoprolol or bisoprolol, which may explain at least in part the apparent difference in clinical results between carvedilol and the latter two β1-selective compounds.


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