β-adrenoceptor blockers in chronic heart failure—a review

Henry Krum
Clinical Pharmacology Unit, Monash University, Alfred Hospital, Prahran, Victoria 3181, Australia

There are now considerable clinical trial data to support the use of β-adrenoceptor blockers in patients with chronic heart failure. The use of β-adrenoceptor blockers as additional therapy to standard treatment for symptomatic systolic left ventricular dysfunction may come as a surprise to many clinicians, as this is the very group of drugs long regarded as contra-indicated in the management of this condition. However, the rationale for their use is based on the increasing body of knowledge regarding the pathophysiology of heart failure, in particular the adverse consequences of disease progression of the neurohormonal vasoconstrictor activation that accompanies this condition.

Introduction

There has been considerable interest in recent years regarding the use of β-adrenoceptor blockers in the management of patients with chronic heart failure. The use of β-adrenoceptor blockers as additional therapy to standard treatment for symptomatic systolic left ventricular dysfunction may come as a surprise to many clinicians, as this is the very group of drugs long regarded as contra-indicated in the management of this condition. However, the rationale for their use is based on the increasing body of knowledge regarding the pathophysiology of heart failure, in particular the adverse consequences of disease progression of the neurohormonal vasoconstrictor activation that accompanies this condition.

Why do we need new drugs for heart failure? Standard modern day pharmacological management of this condition includes an ACE inhibitor, digoxin and a diuretic. Whilst ACE inhibitors have resulted in significant improvements in patient clinical status and mortality outcomes, these benefits are relatively modest. For example, in the CONSENSUS study [1] there was a significant mortality reduction observed with enalapril in comparison with placebo when added to digoxin and diuretic. However, even in the enalapril-treated group, there was a 47% mortality at the end of 12 months in these New York Heart Association (NYHA) Class IV (severely symptomatic) patients. Hence, the need for additional therapies in these patients is great.

This review seeks to summarize current knowledge regarding the use of β-adrenoceptor blockers in this clinical setting. In order to address this topic in a clinically relevant manner, the following issues will be discussed: the known adverse effects of chronic sympathetic activation in heart failure, the theoretical benefits of blockade of this system, the current clinical database of β-adrenoceptor blockers in heart failure and practical issues regarding the administration of these agents to these patients.

Keywords: β-adrenoceptor blockers, congestive heart failure, sympathetic, adrenergic

Role of the sympathetic nervous system in heart failure

Heart failure is characterized by activation of a number of neurohormonal vasoconstrictor systems [2–4] including the sympathetic nervous system, the renin-angiotensin system, vasopressin, and more recently the endothelial-derived peptide, endothelin-1. This neurohormonal activation can be viewed as a compensatory response to the reduction in cardiac output and systemic blood pressure that accompanies systolic ventricular dysfunction. β-adrenoceptor agonism (Figure 1) activates regulatory G proteins to increase intracellular cyclic adenosine monophosphate (AMP) via adenylate cyclase [5] stimulation. Increased cyclic AMP stimulates protein kinase, which in turn phosphorylates calcium channels leading to influx of intracellular calcium and enhancement of coupling of actin and myosin filaments, resulting in an inotropic effect.

Whilst there is generalized sympathetic activation in heart failure, noradrenaline spillover is particularly increased in heart and kidneys [6]. As a consequence of the chronic catecholamine excess that accompanies this activation, there is depletion of catecholamines from storage vesicles in cardiac sympathetic nerve terminals [7], downregulation (decreased density) of β-adrenoceptor on myocardial cells and uncoupling of the receptor from adenylate cyclase [5].

In the short-term, the sympathetic activation that accompanies heart failure is an important compensatory mechanism providing inotropic support and maintaining cardiac output; indeed, that is the rationale for the use of sympathomimetic amines in patients with acutely decompensated heart failure. However, over longer periods of time,
this sympathetic activation may be deleterious, thus providing the rationale for use of β-adrenoceptor blocking agents in this setting. There are several lines of evidence to support the conclusion that long-term sympathetic activation is detrimental in heart failure and contributes to disease progression and adverse clinical outcomes.

Evidence from mechanistic studies

Possible detrimental effects of long-term sympathetic activation derived from mechanistic studies in chronic heart failure include direct myocardial toxicity secondary to long-term catecholamine excess [8], requirement for increased myocardial oxygen consumption [9], myocardial β-adrenoceptor down regulation [5], impaired myocardial function secondary to tachycardia, reduction in threshold for arrhythmogenesis [10] and activation of other neurohormonal vasoconstrictor systems, blockade of the proarrhythmic effects of catecholamines and anti-ischaemic effects via increased coronary blood flow during diastole, and reduced myocardial oxygen demand.

It has also been proposed that restoration of β-adrenoceptor density and receptor-cyclase coupling with the use of these drugs may be a potential mechanism for their beneficial effects. Myocardial β-adrenoceptor downregulation and receptor-cyclase uncoupling in heart failure may limit contractile function [5, 14, 15] and drugs such as metoprolol [16] have been demonstrated to produce significant clinical benefits in this condition. Theoretical benefits of β-adrenoceptor blockers include direct myocardial protection from the toxic effects of catecholamines, reduction in stimulation of other neurohormonal vasoconstrictor systems, blockade of the proarrhythmic effects of catecholamines and anti-ischaemic effects via increased coronary blood flow during diastole, and reduced myocardial oxygen demand.

Evidence from clinical studies

There are also a number of lines of evidence supporting the deleterious effects of chronic sympathetic activation derived from clinical studies.

It has long been observed that patients with diseases associated with chronic catecholamine excess e.g. pheochromocytoma [11] present with myocardial disease indistinguishable from that of dilated cardiomyopathy.

Drugs that augment the effects of catecholamines on the myocardium such as β-adrenoceptor agonists [12] or type III phosphodiesterase [13] inhibitors are associated with adverse mortality outcomes. This was perhaps best demonstrated in the PROMISE study [13] with long-term oral use of the phosphodiesterase inhibitor, milrinone, associated with significantly impaired survival. Similar outcomes were associated with the partial β-adrenoceptor agonist, xamoterol [12]. In contrast to these dismal results with long-term oral treatment, milrinone remains a useful short-term intravenous therapy providing inotropic support to the failing myocardium in decompensated heart failure.

Finally, the accumulating evidence from studies of β-adrenoceptor blockers themselves in heart failure support the underlying rationale for their use: that blockade of the toxic effects of catecholamines on the myocardium is associated with improved clinical status and survival outcomes in these patients.

Rationale for adrenergic blockade in patients with chronic heart failure

The preceding mechanistic and clinical data regarding long-term sympathetic activation in chronic heart failure strongly support a therapeutic role for β-adrenoceptor blockers in this condition. Theoretical benefits of β-adrenoceptor blockers include direct myocardial protection from the toxic effects of catecholamines, reduction in stimulation of other neurohormonal vasoconstrictor systems, blockade of the proarrhythmic effects of catecholamines and anti-ischaemic effects via increased coronary blood flow during diastole, and reduced myocardial oxygen demand.

It has also been proposed that restoration of β-adrenoceptor density and receptor-cyclase coupling with the use of these drugs may be a potential mechanism for their beneficial effects. Myocardial β-adrenoceptor downregulation and receptor-cyclase uncoupling in heart failure may limit contractile function [5, 14, 15] and drugs such as metoprolol [16] have been demonstrated to increase β-adrenoceptor density in this setting. However, at least two other β-adrenoceptor blocking drugs have been demonstrated to produce significant clinical benefits in this condition (carvedilol, bucindolol) and do not appear (at least from one laboratory) to be associated with β-adrenoceptor up-regulation or restoration of receptor-cyclase coupling [17]. Thus, although some β-adrenoceptor blockers do cause up-regulation of β-adrenoceptors, this is unlikely to be the mechanism of benefit of this group of drugs overall.

Effect of β-adrenoceptor blockers on clinical status in patients with chronic heart failure

The intense interest in β-adrenoceptor blockers as a therapeutic modality in the management of chronic heart failure is a result of 20 years of cumulative clinical experience, beginning with the pioneering clinical observations of Swedish [18–20] and other [21, 22] investigators. These early studies were often uncontrolled and involved
The administration of the drugs for only short periods of time, but the clinical experience and data obtained from these studies has subsequently proven invaluable, leading to larger placebo-controlled studies and more widespread clinical use of these drugs.

Short term use of β-adrenoceptor blockers in these early studies [21, 22] was found to result in neutral or adverse clinical outcomes and led many investigators to abandon this therapeutic approach. However, it is now understood that, in the context of recovery of the myocardium from chronic catecholamine stimulation, studies of at least 3 months duration are required to demonstrate clinical benefit with these drugs. Early studies were also important in establishing the need for commencement of β-adrenoceptor blocker therapy at extremely low doses to avoid sudden interference [34–39], predominantly with the sympathoadrenal system.

These studies also established the safety and tolerability of β-adrenoceptor blockers when introduced at low doses to heart failure patients. Many of these studies were conducted with drugs that also possess vasodilator properties in addition to their β-adrenoceptor blocking effects. Such agents include carvedilol, bucindolol and nebivolol. The rationale for the use of these drugs is that the vasodilator component of the drug helps overcome the initial negative inotropic component of the β-adrenoceptor blockade, thus improving tolerability of the drug during the initiation and up-titration phase. Use of such drugs has improved patient tolerability such that only 5–7% of these patients could not tolerate the initiation phase of these studies. Thus, tolerability of initiation of therapy with β-adrenoceptor blockers is comparable with that seen with initiation of ACE inhibitors in heart failure patients in the early 1980s.

The beneficial clinical effects observed with β-adrenoceptor blockers in heart failure in single-centre studies has led to the more widespread evaluation of these drugs. A series of multi-centre clinical studies has been conducted [34–39], predominantly with the β-adrenoceptor blocker–vasodilator carvedilol, but additional multi-centre studies are ongoing with other drugs.

The carvedilol study program [35–39] addressed multiple questions regarding clinical efficacy of this drug in heart failure: use in delaying progression of heart failure, clinical utility in patients with moderate to severe heart failure and whether a clinical dose–response relationship existed. Findings are summarized in Table 2. The overall findings were concordant with those of the previous single-centre studies with the drug. Carvedilol significantly improved left ventricular ejection fraction, NYHA functional class and physician and patient global assessment of heart failure status. Improvements in left ventricular function were found to be dose-dependent, the greatest benefits being seen in those patients randomized to receive the highest dose of the drug [38].

Retardation of progression of disease with carvedilol was also noted in the Australian New Zealand Heart Failure Study [39], where a reduction in left ventricular chamber size was observed in mild heart failure patients treated with β-adrenoceptor blocker, indicating restoration of ventricular contour towards normal. This finding provides strong a priori evidence that excess catecholamines are important in the ventricular remodelling process in heart failure and β-adrenoceptor blockers can interfere with this remodelling in a clinically significant manner. However, significant improvements in New York Heart Association class were not seen in this very mild group of patients, 30% of whom were already NYHA class I (i.e. asymptomatic) at time of entry into the study.

### Table 1: Single centre studies of randomized controlled trials of clinical efficacy of long-term (≥3 months) therapy with β-adrenoceptor blocking agents in patients with congestive heart failure.

<table>
<thead>
<tr>
<th>Study (author, year, reference number)</th>
<th>β-adrenoceptor blockers</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>ΔLVEF (%)</th>
<th>Exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. (1985) [23]</td>
<td>Metoprolol</td>
<td>50</td>
<td>19</td>
<td>NA</td>
<td>No change</td>
</tr>
<tr>
<td>Engelmar et al. (1983) [24]</td>
<td>Metoprolol</td>
<td>40</td>
<td>12</td>
<td>+2.0</td>
<td>Increase</td>
</tr>
<tr>
<td>Gilson et al. (1990) [25]</td>
<td>Bucindolol</td>
<td>24</td>
<td>6</td>
<td>+8.0</td>
<td>No change</td>
</tr>
<tr>
<td>Woodley et al. (1991) [26]</td>
<td>Bucindolol</td>
<td>49</td>
<td>3</td>
<td>+6.0</td>
<td>No change</td>
</tr>
<tr>
<td>Krum et al. (1993) [27]</td>
<td>Carvedilol</td>
<td>49</td>
<td>3.5</td>
<td>+5.5</td>
<td>Increase (submax.)</td>
</tr>
<tr>
<td>Matts et al. (1992) [28]</td>
<td>Carvedilol</td>
<td>40</td>
<td>6</td>
<td>NA</td>
<td>Increase (submax.)</td>
</tr>
<tr>
<td>Olsen et al. (1995) [29]</td>
<td>Carvedilol</td>
<td>60</td>
<td>4</td>
<td>+10.0</td>
<td>No change (submax.)</td>
</tr>
<tr>
<td>Wuiselbaugh et al. (1993) [30]</td>
<td>Nebivolol</td>
<td>24</td>
<td>3</td>
<td>+6.0</td>
<td>No change</td>
</tr>
<tr>
<td>Brien et al. (1994) [31]</td>
<td>Bucindolol</td>
<td>141</td>
<td>3</td>
<td>+4.4</td>
<td>No change</td>
</tr>
</tbody>
</table>

Henry Krum

Table 2  Multicentre studies of clinical efficacy of long-term (≥3 months) therapy with β-adrenoceptor blocking agents in patients with congestive heart failure. (Δ=change from baseline; LVEF=left ventricular ejection fraction; submax = submaximal exercise testing, e.g. 6 min corridor walk test).

<table>
<thead>
<tr>
<th>Study (author, year, reference number)</th>
<th>Drug</th>
<th>Number of Patients</th>
<th>Follow-up (months)</th>
<th>ΔEF(%)</th>
<th>Exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol Dilated Cardiomyopathy Trial Waagstein et al. (1993) [34]</td>
<td>Metoprolol</td>
<td>380</td>
<td>12–18</td>
<td>+6.0</td>
<td>Increase</td>
</tr>
<tr>
<td>Carvedilol Study Program</td>
<td>Carvedilol</td>
<td>366</td>
<td>12</td>
<td>+7.0</td>
<td>No change (submax.)</td>
</tr>
<tr>
<td>Moderate CHF Trial (1996) [36]</td>
<td>Carvedilol</td>
<td>278</td>
<td>6</td>
<td>+5.0</td>
<td>Increase (submax.)</td>
</tr>
<tr>
<td>Severe CHF Trial (1996) [37]</td>
<td>Carvedilol</td>
<td>131</td>
<td>6</td>
<td>+7.0</td>
<td>No change (submax.)</td>
</tr>
<tr>
<td>Dose Response Trial (1996) [38]</td>
<td>Carvedilol</td>
<td>354</td>
<td>6</td>
<td>+3.5 (0.25 mg bd)</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+3.9 (1.25 mg bd)</td>
<td>Increase (submax.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+5.5 (25 mg bd)</td>
<td>Increase (submax.)</td>
</tr>
<tr>
<td>Australia/New Zealand (1995) [39]</td>
<td>Carvedilol</td>
<td>415</td>
<td>6</td>
<td>+5.2</td>
<td>No change (submax.)</td>
</tr>
</tbody>
</table>

Effect of β-adrenoceptor blockade on morbidity and mortality in patients with chronic heart failure

Because β-adrenoceptor blockers have the potential to make patients feel worse in the short-term before long-term clinical improvements are obtained with these drugs, many physicians may be reluctant to provide their patients with this therapy in the absence of an accompanying morbidity and mortality benefit. This is a reasonable approach to drug therapy in heart failure given the poor track record in recent years of many drugs that have improved patient symptoms and well-being only to be subsequently found to be associated with an adverse effect on mortality (e.g. flosequinan [40], milrinone [13], vasaquinone [57]).

This divergence of improved patients well-being and adverse effects on mortality may also be true of β-adrenoceptor blockers. However many of the theoretical effects of β-adrenoceptor blockers indicate that they would provide mortality benefits. Chronic sympathetic activation is associated with adverse mortality outcomes in heart failure. Patients with the highest plasma levels of noradrenaline (a crude marker of sympathetic activation) have the most adverse mortality outcomes [41]. As sympathetic activation is also a marker of disease severity [42], the mortality association may simply reflect patients with the most advanced disease having the greatest mortality. Chronic sympathetic stimulation is associated with proarrhythmias, direct trophic and toxic effects on the myocardium and activation of other neurohormonal systems, all of which may independently lead to adverse mortality outcomes. Thus, it would be reasonably anticipated that use of these drugs should confer beneficial effects on mortality providing a powerful rationale for prescribing such drugs in these patients.

There have thus far been three major multi-centre morbidity studies published addressing this question (Table 3). The first two (the Metoprolol in Dilated Cardiomyopathy [MDC] Trial [34] and the Cardiac Insufficiency Bisoprolol Study [CIBIS] [43]) did not provide conclusive evidence of mortality benefits with β-adrenoceptor blockers, although a trend towards a reduction in mortality and/or need for cardiac transplantation was demonstrated. CIBIS identified Cardiac Insufficiency Bisoprolol Study Program was substantial, only a small number of deaths were recorded in the overall program (53 in total), leading some observers to conclude that a definitive mortality effect with β-adrenoceptor blockers had not been adequately demonstrated. Although there is some merit to this argument, it is also true that the mortality effects were observed with very tight confidence intervals, even in sub-group analyses, indicating that these results were most unlikely to have occurred by chance. Even if the ‘real’ effect of the drug on mortality was half that observed, this still represents a highly significant clinical outcome, and is entirely consistent with meta-analysis of results of previous trials. Nevertheless to address the need for further studies, a series of ongoing mortality trials with bisoprolol (CIBIS II), metoprolol (MERIT), carvedilol (COMET) and bucindolol (BEST) are underway.

Another important finding of the US Multicentre Carvedilol Study Program was the effect of the drug on morbidity and, in particular, hospitalization rate [44]...
agents that can reduce hospitalization may impact favourably selectivity for the (Collaborative Group).


Pharmacological properties of Table 4. Hospitalization accounts for two thirds of the cost pharmacological properties (Table 4). Key pharmacological differences amongst β-adrenoceptor blockers include: relative selectivity for the β1- and β2-adrenoceptor, possession of additional vasodilator properties, differential effects on beta adrenoceptor up-regulation and a variety of ancillary properties. It is unclear at present which, if any, of these properties may be of substantial clinical significance. However, clinical and laboratory assessment of a number of these agents permit some cautious observations to be made. The use of drugs that possess a vasodilator component may be useful in helping overcome the initial negative inotropy of the β-adrenoceptor blocking component of the drug β-adrenoceptor blocker/vasodilators appear to be better tolerated than pure β-adrenoceptor blockers during initiation [46]. It has been suggested by some that the vasodilator component rather than the β-adrenoceptor blocking component of these drugs underlies the drugs

Choice of β-adrenoceptor blocker in heart failure

β-adrenoceptor blocking drugs are a heterogeneous therapeatic group with many individual agents possessing unique pharmacological properties (Table 4). Table 3). Hospitalization accounts for two thirds of the cost of management of the heart failure patient [45] and therefore agents that can reduce hospitalization may impact favourably on overall health care costs.

The overall primary end-point of the US Multicentre Carvedilol Study Program was in fact combined morbidity and mortality outcome, which was significantly reduced with carvedilol therapy. The magnitude of the combined morbidity-mortality benefit was very similar in the Australia & New Zealand study of patients with mild heart failure symptoms [39], and again is consistent with observations made from smaller studies with the drug [27].

Table 3 Randomized, controlled trials of long-term therapy with β-adrenoceptor blocking agents on morbidity and mortality in patients with congestive heart failure. (MDC=Metoprolol in Dilated Cardiomyopathy; CIBIS=Cardiac Insufficiency Bisoprolol Study; US Carvedilol=United States Multicentre Carvedilol Study Program; ANZ Carvedilol=Australia & New Zealand Heart Failure Research Collaborative Group).

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Primary Endpoint</th>
<th>Placebo (Risk of hospitalization)</th>
<th>Carvedilol (Risk of hospitalization)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDC [34]</td>
<td>Metoprolol (583)</td>
<td>Deaths or need for heart transplantation</td>
<td>19 (10.1%)</td>
<td>23 (11.9%)</td>
<td>No effect</td>
</tr>
<tr>
<td>CIBIS [43]</td>
<td>Bisoprolol (641)</td>
<td>Mortality</td>
<td>67 (20.9%)</td>
<td>53 (16.0%)</td>
<td>Hospitalizations for heart failure by 34% (P&lt;0.01)</td>
</tr>
<tr>
<td>US carvedilol [44]</td>
<td>Carvedilol (1197 total)</td>
<td>Progression in mild heart failure</td>
<td>31 (7.8%)</td>
<td>22 (3.2%)</td>
<td>Hospitalization by 65% (P&lt;0.001)</td>
</tr>
<tr>
<td>ANZ carvedilol [39]</td>
<td>Carvedilol (415)</td>
<td>Deaths or hospital admission (all cause)</td>
<td>26 (12.6%)</td>
<td>20 (9.0%)</td>
<td>Total hospitalizations by 33% (P&lt;0.05)</td>
</tr>
</tbody>
</table>

Table 4 Pharmacological properties of β-adrenoceptor blocking agents used in the management of heart failure.

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Selectivity as β-adrenoceptor agonist</th>
<th>Direct vasodilator activity</th>
<th>Activity as α-adrenoceptor agonist</th>
<th>Innate sympathomimetic activity</th>
<th>Auxiliary properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acebutolol</td>
<td>β1 &gt; β2</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>β1 &gt; β2</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>β1 = β2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>β1 = β2</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>β1 &gt; β2</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Dilevotol</td>
<td>β1 = β2</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Labetalol</td>
<td>β1 &lt; β2</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>β1 &gt; β2</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>β1 &gt; β2</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Osmetolol</td>
<td>β1 = β2</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Propranolol</td>
<td>β1 &gt; β2</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Prazosinol</td>
<td>β1 = β2</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Propranolol</td>
<td>β1 = β2</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Xamoterol</td>
<td>β1 &gt; β2</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>
beneficial effects. This is unlikely however, as the vasodilating effects of drugs such as carvedilol are relatively modest and acute vasodilation disappears during chronic therapy with α-adrenoceptor blockers and β-adrenoceptor blockers in combination [47].

A more important pharmacological property may be that agents such as carvedilol and bucindolol are relatively non-selective inhibitors of β1- vs β2-adrenoceptors. In heart failure, there is selective β1-adrenoceptor down-regulation with relative preservation of β2-adrenoceptor density [5] (relative percentages: β1 80% vs β2 20% in normal subjects compared with β1 66% vs β2 40% in CHF patients). If β2-adrenoceptor blockers indeed act as a shield against the toxic effects of catecholamines on the myocardium, blockade of β2-adrenoceptors assumes greater significance.

Blockade of both receptor sub-types does not occur with selective β1-selective drugs such as metoprolol and this may account for differing haemodynamic and neurohormonal effects of these drugs [48]. Interestingly, one of the earliest studies to point towards a beneficial effect of β-adrenoceptor blockers in heart failure was the Beta-blocker Heart Attack Trial (BHAT) [49] in post-myocardial infarction patients. These drugs appear to possess a unique hypotensive effect in ventricular function does not parallel that of early inotropic effects observed with these drugs (the magnitude of which is at least as great as with any other β-adrenoceptor blocker) occur in the absence of β-adrenoceptor up-regulation. In the presence of drugs that abrogate adrenoceptor up-regulation (e.g. metoprolol and bucindolol in heart failure). The patient needs to be subsequently observed for significant worsening at commencement e.g. 3.125 mg carvedilol or 6.25 mg propranolol.

β-adrenoceptor upregulation cannot explain the beneficial effects observed with drugs such as carvedilol and bucindolol in heart failure. These drugs appear to possess a unique pharmacological property (guanine nucleotide modulatable binding [17]) that prevents up-regulation from occurring. Thus, the beneficial effects observed with these drugs (the magnitude of which is at least as great as with any other β-adrenoceptor blocker) occur in the absence of β-adrenoceptor up-regulation.

Even in the presence of drugs that abrogate adrenoceptor up-regulation (e.g. metoprolol [16]), the β-receptor is nearly completely blocked at pharmacological doses of the drug and therefore putative improved inotropic effects that may result from upregulation of receptors and post-receptor activation of cyclic AMP would be blocked at the level of the receptor [14]. In addition, the time course of improvement in ventricular function does not parallel that of pharmacological up-regulation achieved with drugs such as metoprolol. Adrenoceptor up-regulation occurs in minutes to hours, whilst improvements in ventricular function take weeks to months.

Finally, some drugs possess ancillary properties that have been demonstrated in vitro and may turn out to be of great clinical importance. For example, carvedilol possesses both anti-proliferative [50] and anti-oxidant [51] properties that theoretically may play an important role in disease progression in heart failure. Heart failure is a state of increased oxidative stress [52] and this may contribute to disease progression by stimulation of apoptosis (programmed cell death). Furthermore, carvedilol uniquely inhibits endothelin-1 production from cultured endothelial cells [53] and its effects appear to be independent of its β-adrenoceptor blocking, α-adrenoceptor blocking and anti-oxidant effects. Endothelin-1 is of major importance in disease progression in heart failure and plasma levels have been found to be a powerful independent marker of prognosis [54].

The relative contribution of the above ancillary properties vs the underlying β-adrenoceptor blocking effects of these drugs remains to be elucidated in further clinical studies.

**Approach to management of the heart failure patient with β-adrenoceptor blockers**

Two decades of administration of β-adrenoceptor blockers to patients with heart failure has taught us much about how to safely administer these agents to these patients. It is clear that the major difficulties with the use of these agents tend to occur during the initiation and uptitration phase of treatment. Overall about 50% of patients report worsening symptoms during the uptitration phase [55], although this figure may be exacerbated by the concerns of the treating physician. Indeed, recent multicentre studies with these drugs confirm a very high rate of adverse events occurring in both the placebo and active treatment groups [44]. Nevertheless, it is worth persisting with strategies to achieve target doses of β-adrenoceptor blockers, as patients who experience difficulties during uptitration are eventually conferred long-term clinical benefits similar to those who had no problems during initiation [65].

The two major problems during initiation are worsening of underlying heart failure and, in patients receiving vasodilating β-adrenoceptor blockers, symptomatic postural hypotension. In order to minimise the possibility of both problems occurring, it is important to ensure that, before initiation is attempted, patients are stable clinically and on stable doses of their concomitant medication. A β-adrenoceptor blocking drug should not be administered to patients with unstable or decompensated heart failure. Very low doses of β-adrenoceptor blocker should be used at commencement e.g. 3.125 mg carvedilol or 6.25 mg metoprolol. The patient needs to be subsequently observed acutely for a few hours, then reviewed on a 1-to-2-weekly basis whilst uptitrating the drug to target dosage. Despite these concerns, patients can generally be initiated in an outpatient setting.

Postural hypotension, if it is to occur, is generally seen early in patients receiving vasodilating β-adrenoceptor blockers. This can usually be effectively managed by temporarily reducing dose of concomitant ACE inhibitor and/or diuretic to permit establishment and uptitration of the β-adrenoceptor blocker. Another useful modification to therapy is to separate the β-adrenoceptor blocker and ACE inhibitor dosage time by 3 h or greater to allow the vasodilator effects of one drug to wear off before the next drug is administered.

If worsening heart failure occurs with β-adrenoceptor blocker initiation, this can generally be treated by an increase in diuretic dose which usually permits stabilisation of the condition. If necessary, a delay in scheduled uptitration of β-adrenoceptor blocker may be required.

Can we predict which patients will tolerate β-adrenoceptor blockers during initiation? It would be expected that patients most reliant upon sympathetic activation to maintain cardiac output, i.e. patients with severe chronic heart failure, would be those with the greatest difficulties during initiation, however this has not as yet...
been definitively demonstrated [55]. The extreme elderly as well as patients with borderline hypertension and renal impairment are also those who may require close supervision during initiation of therapy.

Conclusions

Twenty years of clinical experience with β-adrenoceptor blockers confirms the seemingly paradoxical view that these drugs are highly efficacious in the management in the heart failure patient. The clinical benefits of these agents in patients refractory to standard therapies for heart failure have been consistently demonstrated: increases in ejection fraction, improved well-being as judged by both patient and physician and reduced progression of ventricular dysfunction. Furthermore, consistent reductions in cardiovascular morbidity associated with decreased hospitalization rates have also been demonstrated in larger studies. Mortality benefits have also been demonstrated, with a meta-analysis suggesting a mortality reduction of 30% when added to standard heart failure therapies [56]. In addition, further mortality data are being accumulated. These clinical data are underpinned by the theoretical and mechanistic expectations of benefit with blockade of sympathetic activation in heart failure. Despite these clinical observations, a number of questions remain unanswered. The exact mechanism of benefit of these drugs remains to be elucidated. It is not clear whether there are clinically significant differences amongst β-adrenoceptor blockers. Use of these agents in patients with severe class IV heart failure have been limited and thus benefits in this patient population have not been definitively demonstrated. It has not been established whether these drugs are useful in patients with asymptomatic left ventricular dysfunction. Ongoing laboratory and clinical studies will attempt to resolve many of these unanswered questions in the years to come.

References

16 Fowler MB. Controlled trials with β-blockers in heart failure: mortality reduction as the prototype. Am J Cardiol 1993; 71: 45C–53C.
27 Krum H, Sackner-Bernstein JD, Goldsmith R, et al. Double-


(Rceived 22 January 1997, accepted 28 April 1997)