

# Beta Blockers and Heart Failure

Deirdre Moran

## Introduction

Beta-blockers were traditionally thought to be contraindicated in heart failure due to their negative inotropic properties. However, recent research has revealed the beneficial effects of treating heart failure patients with beta-blockers.

## What is Heart Failure?

Heart failure is a clinical condition in which the heart is unable to pump sufficient blood around the body to meet its metabolic needs. It is characterised by abnormalities of left ventricular function and neurohormonal regulation, exercise intolerance, shortness of breath, fluid retention and

reduced longevity.<sup>1</sup> Heart failure can be due to systolic or diastolic left ventricular dysfunction. Most patients with heart failure have primarily systolic dysfunction. In two-thirds of patients with systolic dysfunction, the cause is coronary artery disease.<sup>2</sup> However, patients may also have nonischaemic causes of cardiomyopathy such as hypertension, valvular heart disease, myocarditis, systemic disease, toxins, alcohol/drug abuse, or idiopathic cardiomyopathy. Depressed left ventricular ejection fraction (<40%) is the hallmark of systolic dysfunction. Diastolic dysfunction is defined as normal or preserved rest systolic function in the presence of

heart failure signs and/or symptoms.<sup>2</sup>

Heart failure can be viewed as three models – the cardiorenal model, the haemodynamic model

and the neurohormonal model.<sup>3</sup> The primary cause of the cardiorenal model of heart failure is renal hypoperfusion caused by cardiac dysfunction. This leads to oedema and volume expansion due to excessive salt and water retention. Heart failure is also associated with a reduced cardiac output and excessive peripheral vasoconstriction; these symptoms are characteristic of the

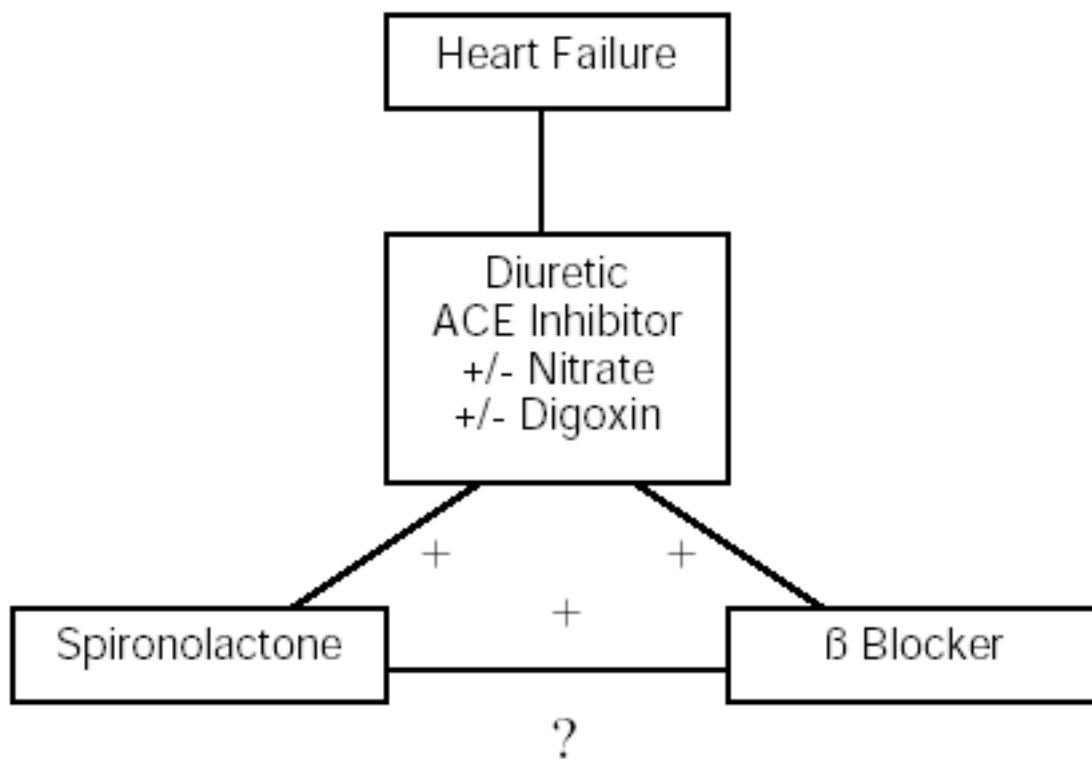
haemodynamic model of heart failure.<sup>4</sup> This model also describes the progressive heart failure which develops from chronically increased preload and afterload. The neurohormonal model of heart failure develops after prolonged expression of endogenous neurohormonal mechanisms. These systems are initially compensatory, but can eventually lead to toxic effects on the myocardium. The two primary neurohormonal systems involved are the sympathetic nervous system and the renin-angiotensin-aldosterone axis (R-A-A).

## Current Treatment of Heart Failure

The treatment of heart failure is targeted at each of these three separate models (Figure 1). The primary treatments for the cardiorenal model are digitalis and diuretics. Digitalis (or its associated glycosides, e.g. digoxin) increases the contractility of the heart. Diuretics relieve pulmonary congestion and peripheral oedema by increasing urine volume, which leads to a decrease in plasma volume. The decreased plasma volume leads to a decreased venous return (preload) to the heart, which in turn decreases the cardiac workload and oxygen demand. The reduced plasma volume also leads to a decreased blood pressure. Therefore, afterload is also decreased. The haemodynamic model is treated with positive inotropic agents and peripheral vasodilators. Angiotensin-converting enzyme (ACE) inhibitors are used to counteract the adverse effects of the long-term stimulation of the R-A-A axis. They decrease the circulating levels of angiotensin II, the effect of which is to cause decreased output of the sympathetic nervous

system, increased vasodilation of vascular smooth muscle, increased levels of bradykinin and decreased retention of sodium and water. Currently, the standard therapy for heart failure involves diuretics and an ACE inhibitor, with or without digitalis glycosides. This line of therapy ignores or incompletely inhibits adrenergic activation, which is one of the primary contributors to progressive left ventricular systolic dysfunction.<sup>2</sup> This 'triple' therapy also only treats the symptoms of heart failure without considering whether an actual improvement in the patient could be attained by identifying the causatory factors of the patient's heart failure. The emphasis of this review will be targeted at the treatment of the neurohormonal model of heart failure involving beta-blockers, which can inhibit the activation of the adrenergic system.

Figure 1. Treatment of Heart Failure



### Adrenergic Activation in the Failing Heart

During rest and when left ventricles are normally functioning, there is no adrenergic support. However, in the failing human heart, the adrenergic system is activated. Over the short term, activation of the sympathetic nervous system has a compensatory effect on cardiac performance and is important in the maintenance of normal cardiac output. Ultimately however, the prolonged increase in circulating noradrenaline (NA) can lead to progressive damage to the failing human

heart. NA produces cardiotoxic effects which cause damage to the cardiac myocytes.<sup>5</sup> Persistent peripheral vasoconstriction and precipitation of ischaemia and arrhythmias are subsequent deleterious effects. NA spillover in the myocardium has been linked to life-threatening arrhythmias. The increase in heart rate, which is caused by activation of the sympathetic nervous

system, can exacerbate the discrepancy between oxygen demand and supply.<sup>6</sup> Progressive cell loss and death are consequences of the combination of local and systemic sympathetic nervous system activation. This leads to worsening of ventricular remodelling, characterised by changes in ventricular geometry, mass, and volume, resulting in a dilated and less contractile chamber. If this vicious cycle of adrenergic activation continues unabated, the dilation of the ventricle worsens, contractility is further reduced and ultimately these may lead to myocardial infarction or

complete ventricular failure.<sup>4</sup> It is important to note that by the time symptoms appear, this cycle of left ventricular dysfunction is well under way. Therefore, it is of paramount importance that diagnosis be made as early as possible to optimise the chances of successful treatment of heart failure.

Within the myocardium, there are 3 types of adrenergic receptor –  $\alpha_1$ ,  $\beta_1$  and  $\beta_2$ . The  $\beta_1$  group of receptors normally predominate. However, in the failing heart, 35-40% of the total number of  $\beta$  receptors are  $\beta_2$  because of selective downregulation in the  $\beta_1$  subtype. There is also a concomitant upregulation in the numbers of  $\alpha_1$  receptors in the failing heart. Cardiac overexpression of  $\beta_2$  receptors results in depressed systolic function and a cardiomyopathy phenotype, whereas the increased levels of  $\alpha_1$  receptors produces concentric hypertrophy of the

ventricle.<sup>5</sup> These data indicate that chronic activation of the adrenergic system can lead to damage to the myocardium. This is the reason that beta-blockers for the treatment of heart failure has now become a distinct reality, as they are capable of inhibiting the sympathetic nervous system's effects on the heart. Traditionally, it was thought that beta-blockers were contraindicated in heart failure patients due to their negative inotropic properties. This was thought to render an already compromised heart even weaker through beta-blockade.<sup>7</sup> However, several clinical trials have been conducted using beta-blockers in combination with diuretics and ACE inhibitors and have resulted in improvements in left ventricular function, symptoms and survival, as well as a reduction in admission to hospital.<sup>8</sup>

### **Types of Beta-Blockers**

Beta-blockers can be divided into three categories, dependent on their properties. 'First-generation' compounds such as propranolol, are non-selective beta-blockers and block  $\beta_1$  and  $\beta_2$  receptors with equal affinity. These compounds have no other important pharmacological

effects other than beta-blockade.<sup>5</sup> The 'second-generation' beta-blockers can be considered to be 'cardioselective' as they have much greater affinity for  $\beta_1$  than  $\beta_2$  receptors. Examples of second-generation beta-blockers are metoprolol and bisoprolol. The final category of beta-blockers – the 'third-generation' – includes carvedilol and bucindolol. Carvedilol is a non-selective, vasodilatory agent with the unique property of having an  $\alpha$ -blocking moiety as well as

an antioxidant effect.<sup>6</sup> The moderate vasodilatory properties of carvedilol are due to the blockade of the  $\alpha_1$  receptors. Bucindolol is also a non-selective beta-blocker with vasodilator properties. The third-generation beta-blockers, therefore, provide a more comprehensive anti-adrenergic effect than do second-generation beta-blockers, due to the fact that they block both  $\beta_1$  and  $\beta_2$  receptors, reduce cardiac and/or systemic adrenergic drive, do not upregulate downregulated  $\beta_1$

receptors and can block  $\alpha_1$  receptors.<sup>5</sup>

### **Clinical Studies**

Several studies have been conducted into the effects of beta-blockade on the condition of the heart failure patient. The CIBIS-II study (cardiac insufficiency bisoprolol study) compared the second-generation drug bisoprolol to placebo. Its findings reported a highly significant reduction

in all cause mortality.<sup>9</sup> The patients included in the study were from New York Heart Association classes III and IV [Classification of the New York Heart Association is as follows: I=no symptoms, II=mild, III=moderate, IV=severe]. Bisoprolol was shown to be superior to placebo for morbidity

and mortality.<sup>8</sup> This study showed a 34% reduction in mortality and a 20% decrease in the risk of hospital admissions to hospital for any reason. The trial was stopped prematurely because of a significant mortality benefit in patients treated with bisoprolol. There have been two trials conducted on the effects of carvedilol, one in Australia and New Zealand (ANZ), the other in the US. The US study was the first to show a mortality advantage with beta-blockers given in chronic

heart failure.<sup>1</sup> These studies supported the contention that carvedilol improves survival and reduces the rate of hospitalisation and worsening heart failure with patients who have heart failure

caused by coronary heart disease and those with primary cardiomyopathy.<sup>10</sup> Carvedilol is indicated for the treatment of heart failure in patients with clinically stable NYHA functional class II

or III.<sup>11</sup> Both of these studies found that carvedilol was superior to placebo for morbidity and

mortality.<sup>8</sup> Carvedilol is currently the only beta-blocker approved for the treatment of chronic heart failure in the US, UK and most other countries. It was approved as a result of the delay in progression of the myocardial disease process and the lowering of the combined risk of morbidity

plus mortality seen in both of these trials.<sup>5</sup> In another study, metoprolol was used in dilated cardiomyopathy (MDC) with patients with mild to moderate heart failure. The outcome of this study was an improved clinical state without effect on survival and a reduction in the need for

transplantation in patients with dilated cardiomyopathy.<sup>8</sup> In addition, metoprolol, compared with placebo, improved left ventricular function, quality of life, hospitalisations, and exercise tolerance. Another trial involving metoprolol was the metoprolol randomised intervention trial in congestive heart failure. This trial included patients with classes II-IV heart failure. The results of this trial showed a reduction in mortality resulting from sudden death or progressive pump failure. Also, mortality was reduced across most demographic groups, including age, nonischaemic and

ischaemic causes and levels of ejection fractions.<sup>5</sup> Metoprolol, therefore, was found to decrease the risk of death and of the combined end point of total mortality and all cause hospital

admissions.<sup>12</sup>

Beta-blockers appear to have an effect as great as or greater than that of ACE inhibitors. However, in most of the trials detailed above, the patients were already taking ACE inhibitors so the benefits of beta-blockade could be in addition to those of ACE inhibitors. Reduction of

mortality by the combination of treatments has been shown to be 46%.<sup>5</sup> This is obviously a highly significant improvement in the progress of successful treatment for chronic heart failure.

### **Cautions and Side-Effects**

Beta-blockers must be administered with careful supervision and initially, the practitioner may need to consult a cardiologist. This is because beta-blockers can cause worsening of heart failure before improvement is seen. Left ventricular ejection fraction tends to worsen initially but

subsequently improves after 6 to 12 months of therapy.<sup>10</sup> Other drugs used in the treatment of heart failure do not cause a similar improvement in left ventricular ejection fraction. Therefore, the strategy for administering all beta-blocking agents for the treatment of heart failure is to start at low doses and to gradually increase the dose over weekly or biweekly intervals. Metoprolol and carvedilol have half-lives which dictate that they must be given twice-daily, whereas bisoprolol can be given once per day. The former compound is highly lipophilic, extensively metabolised and cleared by the liver, whereas the latter compound is less lipophilic and is cleared by both the liver and the kidney. The bioavailability of all of these agents is quite low (20-50%) due to the

extensive first-pass hepatic metabolism experienced by the agents.<sup>5</sup> Carvedilol may result in an increase in serum digoxin concentrations in patients receiving digoxin. Therefore, frequent alterations in concomitant therapy may be a necessity.

While in the short-term, beta-blockade can cause a depression of cardiac function, which leads to a temporary worsening of symptoms, this does not seem to outweigh the long-term therapeutic benefits. Primary adverse effects may include fluid retention, hypotension and bradycardia. Carvedilol can produce substantial vasodilation, which is usually asymptomatic but can be accompanied by dizziness or light-headedness. This effect usually disappears upon repeated dosing. Both selective and non-selective beta-blockers can slow the heart rate and cardiac conduction, and as a result, may cause bradycardia and heart block. If the heart rate decreases to fewer than 50 beats per minute or second-degree or third-degree heart block develops, the dose of beta-blocker should be decreased.<sup>2</sup>

### **What patients are suitable for Beta-Blocker Therapy?**

The current recommendations for determining candidates suitable for beta-blocker therapy

stipulate that the subjects should have a mild to moderate compensated heart failure from nonischaemic or ischaemic cardiomyopathies, with stable NYHA class II to III symptoms on standard treatment (diuretics and an ACE inhibitor), and may be used in conjunction with digitalis

or vasodilators.<sup>2</sup> Subjects should not have a contraindication to beta-blockade such as asthma. If beta-blockers are given to subjects with decompensated heart failure, the myocardial

depression that accompanies initiation of therapy can be life-threatening.<sup>5</sup> Also, NYHA functional class IV heart failure should be considered a relative contraindication for beta-blocker therapy as the evidence from the literature does not conclusively suggest a benefit in this population and the

potential for grave harm exists.<sup>6</sup> Therefore, careful selection of patients with heart failure suitable for beta-blocker therapy is essential.

## Conclusion

The administration of beta-blockers for the treatment of heart failure appears to have its benefits in certain categories of heart failure patients. Previously, beta-blockers were believed to be a contraindication in the treatment of heart failure due to their negative inotropic properties. However, through extensive research and clinical trials, beta-blockers have now become part of the recognised treatment process for heart failure. Beta-blockers can antagonise the effects of an overactive sympathetic nervous system, which is responsible for many of the disease processes leading to the progression of heart failure. Several studies have highlighted the successful clinical effects of beta-blockers – decreased mortality and decreased risk of hospitalisation for the treatment of heart failure. Beta-blockers reduce total and cardiovascular mortality, as a result of a

reduction in pump failure mortality and sudden death.<sup>13</sup> While standard 'triple' therapy for heart failure has improved the quality of life of heart failure patients, this type of therapy only relieves symptoms, which is the reason for success of beta-blocker therapy. Although the beta-blocker data does not demonstrate a 'cure' for heart failure, it has shown that substantial improvement in the prognosis of heart failure can be obtained. There are risks associated with the administration of beta-blockers; they can produce initial worsening of heart failure and must be given under expert supervision. Beta-blockers are also contraindicated in chronic obstructive pulmonary disease and they can cause arrhythmias if therapy is discontinued abruptly. However, these risks are small in comparison to the proven benefits, which can include slowed disease progression and improvement of symptoms. Although initial treatment can put additional demands on the primary care physician, the extra effort can prove worthwhile, especially if comparison is made to the high rates of morbidity and mortality among patients receiving standard treatment. It is hoped that with further trials, the use of beta-blockers in heart failure can reach a conclusion in which the beta-blockers involved are used optimally to produce significant improvements in the life of the heart failure patient.

## REFERENCES

1. Lonn E. Drug treatment in heart failure. *BMJ* 2000; 320:1188-1192.
2. Abraham WT. Beta-blockers: The new standard of therapy for mild heart failure. *Archives of Internal Medicine* 2000; 160(9):1237-1247.
3. Pepper GS. Sympathetic activation in heart failure and its treatment with beta-blockade. *Archives of Internal Medicine* 1999; 159(3):225-234.
4. Mann DL. Mechanisms and models in heart failure. *Circulation* 1999; 100(9):999-1008.
5. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000; 101(5):558.
6. Mehra MR, Uber PA, Aditya KK. Using beta-blockers in patients with heart failure. *Patient Care* 1999; 33(6):205-209.
7. Eagle KA. Update in cardiology. *Annals of Internal Medicine* 2000; 133(6):439-446.
8. Gibbs CR, Davies MK, Lip GYH. Management: digoxin and other inotropes, b-blockers and antiarrhythmic and antithrombotic treatment. *BMJ* 2000; 320:495-498.

9. Cleland JG, McGowan J, Clark A, et al. The evidence for beta-blockers in heart failure. *BMJ* 1999; 318:824-825.
10. Gheorghide M, Cody RJ, Francis GS et al. Current medical therapy for advanced heart failure. *Heart & Lung* 2000; 29(1):16-32.
11. Vanderhoff BT, Ruppel HM, Amsterdam PB. Carvedilol: The new role of beta-blockers in congestive heart failure. *American Academy of Family Physicians* 1998; 58(7):1627-34.
12. Strauss SE. Geriatric medicine. *BMJ* 2001; 322:86-89.
13. Bonet S. Beta-adrenergic blocking agents in heart failure: benefits of vasodilating and nonvasodilating agents according to patients' characteristics: a meta-analysis of clinical trials. *Archives of Internal Medicine* 2000; 160(5):621-627.