Influence of medical intervention on sympathetic activity in heart failure

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Chapter IV

β-blockers in heart failure

Part I: Hemodynamic and clinical effects
Part II: Modes of action

P.A.R. de Milliano, MD; J.G.P. Tijssen, MD, PhD; P.A. van Zwieten, MD, PhD; K.I. Lie, MD, PhD.

PART I

Introduction
Treatment for heart failure may be directed at relieving symptoms and/or improving prognosis. Diuretics are known for many years as therapeutics in heart failure and they are very effective in symptom relief. Vasodilators and inotropes also have beneficial effects on symptom relief especially in the acute phase through changes in cardiac output, filling pressures and renal perfusion. However, none of these treatments that produce short-term relief have been shown to influence the disease process and thereby improve mortality. Indeed, many of these drugs may even lead to untoward long-term clinical outcomes as has been shown for example for milrinone and ibopamine.

There is overwhelming evidence that drugs interfering with the neurohormonal activation in heart failure not only produce symptomatic relief but also are capable of attenuating disease progression with concomitant reductions in both morbidity and mortality. About a decade ago, convincing and large scale evidence showed that ACE-inhibitors by antagonizing the activated renin angiotensin system produced favorable effects. More recently, β-blockers, antagonizing the activated sympathetic system were shown to be beneficial on the long term in moderate severe heart failure both in terms of significant improvements in morbidity and mortality. The RALES study further amplified the concept that drugs that interact in the neurohormonal system have beneficial effects. In this study, spironolactone, a weak, potassium sparing diuretic counteracting aldosteron showed a reduction in mortality in more severe forms of heart failure.

Classes of β-blockers
Depending on their affinity for adrenergic receptors, β-blockers can be divided into 3 classes. Non-selective β-blocking agents have equal affinities for blocking β1 and β2 receptors. They do not block α-receptors. These compounds are not used in the treatment of heart failure.

The second generation β-blockers have a high affinity for β1 receptors as compared to β2 receptors in an attempt to reduce some of the peripheral and pulmonary side effects of β-blockers that are mediated in part through β2-blockade. The selective β1-blockers metoprolol and bisoprolol have been extensively used in heart failure research and have been shown to reduce mortality and morbidity.

Third generation β-blockers (carvedilol, bucindolol) are non-selective in their affinity for β-receptors but have vasodilating properties through their α1-blocking properties. Nebivolol is a third generation β-blocker with marked β1-selectivity and vasodilating properties related to potentiation of nitric oxide. These compounds were originally designed for the treatment of hypertension but were shown to be effective in heart failure as well. The US Carvedilol studies showed a significant reduction in mortality during long-term treatment with carvedilol in patients.
with chronic stable heart failure.* In contrast to the second generation β-blockers, third generation compounds do not upregulate downregulated β₁-adrenergic receptors. Carvedilol also exerts antioxidant properties but the significance of this in heart failure remains unclear. Although their pharmacological profile would suggest that third generation compounds like carvedilol and bucindolol would be more effective than second generation β-blockers (metoprolol, bisoprolol) in the treatment of heart failure there is no robust evidence from phase 3 trials to confirm this conclusion. Limited data suggest that third generation compounds produce more beneficial effects on left ventricular function.⁹ However, other studies demonstrate no difference between a second- and third-generation compound.¹⁰⁻¹² The ongoing Carvedilol or Metoprolol European Trial (COMET) directly compares the effects on mortality in heart failure patients of carvedilol and metoprolol and will give an answer on the question whether, from a clinical point of view there is a difference between second- and third-generation β-blockers.

**Hemodynamic effects of β-blockers in heart failure**

Probably because left ventricular ejection fraction can be determined relatively easily, it is the most frequently used hemodynamic parameter in heart failure research. Besides, it has been demonstrated that ejection fraction is an important predictor of prognosis.¹³⁻¹⁵ There is a remarkable consistency in reported trials with regard to an improvement of left ventricular ejection fraction during chronic treatment with β-blockers.¹¹⁻¹⁶⁻¹⁹ This improvement in ventricular function is due to increased systolic ventricular performance.²⁰⁻²² In turn this increased performance is related to enhanced contractility.²¹ Improvements in diastolic properties with a shift of the Frank-Starling relation up and to the left has been demonstrated for bucindolol²¹, carvedilol²⁵ and metoprolol.¹⁸⁻²⁶⁻²⁷ Acute hemodynamic responses to β-blockers include a decrease in heart rate, systemic vascular resistance and a drop in mean arterial pressure. Mean pulmonary capillary wedge pressure, cardiac index and stroke work do not change.

**Clinical effects of β-blockers in heart failure**

Conflicting results have been published with regard to changes in functional parameters in patients with heart failure during β-blocker treatment. It should be emphasized that in the beginning of treatment with a β-blocker, a temporary increase in symptoms can occur which will disappear on continuation. The Australia-New Zealand trial reported a trend toward worse symptoms and worsening NYHA class at 6 months of treatment, although by 12 months such differences had disappeared.²⁸⁻²⁹ In contrast, the large US trials* of carvedilol have been shown to improve symptoms during long-term treatment although a trend toward improvement in quality of life has not been significant. The effects of β-blockers on functional class were recently addressed in a meta-analysis by Lechat showing a borderline significance on improvement of functional class.¹⁶ However, this favorable effect was not very convincing, probably related to the fact that most
trials had a short duration of follow-up and enrolled patients with class II symptoms, in whom demonstration of clinical benefit may be difficult. The recently published RESOLVD study showed no change in NYHA functional class and quality of life after 6 months of treatment with metoprolol." In contrast, a randomized study by Sanderson et al. comparing metoprolol and carvedilol in a randomized study found significant improvements in all functional parameters for both compounds with no differences between the two agents. The reported influence of β-blockers on exercise capacity is conflicting. Although some studies have reported statistically significant improvement in total exercise duration during treadmill exercise testing, others have not. However, robust conclusions can not be drawn from these observations because of differences in study design, small patient numbers studied (ranging from 10 to 380) and different types of β-blockers used. It seems that most studies with a selective β1-blocker (like metoprolol) show an increase in exercise capacity with the MDC trial with 380 patients as the best example. However, the recently published RESOLVD trial found no difference in the results of a six-minute walking test after 6 months of treatment with metoprolol. Generally speaking, β-blockers do not increase maximal oxygen consumption. The reason for the absence of consistent improvement in functional parameters with the use of β-blockers is likely to be multifactorial. A major concern when interpreting reported results are the patient numbers in individual trials varying from 12 to 4000, relatively short follow-up periods, differences in design, patient selection and assessment of functional parameters. Finally, results of assessment of functional parameters in trials should be interpreted with caution because β-blockers reduce mortality. Thus, more patients in the placebo arm with severe congestive heart failure will be eliminated leading to an apparent improvement or maintenance of functional parameters in placebo treated patients.

**Effects of β-blockers on mortality and (re)hospitalization**

The addition of a β-blocker to conventional therapy is associated with a significant impact on both morbidity and mortality. The initial reports on the effect of β-blockers in heart failure were nonrandomized studies, but they have since been followed by a number of randomized, placebo controlled trials primarily designed to study hemodynamic and functional effects of β-blockers in heart failure. One of the first larger trials designed as a mortality study was the MDC trial in patients with idiopathic dilated cardiomyopathy. CIBIS I included both ischemic and non-ischemic cardiomyopathies but had insufficient power to demonstrate mortality benefits. In 1996, results of the US Carvedilol Heart Failure Study Group were published indicating for the first time a significant mortality and morbidity reduction with carvedilol, a non selective β-receptor antagonist that also blocks α-receptors and exerts antioxidant effects. The contribution of these latter two properties on the beneficial effects in heart failure is a matter of controversy. Concern has been raised about the fact that in this study a relatively large proportion of the
patients was in functional class II with an overall low mortality in the placebo group (7.8%). The absolute number of deaths was low, 31 in the placebo group and 22 in the carvedilol group. The relative risk reduction however, was high: 65% (P<0.001, 95% confidence interval 39 to 80%).

Two recently published trials, CIBIS II\(^5\) and MERIT\(^6\) with bisoprolol and metoprolol respectively were terminated premature because interim analysis showed significant reductions in mortality and hospitalizations. Results of these two large scale trials confirm the meta-analysis\(^6\) of earlier performed, randomized trials indicating that the use of β-blockers (selective or non-selective) is associated with a reduction in mortality of approximately 30% and a reduction of hospitalizations for heart failure of the same magnitude.

The observed reduction in mortality was attributed for a substantial part by a reduction of sudden death emphasizing that β-blockers exert their beneficial effects on mortality at least in part by the prevention of life threatening arrhythmias. It remains unclear whether this action is mediated through
the effect of β-blockers on the sympathetic overactivity, their anti-ischemic effects or both.

Since both bisoprolol (CIBIS II) and metoprolol (MERIT) are highly selective β₁-blockers without any other relevant pharmacological activities it is most likely the β₁-adrenoceptor blockade which explains the beneficial effects of these drugs. These findings probably indicate that the beneficial effect of carvedilol is also based upon β₁-adrenoceptor blockade although this compound displays some additional pharmacological activities.

### Meta-analysis of mortality of randomized, placebo-controlled β-blocker trials in heart failure

Three meta-analyses of the effects of β-blockade on mortality have been published in 1997 and 1998,11 16 34 These analyses supported the concept that β-blocker therapy has a favorable effect on mortality. After these publications, several large scale, randomized trials have been conducted and published recently.5 6 19 We performed a meta-analysis of all placebo-controlled trials with β-blockers in patients with congestive heart failure irrespective of etiology that reported mortality. All 18 studies published in the meta-analysis by Lechat in 1998 were included. A MEDLINE search was performed and identified an additional 4 controlled trials with β-blockers in heart failure reporting on mortality.

Thus, a total of 24 trials qualified for inclusion and are summarized in table 1.5 6 19 21 22 25 29 30 32 33 34 The outcome measure used in this meta-analysis was all cause mortality. For each trial, 2x2 tables were constructed for the number of β-blocker- and placebo-treated patients who died. Relative risks (RR) and absolute risk differences (ARDs) were calculated with placebo or β-blocker as the reference group, so that treatment benefit was associated with a RR less than 1 or an ARDs less than zero. The relative risk reduction was calculated from the formula (1-RR)x100%. Negative ARDs were expressed as number of events avoided per 1000 patients treated, and numbers needed to treat as the reciprocal of the ARDs. Overall event rates were calculated as weighted averages of the trial-specific rates with weights proportional to the total sample sizes of the trials. The overall point estimates for RR and ARD were calculated using Mantel-Haenszel estimate for the common RR and the inverse variance weights formula for the common ARD.48 The corresponding 95% confidence intervals were calculated by the test-based method using the Mantel-Haenszel chi-square statistic.48

<table>
<thead>
<tr>
<th>Relative risk (95%-CI)</th>
<th>Mean follow up (months)</th>
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<tbody>
<tr>
<td>0.89 (0.09 - 8.50)</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>3</td>
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<tr>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1.07 (0.61 - 1.86)</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>3</td>
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<tr>
<td>0.50 (0.05 - 5.17)</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>0.65 (0.12 - 3.38)</td>
<td>3</td>
</tr>
<tr>
<td>0.79 (0.57 - 1.10)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>3</td>
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<tr>
<td></td>
<td>4</td>
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<td>4</td>
</tr>
<tr>
<td>0.73 (0.14 - 3.93)</td>
<td>3.5</td>
</tr>
<tr>
<td>0.30 (0.14 - 0.63)</td>
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</tr>
<tr>
<td>0.60 (0.23 - 1.56)</td>
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</tr>
<tr>
<td>0.23 (0.05 - 1.17)</td>
<td>6.5</td>
</tr>
<tr>
<td>0.50 (0.07 - 3.40)</td>
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</tr>
<tr>
<td>0.73 (0.43 - 1.23)</td>
<td>19</td>
</tr>
<tr>
<td>0.68 (0.56 - 0.82)</td>
<td>16</td>
</tr>
<tr>
<td>0.67 (0.55 - 0.82)</td>
<td>12</td>
</tr>
<tr>
<td>0.47 (0.21 - 1.06)</td>
<td>6</td>
</tr>
<tr>
<td>1.02 (0.13 - 8.26)</td>
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</tr>
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<td>0.67 (0.55 - 0.83)</td>
<td>10.4</td>
</tr>
<tr>
<td>0.92 (0.82 - 1.02)</td>
<td>24</td>
</tr>
<tr>
<td>0.73 (0.68 - 0.79)</td>
<td></td>
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<tr>
<td>0.76 (0.71 - 0.82)</td>
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</tbody>
</table>
Trials of β-blockers vs. Placebo

Figure 1 Relative risk of total mortality, with 95% confidence intervals of published trials of treatment of heart failure with β-blockers. In 7 trials, no deaths were observed and relative risk could not be calculated. Therefore, they are not included in figure 1.
The overall relative risk is standardized

received placebo, compared with 984 deaths (12.6%, standardized 13.0%) among 7802 patients randomized to a β-blocker. Figure 1 summarizes the relative risks of each individual trial.
There was a statistically significant 27% reduction in risk associated with β-blocker treatment (RR 0.73; 95% CI 0.67 – 0.79; P=0.00001). The absolute risk reduction was 4%, which implies that, over approximately 1 year, β-blockers prevent 4 (95% confidence interval 2.8-5.2) deaths per 100 patients treated, and that it would be necessary to treat 25 patients to prevent one death.
Based on the results of this meta-analysis and the results of previously published meta-analyses there is now convincing evidence supporting a beneficial effect of β-blockers on mortality in chronic heart failure.
PART II

Modes of action of β-blockers in heart failure

Although the beneficial effects of β-blockers in heart failure are now firmly established, their mechanisms of action are only partly elucidated. Apart from their direct effects on the myocardial β-receptors, they probably also influence calcium homeostasis and have metabolic and antiremodeling effects. In addition, β-blockers exert an effect at the presynaptic level and modulate norepinephrine (NE) release and re-uptake (Tables 2 and 3). However, the relative contributions of these (proposed) mechanisms of action are unknown but will probably be unraveled in the future.

Table 2

<table>
<thead>
<tr>
<th>Levels of action of β-adrenergic blockers in heart failure</th>
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<tbody>
<tr>
<td>Reduction of sympathetic tone by a central effect</td>
</tr>
<tr>
<td>Modulation of norepinephrine release by presynaptic receptors</td>
</tr>
<tr>
<td>Interaction with RAAS system</td>
</tr>
<tr>
<td>Blockade of β receptors on myocyte</td>
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<tr>
<td>Interference with signal transduction</td>
</tr>
<tr>
<td>Interference with Calcium-homeostasis</td>
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Table 3

<table>
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<tr>
<th>Possible mechanisms by which β-blockers exhibit their effect in heart failure</th>
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<tbody>
<tr>
<td>Reverse remodeling</td>
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<tr>
<td>Anti-ischemic effect</td>
</tr>
<tr>
<td>Metabolic benefit</td>
</tr>
<tr>
<td>Inhibit maladaptive growth</td>
</tr>
<tr>
<td>Inhibit apoptosis</td>
</tr>
<tr>
<td>Improvement of systolic function</td>
</tr>
<tr>
<td>Improvement of diastolic function</td>
</tr>
</tbody>
</table>

Receptor level

Pathophysiology of adrenergic receptors

The main way to regulate contractility in the human heart is the β-adrenergic signal transduction pathway on the myocyte, shown schematically in figure 2.

On the human myocyte, 3 adrenergic receptors are distinguished: β₁, β₂, and α₁. Signal transduction from the adrenergic receptor is via the 'stimulatory' G proteins to the effector enzyme adenyl cyclase that converts the substrate ATP to cAMP. cAMP is (1) positively chronotropic, (2) positively inotropic and (3) growth promoting. α₁-Receptors are coupled via a different G-protein and primarily activate growth-promoting proteins.

The ability of extrinsic stimuli such as neurotransmitters (NE) and neurohormones (epinephrine)
to stimulate $\beta$-adrenergic receptors to increase heart rate and contractility is attenuated in the failing heart because of $\beta$-receptor downregulation$^{49,51}$ and changes at the level of signal transduction (G-proteins$^{52,53,54}$ and adenylate cyclase.$^{51,55,56}$) These alterations in the so called modulated contractile function result in a diminished myocardial reserve$^{51}$ and exercise response.$^{57}$

Given the fact that (1) NE levels in the synaptic cleft are increased in heart failure with a resulting overexposure of myocardial $\beta$-receptors (2) NE is mildly $\beta_1$ selective (3) overexpression of the $\beta_1$-adrenergic receptor produces an overtly cardiomyopathic phenotype and (4) the down-regulation of $\beta$-receptors appears to be a selective downregulation of the $\beta_1$-subtype all suggest that the $\beta_1$ receptor plays an important role in the progressive deterioration in systolic function and progression in remodeling.

The role of the $\beta_2$ receptor is less clear. In animal models, $\beta_2$-adrenergic overexpression can increase contractility but the effect appears to be dependent on the extent of overexpression.$^{59}$ It is suggested that prolonged overexpression of $\beta_2$ receptors and $\beta_2$ receptor overexpression related to pressure overload exacerbates the development of heart failure.$^{59}$

**Apoptosis**

In recent years it is increasingly recognized that the process of apoptosis, or programmed cell death, plays an important role in the development of cardiomyopathy and heart failure.$^{50}$ In vitro experiments with isolated cardiac myocytes indicate that chronic catecholamine stimulation induces
apoptosis. The apoptotic effect of β-adrenergic stimulation appears to be mediated largely by the β₁ receptor as was demonstrated in several animal studies with overexpression of the β₁-adrenergic receptor.

Adrenergic receptors and β-blockers
In failing human myocardium, metoprolol induces an upregulation in β-receptor expression and a down-regulation in G_{i/o} proteins. These alterations accompany improvements in systolic function suggesting a causal relation. However, carvedilol, a non-selective β-blocker, can improve myocardial function without causing changes in β-receptor expression. The pathophysiological importance of changes in β-receptor signal transduction and the influence of β-blockers on these pathways remain uncertain. It might well be possible that changes in β-receptor signal transduction are partially adaptive and serve to protect the heart from harmful β-adrenergic stimulation. The beneficial effects of β-blockers can thus be regarded as a further protection of the myocytes from catecholamines-induced cardiac apoptosis and necrosis.

Finally, β-adrenoreceptor polymorphism of both the β₁- and β₂ receptor can be related to survival and possibly, response to therapy. Further research will elucidate the clinical relevance of polymorphism and mutations which is now just at the beginning of a new way of understanding of the pathophysiology of heart disease and novel possibilities of therapy.

Calcium homeostasis and diastolic properties
Abnormalities in myocyte calcium handling may contribute to myocardial dysfunction. These abnormalities include an increase in diastolic calcium levels, a reduction in calcium release from the sarcoplasmic reticulum on stimulation and delayed re-uptake of calcium by the sarcoplasmic reticulum. One could hypothesize that these abnormalities correlate to increased myocardial stiffness, decreased contractility and delayed relaxation, respectively. Although the precise mechanism is unknown, there is strong evidence that β-blockers influence calcium homeostasis resulting in a decreased left ventricular end-diastolic pressure from both improved (active) early isovolumic relaxation and (passive) late relaxation.

Negative chronotropic activity
The negative chronotropic effect induced by β-blockers is likely to offer hemodynamic and anti-ischemic effects to the myocardium. A reduced heart rate during treatment with a β-blocker will result in a longer diastolic phase and a better perfusion of the myocardium. In addition it has been suggested that a redistribution of flow from non-ischemic to ischemic myocardial regions can be achieved with β-blockade resulting in a more homogenous distribution of blood in the myocardium. Better oxygen and nutrition delivery can possibly improve systolic and diastolic performance directly and through an increase of adrenergic receptor densities especially in hibernating myocardium.
However, the various actions of β-blockers go beyond their negative chronotropic effect since the improvement in systolic function occurs rather late and it is preceded by the slowing of heart rate and correction of neurohormonal derangements. In addition, an improvement of the force-frequency relationship can attribute to the observed beneficial effects of β-blockers irrespective of heart rate.  

**Metabolic and antiremodeling effects**

It was recently demonstrated that a reduction in oxidative metabolism can be obtained with metoprolol together with a slight improvement in left ventricular function supporting the concept that there is an energy-sparing effect of β-blocker therapy. Myocardial energy demands and oxygen consumption can be reduced by a reduction in heart rate and inotropy with β-blockers thus facilitating the repletion of energy stores. This may allow energy to be directed to repairing cell injury and restoring contractile elements thus facilitating the biological recovery of myocytes. In addition, β-blockers can also alter metabolic substrate utilization by reducing lipolysis that is known to occur by β-adrenergic stimulation.

Antiremodeling effects were seen using magnetic resonance imaging with a decrease in both left ventricular end-diastolic and end-systolic volume index and an increase of left ventricular ejection fraction after six months of treatment with metoprolol as compared with placebo.

**Central and presynaptic effects of β-blockers**

Sympathetic overactivity is a key feature of heart failure that can be considered initially as compensatory for a decreased cardiac output but eventually aggravates the disease process. The importance of excessive sympathetic activity is suggested by elevated plasma levels of NE that have been correlated to poor prognosis and reduced survival. These increased levels of NE are also detected in the synaptic cleft in the myocardium and are considered the result of impaired re-uptake of NE in the presynaptic neuron (the main way to inactivate NE) and increased release of NE.

Whether β-blockers reduce efferent sympathetic outflow to the heart is a matter of controversy. Increased neuronal release of NE can be the result of stimulation of β-adrenergic receptors in intrathoracic ganglia and on intrinsic cardiac neurons resulting in an increased firing rate of postganglionic cardiac sympathetic nerves and an increased neuronal release of NE. It can be hypothesized that long-term blockade of these receptors would cause an inhibition of sympathetic outflow to the heart resulting in decreased levels of NE within the synaptic cleft. Although β-blockers can exhibit some influence on these presynaptic sympathoexcitatory β-receptors and thereby decrease NE release, it seems unlikely that the overall effect can be explained by this mechanism. To make things even more complex, presynaptic neurons contain α-receptors that inhibit sympathetic outflow. These effects are, therefore, counterregulatory to the effects of β-receptors on the same presynaptic neuron. It was recently demonstrated that carvedilol, in contrast to other
β-blockers, enhanced cardiac NE release in the human heart, most likely as a consequence of presynaptic α₂-blockade.¹

Another mode of action of β-blockers might be an interaction between the presynaptic re-uptake of NE from the synaptic cleft (the main mechanism by which NE is inactivated). Improved re-uptake of NE will result in decreased levels of NE in the synaptic cleft and therefore less toxic effects on the cardiac myocyte. Whether this mechanism is operative remains to be established. It has been shown that β-blockers have a presynaptic effect as measured by improved uptake of ¹²³I-MetaIodoBenzylGuanidine, a structural analogue of NE, sharing the same uptake and storage mechanisms.²

**Interference of β-blockers with the renin angiotensin system**

Interaction between angiotensin II (ANG II) and the sympathetic nervous system are known for many years.¹⁴ The modes of action of ANG II on the sympathetic nervous system include a central action to increase sympathetic outflow, stimulatory effects on sympathetic ganglia and the adrenal medulla and actions at sympathetic nerve endings to facilitate sympathetic NE release. The activity of the sympathetic nervous system is one of the factors that determine the rate of renin release by the kidneys. Since the rate of renin release is the limiting step in the formation of ANG II, sympathetic activity is an important factor that determine the circulating levels of ANG II.

β-blockers will also result in a further deactivation of the renin angiotensin system, even in the presence of an ACE inhibitor⁵⁵ resulting in decreased levels of angiotensin II. In turn, these lower levels of angiotensin II will lower the presynaptic NE release as angiotensin II facilitates presynaptic NE release through presynaptic angiotensin II receptors.⁶⁰

**Conclusions**

The beneficial effects of β-blockers on both morbidity and mortality in heart failure have been convincingly shown in recently conducted double blind, placebo controlled trials. Our meta-analysis involving more than 15,000 patients confirm these results. In addition, β-blockers will improve left ventricular ejection fraction and diastolic properties. Generally speaking, β-blockers will not influence functional parameters although an improvement in NYHA classification has been reported.

The exact cellular mechanisms responsible for these salutary effects of chronic β-blockade have not been fully defined. However, there is strong evidence that β-blockers exert their effects at several levels in the myocardium including upregulation of β-receptors, prevention of NE-induced toxicity, influence on calcium-homeostasis, anti-ischemic effects, presynaptic modulation of NE handling and through an interaction with angiotensin II. Future research at the cellular level will further elucidate the exact mechanism(s) of action.
Addendum

Awaiting publication of this manuscript two additional randomized, placebo-controlled studies of β-blockers in heart failure were published. The Carvedilol Prospective Randomized Cumulative Survival Study (Copernicus) included 2289 patients with more severe forms of heart failure (NYHA functional class III+ and IV) and an ejection fraction <25%. After a mean duration of follow-up of 10.4 months, the study was discontinued prematurely because of significant difference in the primary endpoint between the two groups. There were 190 deaths in the placebo group and 130 deaths in the carvedilol group. This difference reflected a 35% decrease in the risk of death with carvedilol. The cumulative risk of death at one year was 18.5% in the placebo group and 11.4% in the carvedilol group. The combined risk of hospitalization and death was 24 percent lower in the carvedilol group (P<0.001).

The Beta-blocker Evaluation of Survival Trial (BEST) randomized 2708 patients with heart failure functional class III and IV and an ejection fraction <35% to bucindolol or placebo. The mean duration of follow-up was 2 years. A total of 449 patients died in the placebo group (33%), as did 411 in the bucindolol group (30%, hazard ratio 0.90, P=0.10). Bucindolol reduced the proportion of patients hospitalized for heart failure (hazard ratio 0.78, P<0.001). Of concern is the fact that approximately 25% of the patients in both the placebo and the bucindolol group permanently discontinued study medication. In addition, the rate of use of open-label β-blockers was relatively high (10% in the placebo group and 6% in the bucindolol group, P<0.001). These differences might have influenced the final results of the BEST study. Although the BEST study showed no significant difference in the primary endpoint, a trend toward a survival benefit was observed with bucindolol. The results of both Copernicus and, to a lesser extend the BEST study are in line with our meta-analysis.

References


Chapter IV


