Beta-blockers and heart failure

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Heart failure is a common disease that progresses slowly and is associated with a very poor prognosis. Some beta-blocking agents have been shown to reduce mortality and to improve quality of life in patients with mild to moderate cardiac dysfunction. The authors review the current data on pathophysiology of heart failure, the effects, mechanisms of action and pharmacological differences of beta-blocking drugs, summarise the most important studies with stress on COPERNICUS (Carvedilol in ProspEctive RanDomised Cumulative Survival) trial, which first demonstrated that the multiple action adrenergic inhibitor carvedilol is also beneficial in patients with severe heart failure. J Clin Basic Cardiol 2001; 4: 11–14.

**Key words:** beta-blockers, heart failure, COPERNICUS

When beta-adrenergic blocking agents were put on the pharmacological market about 40 years ago, these drugs were considered to be contraindicated in patients with heart failure. Sympathetic stimulation was thought to be profitable for a failing heart. It was concluded that negative inotropic and chronotropic effects of beta-blocking agents worsen the course of this disease.

However, concepts in pathophysiology of heart failure have changed. Obviously, chronic activation of the sympathetic nervous system damages the myocardium. Moreover, clinical trials have shown that beta-blocking drugs can reduce mortality in patients after myocardial infarction and with symptomatic chronic heart failure.

**Definition, Epidemiology and Prognosis of Heart Failure**

Heart failure is quite difficult to define. This syndrome shows a disturbance of circulation due to cardiac dysfunction, which leads to a reduction of blood flow and decreases tissue oxygen supply. The heart is no longer able to perform the metabolic requirements of the body. Essential features for the diagnosis of heart failure are clinical symptoms (dyspnoea, fatigue, oedemas) and findings of cardiac dysfunction [1] (Table 1).

Heart failure represents mainly a disease of the elderly. With regard to data of the Framingham Heart Study, 0.4–1 % of the total population suffers from cardiac dysfunction. It occurs in less than 1 % of individuals younger than 55 years, about 2–5 % between the age of 65 and 75 and rises up to 10 % in people in their 80s.

The prognosis remains poor. The 5-year survival rate of patients with heart failure is about 25 % in men and 38 % in women [2]. In severe stages of the disease, quality of life as well as mortality rates are comparable with those of cancer.

**Pathophysiology of Heart Failure**

Reduced cardiac output occurs because of two different mechanisms: systolic or diastolic dysfunction. The most common causes for cardiac dysfunction are coronary artery disease and hypertension. Valvular diseases, idiopathic dilated cardiomyopathy, alcohol induced and myocarctis induced cardiomyopathy are other important reasons.

First therapy strategies considered heart failure to be a disorder of fluid retention. It has been suggested that “forward failure” causes a declined renal blood flow and due to that an impairment of sodium and water excretion [3] and further an inability of the heart to deal with venous blood from the periphery. Therefore this may lead to an increase in venous pressure with development of oedemas (“backward failure”) [4]. Diuretics and digitalis seemed to be the treatment of choice in the “oedema model”.

Later on, it was recognized that an impaired cardiac function was associated with chronic constriction of veins and arteries [5]. The rise of preload and afterload leads to left ventricular hypertrophy and dilatation. Reduction of renal perfusion causes oedema and pulmonary congestion. Reduced perfusion of skeletal muscles is followed by reduced exercise capacity. Due to this “cardiocirculatory model” vaso-dilators seemed to be an ingenious therapy.

In the last 20 years the “neurohumoral model” was developed [6]. Neurohumoral systems, renin-angiotensin-aldosteron-system (RAAS) and local vasoactive peptides as well as the sympathetic nervous system are chronically activated in heart failure. This may lead to coronary and systemic vasoconstriction and further to an enhanced retention of sodium and water. Vasoconstriction reduces myocardial oxygen supply, which results in cardiac myocyte dysfunction and necrosis. In addition, there is strong evidence that angiotensin II and catecholamines as well as cytokines have a direct toxic effect on cardiac myocytes and trigger apoptosis [7, 8]. This leads to further cardiac dysfunction and a *circulus vitiosus* forms causing the continual progression of the disease.

**Table 1. European Society of Cardiology guidelines for the diagnosis of heart failure [1]**

<table>
<thead>
<tr>
<th>Essential features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• symptoms of heart failure (breathlessness, fatigue, ankle swelling)</td>
</tr>
<tr>
<td>• objective evidence of cardiac dysfunction (at rest)</td>
</tr>
<tr>
<td>Non-essential features</td>
</tr>
<tr>
<td>in cases where the diagnosis is in doubt, there is a response to treatment directed towards heart failure</td>
</tr>
</tbody>
</table>

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Therefore, agents which are able to reduce the neurohumoral and nervous activity like ACE-inhibitors, beta-blockers and angiotensin II-antagonists should be beneficial.

Cardioprotective Effects of Beta-Blocking Agents (Table 2)

Beta-blockers cause a competitive inhibition of beta-adrenergic receptors. Most of the myocardial beta-receptors are of the beta1-subtype, just a few are of the beta2-subtype. Sympathetic nervous system activation is prolonged in patients with heart failure. There is a down regulation of beta1-receptors in the failing heart [9]. They are reduced in number and density, whereas the number of beta2-receptors remains unchanged. The percentage of beta2-receptors increases from 20% up to 40%.

The plasma levels of norepinephrin are elevated. Catecholamines have a direct toxic effect on cardiac myocytes. Beta-stimulation leads to an elevation of cAMP and, therefore, to an increase in intracellular calcium. Prolonged activation in heart failure may be the reason for calcium overload and myocyte death [10]. This is considered to be one of the key-points of the beneficial effects of beta-blockers.

Reduction of the heart rate prolongs diastole and, due to this, increases coronary perfusion time. A low heart rate is also associated with a lower myocardial oxygen demand and, therefore, myocardial ischaemia is reduced [11].

Other possible effects of beta-blockers on the myocardium are a reduction of cardiac arrhythmias, prevention of coronary plaque ruptures by modifying the atherosclerotic process even when no effect on platelet aggregation could be demonstrated [12].

Concerning the haemodynamic effects of beta-blockers, one must distinguish between acute and chronic changes. Beta-blockers act as negative inotropic and negative chronotropic agents because of their reduction of cardiac index in the short term [13, 14]. Applications at the wrong time in an inadequate dose can worsen clinical symptoms.

The results of studies in patients with dilative and ischaemic cardiomyopathy demonstrate that chronic administration of beta-blockers leads to a constant decreased heart rate, whereas blood-pressure remains largely unchanged. There was no negative effect on cardiac index, sometimes cardiac index was even increased [15, 16].

Beta-blockers play an important role in the neuroendocrine system. Activation of beta1-adrenoceptors in the kidney leads to release of renin, which stimulates angiotensin II consecutively. Angiotensin II represents a potent vasoconstritor which increases vascular peripheral resistance. It also leads to renal vasoconstriction, to the release of aldosteron and, therefore, to salt and water retention. Catecholamines as well as angiotensin II have additional direct toxic effects on cardiomyocytes. Beta-blockers can interrupt these neurohumoral activation pathways.

Differences between Beta-Blocking Drugs

Beta-blockers differ in various pharmacologic qualities like selectivity for beta1 and beta2-receptors, their intrinsic activity (ISA), their action on other adrenergic receptors, their ability of vasodilatation as well as their antioxidative and antiproliferative effects (Table 3) [17].

In comparison to the normal myocardium, the portion of beta2-receptors rises from 20% to 40% in the failing heart. So, non-selective agents that block both types of receptors may be more effective.

Beta-blockers with intrinsic sympathomimetic activity (ISA) such as labetalol may block or stimulate sympathetic effects in order to achieve a high or low level of norepinephrine. However, the use of such agents in patients with severe left ventricular dysfunction has been associated with increased mortality [18]. Therefore beta-blockers with ISA should not be prescribed to patients with heart failure.

Beta-blockers can induce vasodilatation by alpha1-receptor-blockade (carvedilol), by an agonistic effect to peripheral beta-receptors (celiprolol) or by direct effects (bucindolol). The reduction of preload and afterload is responsible for the haemodynamic benefits of these drugs.

Antiproliferative and antioxidant effects have been shown for carvedilol in vitro and in vivo in hypertensive patients [19]. Clinical significance is not yet proven.

Clinical Trials

Various studies have shown beneficial effects of beta-blocking agents in patients with heart failure.

In MDC (Metoprolol in Dilated Cardiomyopathy) trial metoprolol reduced clinical deterioration and improved symptoms and cardiac function in comparison with placebo. However, mortality was not reduced [20].

MERIT-HF (Metoprolol CR XL Randomised Intervention Trial in Congestive Heart Failure) could report a significant reduction of mortality by using slowly released metoprolol [21].

Whereas CIBIS II (The Cardiac Insufficiency Bisoprolol Study) did not show significant improvement in survival using bisoprolol (1.25 mg–5mg) in congestive heart failure, CIBIS II with a higher target dose (1.25 mg–10 mg) of bisoprolol resulted in reduced mortality and hospitalisation rates [22, 23].

More data and experience in clinical trials exist with carvedilol than with any other beta-blocking drug. The US Carvedilol Program, the Australia-New Zealand Trial or MOCHA (Multicenter Oral Carvedilol Heart failure Assessment) demonstrated a dose-related improvement of left ventricular function and a reduction in mortality rates [24–26]. Most of these former mentioned beta-blocker trials have provided evidence on beneficial effects of beta-blockade in mild to moderate heart failure. In patients with severe heart failure, there has been a lack of significant evidence on these drug-effects. The BEST and COPERNICUS trials were the first trials to evaluate the role of beta-blockade in this patient population.

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**Table 2. Cardioprotective mechanisms of beta-blockers**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiischaemic effect</td>
<td>Prevention of catecholamine toxicity</td>
</tr>
<tr>
<td>Antinarrhythmic effect</td>
<td>Reduction of neurohumoral activity</td>
</tr>
<tr>
<td>Reduction of preload and afterload</td>
<td>Vasodilatation, their action on other adrenergic receptors, their ability of</td>
</tr>
<tr>
<td>Haemodynamic effects</td>
<td>Modification of the atherosclerotic process</td>
</tr>
</tbody>
</table>

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**Table 3. Various beta-blocking agents and their differentiation with respect to beta1-selectivity, ISA and vasodilatation** [17]

<table>
<thead>
<tr>
<th>Agent</th>
<th>Beta1-selective</th>
<th>ISA</th>
<th>Vasodilatation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bucindolol</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Labetalol</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pindolol</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Propranolol</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sotalol</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
The aim of BEST (Beta Blockers Evaluation Survival Trial) was a comparison of bucindolol with placebo added to standard therapy in patient with severe heart failure [27]. The study was stopped because there was no significant difference in all cause mortality between bucindolol and placebo, probably due to the intrinsic sympathomimetic activity of bucindolol [28].

COPERNICUS (Carvedilol OI Prospective Randomised Cumulative Survival Study) was the first randomised, placebo-controlled trial to demonstrate significant benefits of beta-blockade in patients with severe chronic heart failure. The study was multi-center, multi-national and double-blind. Carvedilol or placebo were added to optimised standard treatment with ACE inhibitors, diuretics and in many cases digitalis. 2289 patients with stable severe chronic disease were enrolled. The starting dose was 3.125 mg carvedilol twice a day and was up-titrated every 2 weeks to a target dose of twice daily 25 mg. The COPERNICUS trial was stopped early in March 2000 due to the highly significant survival benefit in the patient group treated with carvedilol. The responsible Data Safety Monitoring Board considered it unethical to let patients continue taking placebo and recommended open label carvedilol treatment to all patients. Primary results were presented at the 22nd Congress of the European Society of Cardiology in Amsterdam in August 2000 [29] and during the American Heart Association’s 73rd Annual Scientific Sessions in New Orleans in November 2000 [30] (Table 4).

The primary endpoint was all-cause mortality, which was highly significantly reduced by 35 % in the carvedilol treatment arm (p < 0.00013). Secondary endpoints were the combination of all cause mortality with the hospitalisation rates for either heart failure, cardiovascular hospitalisations or all cause hospitalisations. Additionally, the impact of carvedilol or placebo on quality of life was investigated. All these endpoints were also significantly beneficial in the carvedilol group. The drug was tolerated well – fewer adverse events and lower withdrawal rates were reported for carvedilol than for placebo. So, based on the currently published evidence of beta-blockers in severe heart failure, only carvedilol can be recommended for treatment of these patients. Carvedilol differs from metoprolol and bisoprolol because of blocking beta1, beta2 and alpha1 adrenergic receptors. The comprehensive adrenergic blockade may be even an advantage because of the raised portion of beta2 receptors in the failing heart. Beta1-selective agents get more non-selective with higher doses, which may be the reason for the benefits in reducing mortality in MERIT-HF and CIBIS II in comparison with MDC and CIBIS. The vasodilating effect of carvedilol by blocking alpha1-receptors seems to improve haemodynamic balance. However up to now, no data from large-scale trials that compare carvedilol and other beta-blocking drugs in heart failure are available. The COMET study (Carvedilol Or Metoprolol European Trials) comparing carvedilol and metoprolol in more than 3000 patients with heart failure is still going on. First results are expected in 2002.

Some other carvedilol studies are ongoing like CARMEN (Carvedilol ACE inhibitors Remodelling Mild heart failure Evaluation) which examines the effect of the combination of enalapril and carvedilol versus enalapril or carvedilol alone on LV-remodelling in patients with heart failure, the CHRISTMAS study (Carvedilol Hibernation Reversible Ischemia Trial) investigating the effects of carvedilol in patients with or without hibernating myocardium and the CAPRICORN which investigates the effect of carvedilol on mortality in patients with left ventricular dysfunction early after myocardial infarction. Results will be presented at the 50th Meeting of the American College of Cardiology in March 2001.

**Conclusions**

Beta-blocking agents are established as a part of standard therapy in patients with heart failure. They have been shown to reduce mortality and to improve quality of life by decreasing sympathetic drive, which is chronically increased in heart failure, and by disturbing and interrupting neurohumoral pathways. Because of the acute haemodynamic effects of beta-blockers the initial dose should be very low and should be titrated up to a target dose carefully (Table 5). Most of the studies were done in patients with mild to moderate heart failure. The COPERNICUS trial demonstrated that the multiple action adrenergic inhibitor carvedilol is also very beneficial in patients with stable severe heart failure in reducing mortality and improving symptoms and left ventricular function. Carvedilol is certainly the most investigated beta-blocking agent in patients with heart failure and favourable data. Its efficacy may be due to blocking beta1, beta2 and alpha1 receptors. However, no data comparing carvedilol with beta-selective drugs are available now: Large-scale trials are ongoing and will hopefully help us finding the optimal therapy in the future.

**References:**


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**Table 4. Studies on beta-blockers in heart failure**

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>NYHA IV patients</th>
<th>Placebo-mortality</th>
<th>Risk reduction/mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol</td>
<td>Carvedilol</td>
<td>2.9 %</td>
<td>11.1 %</td>
<td>65 %</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol</td>
<td>3.6 %</td>
<td>11.0 %</td>
<td>34 %</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>Bisoprolol</td>
<td>16.8 %</td>
<td>13.2 %</td>
<td>34 %</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol</td>
<td>100 %</td>
<td>19.7 %</td>
<td>35 %</td>
</tr>
</tbody>
</table>

**Table 5. Starting and target dose of various beta-blockers used in heart failure**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg q.d.</td>
<td>10.0 mg q.d</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>12.5 mg q.d.</td>
<td>200 mg q.d.</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg b.i.d.</td>
<td>6.25–25 mg b.i.d.*</td>
</tr>
</tbody>
</table>

* for patients > 85 kg 50 mg b.i.d.
30. Packer M, on behalf of the COPERNICUS investigators. Effects of carvedilol on the survival of patients with severe chronic heart failure. Data presented at the 73rd Meeting of the American Heart Association, Nov. 11–15, 2000, New Orleans, USA.
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