REVIEW

Benefits of beta-blockers in heart failure

Sleiman OI, Murin J, Ghanem WM

1st Department of Internal Medicine, University Hospital, Faculty of Medicine, Comenius University, Bratislava, Slovakia.
Ossamasleiman@hotmail.com

Abstract

The problem of heart failure (HF) has become a topic of great interest. Until recently, the use of beta-blockers in patients with HF was considered as a contraindication. Times have changed and the contra-indicated drug is now an advised and preferred one to be used in HF patients with certain advised recommendations for its use in a safe and beneficial way. Still we need to emphasize the benefits of these agents in order to achieve more application in HF patients.
Here we try to stress the proved beneficial effects of beta-blockers by major studies in HF patients, and to supply the reader with practical information regarding the use of these agents with a look at the frequency of using them and the possible reasons behind their underuse. The files of heart failure patients admitted to 1st Internal Department in the University Hospital in Bratislava in the period between January and December 1997 were checked to show the magnitude of using beta-blockers in them. Among 150 patients admitted during the above mentioned period only 30 patients (20 %) received beta-blockers. It seems that beta-blockers have to be used in all patients with HF with reduced ejection fraction unless a real contraindication exists, but the actual data shows that beta-blockers are still underused. ***(Tab. 2, Ref. 30.)***
Key words: heart failure, beta-blockers, mortality, sudden death.

It is clear now that the proved benefits of beta-blockers in heart failure (HF) patients acquire from us more consideration of these agents when we prescribe treatment. The famous studies and trials which tested the effects of beta-blockers in HF patients as US Carvedilol Heart failure Study (1), MERIT-HF (2, 3) and CIBIS-II (4) (mentioned in details in part I) have attracted our attention to the great benefits which can be achieved by putting our patients on one of these agents. Now we look at these agents as a great tool for decreasing mortality and morbidity in HF patients in addition to the economic benefit of their incorporation in our prescriptions.

How to explain the beneficial effects of beta-blockers?

The following table 1 shows some of the possible mechanisms by which beta-blockers work in HF patients.

Beta-blockers in addition act as anti-ischemic drugs, with anti-renin-angiotensin properties, they prolong coronary diastolic filling time, inhibit stimulatory anti $beta_1$-receptor autoantibodies, augment atrial and brain naturetic peptide, lower plasma endothelin-1 levels (carvedilol), and stimulate the endothelial L-arginine/nitric oxide pathway (nebivolol) (5). Regarding the point of up-regulation of beta-receptors it is now known that while some of the beta-blockers as metoprolol and bisoprolol cause up-regulation of these receptors carvedilol does not do so, the point which stresses the importance of other mechanisms by which beta-blockers improve the situation in HF patients. As the up-regulation process occurs within hours to days of treatment with beta-blockers, clinical improvement may take several months to take place. Even it is noticed that ventricular improvement may occur without an increase in beta-receptors density (6).

Catecholamines cause shifting of substrate utilization from glucose to fatty acids reducing by this the efficiency of the heart, the process which can by reversed by beta-blockers. The abilily of beta-blockers to decrease the risk of sudden death adds one of the important factors why they improve survival in HF patients.

1st Department of Internal Medicine, University Hospital, Faculty of Medicine, Comenius University, Bratislava, Slovakia

Address for correspondence: O.I. Sleiman, MD, 1st Dept of Internal Medicine, University Hospital, Mickiewiczova 13, SK-813 69 Bratislava 1, Slovakia.
Phone/Fax: +421.2.52925875

Tab. 1. Some possible mechanisms of beta-blockers actions in HF patients.

Up-regulation of beta-receptors
Increased myocardial catecholamine stores
Decreased heart rate
Improved ventricular contractility and synchrony
Inhibition of norepinephrine-mediated muscular hypertrophy
Prevention of norepinephrine-mediated apoptosis
Decreased central sympathetic outflow
Antiarrhythmic effect

Elevated norepinephrine level causes long-term beta-receptor down-regulation which results in attenuation of inotropic activity, while alpha-receptor stimulation leads to myocyte hypertrophy via activation of C-MYC oncogene regulating system (7) thus contributing to a great extent in the remodeling process. Low output status and the increased afterload due to vasoconstriction can accelerate the rate of myocardial cell death in the failing heart in addition to apoptosis (8)caused by the direct effect of catecholamines on heart muscles cells. The radical change noticed in myocardial gene expression (reinduction of fetal genes and myosin heavy chains isoform shifts) secondary to elevated levels of catecholamines is an important part in the scenario of progression of HF.

Secondary to sympathetic stimulation vasoconstriction occurs in kidneys thus elevating level of renin-angiotensin which can contribute further to ventricular remodelling by promoting smooth muscle cell growth via C-FOS oncogene pathway (7), causing smooth muscle cell growth in peripheral vascular network impairing arteriolar dilating ability by inhibiting distensibility, enhancing norepinephrine release and its systemic effect and increasing interstitial deposition of collagen.

When we put all the above data together we can judge that beta-blockers exert their greatest beneficial effects through the reduction of sympathetic nervous system activity.

When to use beta-blockers in heart failure?

The well known beneficial effects of beta-blockers on mortality and morbidity in HF patients create a suggestion that every HF patient should be a candidate for receiving one of the beta-blockers known to work in HF. M. Califf stated that all HF patients with EF less than 40 % and no contraindication to beta-blockers therapy should have them intiated (9). J. Cohn (10) suggests the use of carvedilol in patients whose ventricles remain dilated and whose ejection fractions remain depressed while on conventional therapy, whereas M. Fowler (11) states that patients with NYHA class II or III HF who have been stabilized through therapy with ACEIs and diuretics can expect an improvement in the quality as well as the quantity of life with beta-blocker therapy. M. Packer said commenting on the results of COPERNICUS study (12): what we hope is that the results of COPERNICUS will be so compelling and so persuasive that physicians will no longer have an excuse not to use beta-blockers for HF.

Are all beta-blockers similar in their actions?

Certainly not. The down-regulation of $beta_1$-receptors in HF patients is well established, the fact which was stressed upon by Bristow and coworkers (13) when they watched the effects of $beta_1$ and $beta_2$ agonists on failing heart muscles. That was the reason behind the suggestion that the failing heart depends on $beta_2$-receptors for the maintenance of its contractility and the expectations that the usage of beta-selective blockers is superior to that of non-selective ones. Swedberg et al. (14) supported this by his research using alprenolol which was associated with clinical deterioration in HF patients who used this drug. But this was not everything because the debate about the superiority of selective beta-blockers led to more studies (15) which did not agree with that theory, showing that there were no differences in the magnitude of the negative inotropic effects of nonselective beta-receptor blockade compared with selective blockade in patients with HF. In addition to that it was clear from the long term follow-up studies that when a nonselective beta-blocker was used as carvedilol (16, 17), better results were obtained as reduction in mortality reaching up to 67 %. It is worth noting that while we use nonselective beta-blockers, the chance of exposing patients to unwanted side effects (for more details see below) is greater through $beta_2$-mediated actions. So the use of a selective beta-blocker reduces the side effects which can be reduced further by the use a sustained-release $beta_1$-selective drug (which can be advantageous in patients with obstructive lung disease, smokers, physically active patients, diabetics, those with lipid disorders, pregnancy, and portal hypertension) (18).

Now there are some more data suggesting that $beta_1$-blockade helps in prevention of apoptosis (myocardial necrosis occurs by the stimulation of $beta_1$-receptors through cAMP-dependent process) and that $beta_2$-receptor stimulation inhibits apoptosis as well (5), the points considered as a big plus to the use of a selective beta-blocker. Regarding the surprising renoprotective effect of beta-blockers in HF patients (see above) it appears that with $beta_1$-selective blockers there would be less chances to decrease renal blood flow and glomerular filtration rate than with non-selective ones the fact which makes the use of selective beta-blockers more favourable. But in contrast to that recent data (19) showed that the use of carvedilol but not metoprolol improved renal hemodynamics in patients with chronic HF. It must however be remembered that selectivity is a relative term because as low concentrations of $beta_1$-blockers have little impact on $beta_2$-mediated effects higher plasma concentrations of $beta_1$-blockers will increasingly inhibit $beta_2$-mediated responses. In this context it is convenient to mention some selective $beta_1$-blockers in order of selectivity (bisoprolol = nebivolol > atenolol > metoprolol > acebutolol = celiprolol), while (alprenolol, carvedilol, mepindolol, nadolol, oxprenolol, pindolol, propranolol, sotalol and timolol) are nonselective beta-blockers.

Some researches were interested in comparison between the effects of different beta-blockers. *MEXIS* study (20, 21) compared between the influences of metoprolol and xamoterol on HF patients after myocardial infarction. After one year of follow-up and the use of traditional treatment of HF it was found that the efficacy of both drugs in improving exercise tolerance, quality of life, and signs of HF were comparable, however the use of xamoterol in contrast to metoprolol was associated with impairment of left ventricular systolic function.

Another more interesting comparison was between carvedilol and metoprolol in HF patients the results of which were published recently (22). This study enrolled 150 patients with moderately

severe HF who were randomised to receive carvedilol or metoprolol. After a follow-up period of about 15 months there was a significantly greater improvement in EF and a better heart rate control during exercise in the carvedilol group compared to metoprolol. In contrast metoprolol showed greater increases in maximal exercise capacity than carvedilol. Death rate and urgent heart transplantation were lower in the carvedilol group. In this field COMET study (23) is supposed to inform us more about the superiority of one of these two drugs.

Very recently a paper appeared summarizing the work done in the field of HF and beta-blockers (24). It mentioned that among the most famous studies performed there was a trend towards a better survival when vasodilating beta-blockers were used compared to nonvasodilating ones as these vasodilators (e.g. celiprolol ($beta_2$-ISA), carvedilol ($alpha_1$-antagonism) and nebivolol (activation of NO synthase)) have the advantage of reducing peripheral resistance.

Choosing lipophilic agents as metoprolol, timolol or propranolol is associated with decrease in mortality in coronary heart disease, particularly sudden death since these agents can cross blood brain barrier so restoring vagal tone and decreasing the risk of ventricular fibrillation. In general it is noticed that key studies illustrate that cardioprotective efficacy is associated with moderate or high lipophilicity (25) whereas the best known hydrophilic drugs, (sotalol and atenolol) did not prove to lower the risk of sudden death (26). In this context we mention here that the ability of atenolol in reducing cardiovascular events and stroke was not significant in hypertensive patients in contrast to hydrochlorothiazide and amiloride which had significant results (26).

Beta-blockers which possess intrinsic sympathomimetic activity (ISA) (acebutolol, oxprenolol and pindolol) show lower tendency to cause bradycardia but there is little evidence to support the hypothesis that ISA is a clinically useful characteristic (25), even it was shown that these agents were associated with less reduction in mortality in patients with acute myocardial infarction (18). Agents with ISA do not reach the maximal effect of a full agonist because they are unable to occupy fully beta-receptors. Perhaps these agents can be useful in patients with low heart rate, low HDL -cholesterol or high triglycerides (18).

In contrast to old thoughts it seems now according to a recent study (27) that the use of a sustained-release formulation of metoprolol does not produce better hemodynamic effects than an immediate-release formulation in HF patients.

How to use a beta-blocker?

It is now well known that simple cardiac insufficiency is not a contraindication to the use of beta-blockers when they are used in a proper way and at doses recommended.

The following table 2 shows the points have to be considered when a beta-blocker is to be used in HF patients.

It seems crucial to mention here that attenuating sympathetic activity must be gradual otherwise detrimental results can be expected as it was shown by MOXCON trial (28) where moxonidine was used in HF patients. Moxonidine was successful in reducing norepinephrine level but it caused a significant increased mortality due to unclear reasons one of which might be the too effective and rapid sympathetic activity suppression.

Tab. 2. How to use beta-blockers in HF patients.

1. Patients have to be stable for at least two weeks
2. Patients have to be informed about expected clinical deterioration at the onset of treatment increament
3. To be given in addition to diuretics, ACEIs, and digitalis
4. Out-patient treatment in patients with NYHA I-III
5. In-patient treatment in patients with NYHA IV
6. Starting dose: 1/10 of the target dose
7. Dosage to be increased (doubled) at least every two weeks before which the patient has to be examined. Clinical improvement could be noticed at least after 3 months
8. Target doses: carvedilol 25 mg b.i.d., metoprolol 100 mg b.i.d. bisoprolol 5 mg b.i.d.
9. Care to be payed that no real contraindication exists

Do HF patients tolerate beta-blockers?

Statistics showed that bucindolol was tolerated by (95—100 %) of HF patients in the trials performed in the early 90s, while the tolerability of metoprolol was (79—100 %) in the late 80s (6). From the above discussion considering major trials performed on beta-blockers it is clear that this therapy was well tolerated in most instances.

Certain parameters were considered by different studies and trials to judge the therapy untolerable or titration as failed, such as progression of HF (increased orthopnea or dyspnea, dizziness and tiredness with or without hypotension or bradycardia), titration failure (a dose titration time of >100 days), failure to reach the target dose of a given beta-blocker, or the need for adjustment of concomitant treatment.

One of the interesting papers appeared recently (29) showed that beta-blockers titration failure was not predicted by the severity of HF while preserved systolic blood pressure may indicate normal titration.

It was shown that most patients with HF tolerate beta-blockers due to the preservation of passive late diastolic function and ventriculo-arterial coupling (15).

Beta-blockers still underused in HF patients!

It seems interesting that eventhough 22 randomised placebo controlled trials of beta-blockers collectively demonstrate a 23 % relative reduction in mortality, recent reports from the USA and Europe indicate that only 30—40 % of post-myocardial infarction patients are expected to receive a beta-blocker (30) and that only 5—15 % of HF patients eligible to receive a beta-blocker are being treated with one of these agents (12).

The files of heart failure patients admitted to 1st Department of Internal Medicine, University hospital in Bratislava in the period between January and December 1997 were checked to show the magnitude of using beta-blockers in them. Among 150 patients admitted during the above mentioned period only 30 patients (20 %) received beta-blockers. This point emphasizes the need for more application of these agents.

The reasons for the under-use of beta-blockers in HF patients are complex and multi-factorial (12). It is clear that tolerability of beta-blockers is not the reason behind that, since most of patients

treated with these agents tolerated them. It seems that for many doctors, treating HF patients with beta-blockers (which is relatively a new policy) conflicts with their early training to which they are still used. The appearance of HF after myocardial infarction was often cited as a reason to withhold or even to withdraw beta-blockers so it will be hard to re-educate physicians about the effectiveness of this drug class (12). Part of the reason for this underuse could be the results reported from the *BEST* trial with bucindolol which showed no benefit overall with the beta-blocker and raised the possibility that it may even be deleterious in severe HF (12).

Selectivity and side effects of beta-blockers

As it has been discussed before most of the side effects seen when a beta-blocker is used are due to $beta_2$-blockade. Here some clinical points are discussed in more details:

— Bronchoconstriction: which is seen when a non-selective beta-blocker is used but we do not have to forget that even a highly selective $beta_1$-blocker is not totally safe in patients with reversible airways disease (5).

— Hyperglycaemia: it is noticed that non-selective beta-blockers can cause a small increase in blood sugar, however $beta_1$-blockers can increase insulin resistance and HbA1c which can be prevented if potassium and weight changes are avoided.

— Hypoglycaemia: non-selective beta-blocker can delay the return of insulin-induced low blood sugar levels to normal and hypoglycaemic signs can be modified (5), that is why for a patient who is on insulin therapy $beta_1$-selective blocker would be the agent of choice.

— Cigarette smoking: blood pressure changes occur in smokers with non-selective beta-blockers but not with selective ones. It is interesting that the anti-ischemic effect of propranolol in patients with coronary heart disease are abolished by cigarette smoking.

— Blood lipid: changes in lipid profile as increase in VLDL and triglyceride and decrease in HDL are more marked with non-selective beta-blockers than selective ones. It is even stated that blood lipid changes with highly selective $beta_1$-blockers as bisoprolol are minimal or absent (5).

— Muscle metabolism: non-selective beta-blockers impair exercise duration and training more than selective-blockers reflecting the influence of non-selective blockers on muscle metabolism and physical performance.

As it is clear now that with paying some attention to the side effects which may appear in some patients and avoiding prescribing these agents to those where a real contraindication exists, beta-blockers are considered as agents of promising future for HF patients.

References

1. Colucci W.S., Packer M., Bristow M.R. et al.: US carvedilol heart failure study. Circulation 1996; 94: 2800—2806.

2. The International Steering Committee on behalf of the MERIT-HF Study Group: Rationale, design and organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). Amer J Cardiol 1997; 80 (9B): 54—58.

3. MERIT-HF Study Group: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999; 353: 2001—2007.

4. CIBIS-II Investigators and Committees: The Cardiac Insufficiency BIsoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353: 9—13.

5. Cruickshank J.M.: Beta-blockers continue to surprise us. Europ Heart J 2000; 21: 354—364.

6. Eichhorn E.J.: The paradox of beta-adrenergic blockade for the management of congestive heart failure. Amer J Cardiol 1992; 92: 527—538.

7. Colucci W.S., Braunwald E.: Pathophysiology of heart failure. P. 394—395. In: Braunwald E. (Ed.): Heart disease. Philadelphia, Saunder 1997.

8. Metra M., Nodari S., DAloia A. et al.: A rationale for the use of beta-blockers as standard treatment for heart failure. Amer Heart J 2000; 139; 511—521.

9. Califf M., O Connor M.: beta-blocker therapy for heart failure: The evidence is in, now the work begins. J Amer Med Ass 2000; 283: 1335—1336.

10. Cohn J.N.: Beta-blockers in heart failure. Europ Heart J 1998; 19: 52—55.

11. Fowler M.B.: Beta-blockers in heart failure: Do they improve the quality as well as the quantity of life? Europ Heart J 1998; 19: 17—25.

12. Packer M.: COPERNICUS: final results show 35 % decrease in mortality with carvedilol in heart failure patients. 22nd Congress of the European Sociaty of Cardiology. Amsterdam, August 31, 2000.

13. Bristow M.R., Ginsburg R., Umanis V. et al.: $beta_1$ and $beta_2$-adrenergic receptor subpopulations in failing and non-failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective 1-receptor downregulation in heart failure. Circulat Res 1986; 59: 297—309.

14. Swedberg K., Hjalmarson A., Waagstein F. et al.: Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. Brit Heart J 1980; 44: 117—133.

15. Haber H.L., Simek C.L., Gimple L.W. et al.: Why do patients with congestive heart failure tolerate the intiation of beta-blocker therapy? Circulation 1993; 88: 1610—1619.

16. Packer M., Colucci W.S., Sackner-Bernstein J.D. et al.: Double blind, placebo controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Circulation 1996; 94: 2793—2799.

17. Colucci W. S., Packer M., Bristow M.R. et al.: US carvedilol heart failure study. Circulation 1996; 94: 2800—2806.

18. Borchard U.: Pharmacological properties of beta-adrenoreceptor blocking drugs. J Clin Bas Cardiol 1998; 1: 5—9.

19. Abraham W.T., Tsvetkova T., Lowes B.D. et al.: Carvedilol improves renal hemodynamics in patients with chronic heart failure. J Card Fail 1998; 4: 3—7.

20. Persson H., Rythen-Alder E., Melcher A. et al.: Effects of beta-receptor antagonists in patients with clinical evidence of heart failure after myocardial infarction: double blind comparison of metoprolol and xamoterol. Brit Heart J 1995; 74: 140—148.

21. Persson H., Eriksson S.V., Erhardt L.: Effects of beta-receptor antagonists on left ventricular function in patients with clinical evidence of heart failure after myocardial infarction. A double blind comparison of me-

toprolol and xamoterol. Echocardiographic results from the metoprolol and xamoterol infarction study (MEXIS). Europ Heart J 1996; 17: 741—749.

22. Metra M., Giubbini R., Nodari S. et al.: Differential effects of beta-blockers in patients with heart failure: a prospective randomised, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 2000; 102: 546—551.

23. Witte K., Thackray S., Banerjee T. et al.: Update of ELITE-II, BEST, CHAMP and IMPRESS clinical trials in heart failure. Europ J Heart Failure 2000; 2: 107—112.

24. Bonet S., Agusti A., Arnau J. et al.: beta-adrenergic blocking agents in heart failure: Benefits of vasodilating and nonvasodilating agents according to patients characteristics: A meta-analysis of clinical trials. Arch Intern Med 2000; 160: 621—627.

25. Kendall M.J.: Clinical relevance of pharmacokinetic differences between beta-blockers. Amer J Cardiol 1997; 80 (Suppl. J): 15—19.

26. MRC Working Party: Medical Research Council Trial of treatment of hypertension in older adults: Principle results. Brit Med J 1992; 304: 405—412.

27. Kukin M.L., Mannino M.M., Freudenberger R.S. et al.: Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. J Amer Coll Cardiol 2000; 35: 45—50.

28. Swedberg K.: Importance of neuroendocrine activation in chronic heart failure. Impact on treatment strategies. Europ J Heart Failure 2000; 2: 229—233.

29. Anthonio R.L., van Veldhuisen D.J., Breekland A. et al.: Beta-blocker titration failure is independent of severity of heart failure. Amer J Cardiol 2000; 85: 509—512.

30. Dargie H.: The CAPRICORN Steering Committee: Design and methodology of the CAPRICORN trial: a randomised double blind placebo controlled study of the impact of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. Europ J Heart Failure 2000; 2: 325—332.

Received May 10, 2001.
Accepted July 6, 2001.