Use of Beta-Blockers in Chronic Congestive Heart Failure

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Abstract

The sympathetic nervous system and renin angiotensin agents play an important role in heart failure both as a marker of severity of disease and also as a deteriorious factor for congestive heart failure. A beta-blocker in those patients used to be contraindicated. There has been evidence that the blocking effect of alpha and beta-receptors may ameliorate symptoms and retard progression of the disease. In early studies[1,2], the usage of a beta-blocker in mild to moderate congestive heart failure could improve symptoms, increase exercise capacity, and decrease heart size. Recently large clinical randomized, double-blind, placebo-controlled trials exhibited long-term treatment of beta-blockers, in chronic heart failure could improve cardiac function, alleviate symptoms, reduce the all-cause mortality and also risk of cardiovascular hospitalization[3,4]. The appropriate dose and gradual adjustment over time with patient selection will increase benefit and decrease the adverse effects. In the future, beta-blockers may be the fourth component of the standard regimen of ACE inhibitors, diuretics and digoxin in many patients with congestive heart failure

Key word : Heart Failure, Beta Blocker

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It is widely accepted that neurohormonal changes play an important role in the pathophysiology of congestive heart failure (CHF)[5,6]. Many neurohormonal substances can exacerbate CHF. Worsening cardiac failure results in decreased cardiac output with progressive elevation of renin, angiotensin, and catecholamines[7]. Excess catecholamines (noradrenalin and adrenalin) impair myo-

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cardial cell biologic properties and produce beta-receptor dysfunction[8].

There are an increasing number of studies which suggest that beta-blockers may be of benefit in patients with chronic heart failure. Although beta-blockers have negative inotropic activity, their usage leads to symptomatic improvement and even improved survival in some patients with CHF[9-11].

Even-though angiotensin converting enzyme (ACE) inhibitors have been shown to reduce symptoms and mortality of patients with congestive heart failure and lower levels of angiotensin II and aldosterone in these patients, they only minimally lower plasma adrenalin and noradrenalin levels. These level strongly correlated with survival of CHF patients with values > 600 pg/ml identifying the subgroup at highest risk[12].

Rationale for Use of Beta-Blockers

Even in the presence of ACE inhibition, there continues to be progressive sympathetic activation in chronic CHF[13]. This activation can exacerbate left ventricular systolic dysfunction by promoting both myocyte cell loss and dysfunction. High noradrenalin levels produce myocardial cell necrosis by causing ischemic and cellular energy depletion[14]. Moreover, noradrenalin enhances cellular growth, ventricular remodeling and cytokines expression, all of which accelerate apoptosis[15].

Long-term exposure to catecholamines cause a reduction in responsiveness to beta-adrenergic agonists due to desensitization of the beta-receptors[11]. Some patients with dilated cardiomyopathy have circulating antibodies to the Beta-1 adrenergic receptors[16,17]. This may contribute to functional impairment of the receptor. Beta-blockers may counteract this response[15,17,18].

There are two types of beta-receptors in ventricular myocardium, beta-1 and beta-2. In myocardium of the failing heart, there is a selective reduction in the density of the beta-1 but not beta-2 receptors[19,20]. In the failing myocardium, beta-1-receptor density is reduced by 60-70 per cent, the beta-2-receptor is uncoupled by approximately 30 per cent, and G-protein inhibitory receptor activity is increased by 30-40 per cent. As a consequence, the failing heart is more dependent upon beta-2-adrenergic receptors for inotropic support[21]. Thus, despite elevated circulating noradrenalin levels, there is desensitization to the beta-receptor pathway resulting in a net reaction of systolic performance. Additionally, beta-2-receptor stimulation may increase the propensity for ventricular fibrillation which can be prevented by beta-2-receptor blockade[21].

Beta blockade increases the inotropic sensitivity to circulating catecholamines in patients with CHF by upregulating myocardial beta-1-receptor density, partially reversing the usual reduction in beta-1-receptor seen in these patients[22,23]. This effect can result in subsequent improvement in systolic contractile function and enhance exercise tolerance.

In patients with CHF, beta-blockers also appear to reduce the circulating level of vasoconstrictors such as plasma renin activity[24] and plasma noradrenalin levels[25,26]. In addition to these benefits, beta-blockers may also lower the level of endothelin which is another potent vasoconstrictor that is present in increased concentration in CHF[27]. Apart from the mentioned possible hemodynamic benefits, beta-blockers can decrease the incidence of sudden death after a myocardial infarction.

Clinical Trials of Beta-Blockers in CHF

The first uncontrolled report that beta-blockers were of therapeutic benefit was by Waagstein et al in 1975[28]. He found that giving metoprolol to seven patients with congestive cardiomyopathy resulted in improvements in ejection fraction and overall clinical status and drug withdrawal resulted in clinical deterioration. Subsequently, Hall et al reported that clinical improvement with metoprolol was observed only after 3 months treatment[29] which suggests that the benefits are related to a gradual improvement in the biologic properties of the heart rather than to acute pharmacological actions of beta-blockers. Subsequent reports have consistently confirmed beneficial effects after three to six month periods of follow-up in CHF patients receiving bucindolol (a nonselective beta-blocker with direct vasodilatory activity)[24], bisoprolol (a beta-1 selective)[30], and carvedilol (a combined non selective beta and alpha-1 blocker)[31-33]. These late benefits included the improvement in left ventricular ejection fraction and reduction in symptoms observed with carvedilol and dose-dependent improvement in left ventricular ejection fraction in patients with idiopathic dilated cardiomyopathy (but not patients

with ischemic cardiomyopathy)[34]. Bucindolol was shown to significantly increase left ventricular ejection fraction, cardiac output, and left ventricular stroke work, and reduction in end-diastolic pressure and volume in CHF patients[35]. It was also suggested that bucindolol increased the force of contractions in the failing heart since + dP/dt max and end-systolic elastance were increased with therapy .

Exercise capacity : Many studies reported similar improvement of exercise capacity after administration of beta-blockers in CHF patients due to either idiopathic dilated cardiomyopathy or ischemic heart disease[36-38]. This improvement is associated with reduction in maximal VO_2 (oxygen utilization) which is probably due in part to an attenuation in the heart rate response to exercise. Nonselective beta-blockers, carvedilol and bucindolol have shown to increase the ejection fraction similar to a selective beta-blockade, metoprolol. However, in contrast to the metoprolol studies, there was only mild enhancement of maximal exercise performance[31,32,34]. In addition, the nonselective beta-blockers, propranolol and carvedilol did not prevent patients from getting benefit from exercise training[39].

Effect on patients outcome; secondary prevention trials with beta-blockers post-myocardial infarction (MI) have shown a survival advantage for patients subgroups with left ventricular dysfunction[40-42]. The odds ratio for mortality in propranolol-treated patients in the Beta Blocker Heart Attack Trial (BHAT) was 0.69, and in the timolol-treated group in the Norwegian Timolol Study was 0.60[41,42]. Similar to the Cardiac Arrhythmia Suppression Trial (CAST), the odds ratio for mortality was 0.60 in patients taking beta-blockers.

The Swedish Metoprolol in Dilated Cardiomyopathy (MDC) Trial[4] randomized 383 patients to placebo or metoprolol beginning at a dose of 10 mg and increasing slowly to a maximum of 150 mg/day). The eligible patients had to have dilated (non ischemic) cardiomyopathy with NYHA class III-IV, ejection fraction <40 per cent, systolic blood pressure >90 mmHg and able to tolerate metoprolol testing dose (5 mg BID for seven days). Follow-up at 12 to 18 months revealed no benefit in total mortality alone, (12% & 10%) however, the metoprolol group had borderline reduced risk (P=0.058) of the combined primary end point (total mortality or need for transplantation). The metoprolol group had a much less likelihood of progressing to cardiac transplantation [2 of 194 (1%) *versus* 19 to 189 (10%)], a greater increase in ejection fraction (12% and 26%) and exercise tolerance and more patients with subjective improvement in the quality of life.

The Italian Multicentre Cardiomyopathy Study (SPIC), prospectively enrolled 586 patients with dilated cardiomyopathy, 175 of whom received a maximally tolerated dose of metoprolol[2]. The metoprolol treated group showed survival and transplant free survival benefit at seven years (81% and 60%, 69 and 49%), P< 0.001). The relative risk reduction for all-cause mortality and the combined endpoint of mortality or transplantation with metoprolol were 51 per cent and 34 per cent, respectively. Another study, the MERIT-HF trial[3] randomized 4000 patients with class III to IV CHF to placebo or metoprolol. The mean metoprolol dose was 163 mg/day. The study was prematurely terminated when a 35 per cent reduction in all-cause mortality and all cause hospitalization was observed in the metoprolol group at 12 months. Similar to CIBIS II (Cardiac Insufficiency Bisoprolol) which was prematurely stopped after an average follow-up of 1.4 years of 2,647 patients with class III and IV CHF and ejection fraction less than 35 per cent[3]. This study found significant reduction in the total all-cause mortality with bisoprolol compared to placebo (11.8% and 17.3%) and annual mortality was reduced by 32 per cent (8.8% and 13.2%), hazard radio 0.66, p <0.0001). There was also reduction of sudden cardiac death by 44 per cent (3.6 and 6.3%), P <0.001) but there was no significant reduction in death from CHF. Bisoprolol therapy resulted in a 15 per cent reduction in hospital admissions for CHF (P < 0.0001) with more admissions for stroke in the bisoprolol group (2.3% and 1.2%, P = 0.04).

The combined US carvedilol CHF studies, including PRECISE (Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise), US Carvedilol Heart Failure Study, and MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment) were initially designed to evaluate nonfatal endpoints. However, mortality, which was not a designed primary endpoint, was also measured to assess safety and patient benefit. The studies were prematurely terminated[31,32,34] by the data safety monitoring board since carvedilol treated patients

had a 67 per cent reduction in mortality (RR = 0.33, 95% CI 0.19-0.59, P <0.001) after 6 months of follow-up. This benefit was similar regardless of sex, age, heart failure etiology, ejection fraction, exercise tolerance, systolic blood pressure or heart rate. There was also reduction in death due to progressive heart failure (0.7% and 3.3%) and sudden death (1.7% and 3.8%) with 27 per cent reduction in need for hospitalization. The smaller Australia-New Zealand Heart Failure Study randomized 415 patients with ejection fraction <45 per cent and NYHA class II or III to carvedilol (average dose 41 mg/day) or placebo[37]. This study demonstrated no significant difference in cardiac mortality (18% and 20%) but as observed in PRECISE, ejection fraction increased (5.3%) in the carvedilol group without any change in the 6 minute walk distance, NYHA class, or treadmill exercise performance.

There was little data on controlled trials of usage of other beta-blockers in CHF. Krittayaphong [43] et al prospectively enrolled 22 patients with idiopathic dilated cardiomyopathy who had left ventricular ejection fraction less than 40 per cent to either placebo or atenolol. At 3 months' follow-up there was no significant change of exercise capacity, left ventricular ejection fraction or its diameter. However, there was significant reduction of pulmonary artery wedge pressure[44].

Clinical use of Beta Blockers in Heart Failure[45]

The experiences from clinical trials indicate that as do ACE inhibitors, beta-blockers can alleviate the symptoms of heart failure, improve clinical status, and enhance the overall sense of well-being. In addition, as with ACE inhibitors beta-blockers can reduce the risk of hospitalization and death.

These benefits of beta-blockers were observed in patients already receiving ACE inhibitors, suggesting that a combined blockade of two neurohormonal systems can produce additive and potentially synergistic effects.

Which patients should receive a Beta-Blocker for heart failure?

There is overwhelming information indicating that most patients with heart failure should be considered candidates for long-term treatment with a beta blocking drug.

Clinical benefits have been reported in a cohort of patients with a wide range of demographic and clinical features, most patients with mild, moderate symptoms as well as those with and without underlying coronary artery disease.

Ambulatory patients with class II and III symptoms seem to be especially well suited for treatment with beta-blockers. The patients in this group should be considered unstable with conventional medication, and are likely to experience clinical deterioration during the ensuing 12 months [31,32,34]. Such patients should receive treatment with a beta-blocker to reduce the risk of future deterioration.

Should Beta-Blockers be used instead of an ACE inhibitor for the treatment of heart failure?

Most of the experience with beta-blockers in heart failure has been in clinical trials that enrolled patients already receiving an ACE inhibitor, and thus, beta-blockers should be used together with ACE inhibitors in the management of heart failure. Such an approach is reasonable not only from a clinical perspective, but also from a pathophysiological point of view. Because the neurohormonal activation in heart failure involves both the sympathetic nervous system and the renin-angiotensin system, it is logical to use antagonists of both systems (beta blockers and ACE inhibitors) in the treatment of patients with this disorder.

How should the side effects of Beta-Blockers be managed?

Initiation of treatment with a beta-blocker can produce three types of adverse reactions that need attention.

1. Hypotension: Drugs that block ß-receptors may produce hypotension, particularly if they also block α_1 – receptors[46-48]. As with other α_1 - blockers, vasodilatory side effects from carvedilol are generally seen within 24 to 48 hours of the first dose or the first increments in dose, but these usually disappear with repeated dosing without any change in the dose of carvedilol of background medications.

2. Worsening heart failure. Short-term therapy with drugs that block ß-receptors can lead to worsening heart failure by two independent mechanisms. Firstly, blockade of $ß_1$ or $ß_2$- receptors can interfere with the positive inotropic support provided by endogenous catecholamines[49]. Secondly, by reducing renal flow, beta blockade can cause sodium retention and thereby exacerbate loading conditions in the failing heart[50].

Interestingly, both mechanisms by which beta blockade may adversely affect cardiac function, renal perfusion and sodium balance, can be antagonized by α-adrenergic blockade[51]. This may explain why a significant increase in the risk of heart failure (often requiring hospitalization) has been reported in clinical trials with metoprolol and propranolol[40] but not with carvedilol[4].

3. Bradycardia and heart block: Always occurs in patients with significant underlying conduction-system disease or in those taking other medications that can interfere with the actions of the nervous system on the sinus or atrioventricular node.

In most cases, the early side effects of beta-blockade subside over time by the beneficial effects of treatment on LV function, whereas, tolerance frequently develops to the vasodilatory actions, at least in the case of drugs with a-blocking properties. Consequently most of the adverse effects of early therapy with beta- blockers in heart failure are short-lived and if therapy with the beta-blocker is maintained, it will be predictably superseded within weeks by a progressive improvement in the patients' clinical status. Indeed, clinical improvement after initiation of treatment with a beta-blocker is usually delayed. A reduction in signs and symptoms of heart failure is not usually seen until 6 to 12 weeks of continuous treatment with a beta-blocker at therapeutic doses[31,32,34].

SUMMARY

There is increasing evidence of the benefit of beta-blockers in patients with CHF. Although there was initially some concern that these benefits might not apply to patients with coronary artery disease[30,45,46] subsequent trials have demonstrated that improvements in exercise duration, stabilization of left ventricular function, and mortality are similar in ischemic and nonischemic cardiomyopathies.

Therapy should be started at very low doses (3.125 mg BID for Carvedilol, 6.25 mg BID for Metoprolol, and 1.25 mg QD for Bisoprolol) with possible adjustment of diuretic and ACE inhibitors dosage. The dose doubled at weekly intervals until the target doses are reached (25-50 mg BID Carvedilol, 50-75 mg BD Metoprolol, and 5-10 mg QD for Bisoprolol) on symptoms become limiting. A lower starting dose is necessary for patients with recent decompensation or systolic blood pressure below 85 mmHg[51]. Equivalent dose of Atenolol at the beginning is 6.25 mg OD and the target dose is 50 mg OD. Every effort should be made to achieve the target dose since the improvement appears to be dose-dependent. Given the survival benefit, beta-blokers may be the fourth component of the standard regimen of ACE inhibitors, diuretics, and digoxin in many patients with CHF.

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REFERENCES

1. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993; 342:1441-6.
2. Di Lenarda A, De Maria R, Gregori D, et al, on behalf of the SPIC (Italian Multicentre Cardiomyopathy Study) Group. Long term survival effect of Metoprolol in dilated cardiomyopathy. Heart 1998;79:337-44.
3. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. Lancet 1996; 353:9-13.
4. Packer M, Bristow, MR, Cohn, JN, et al for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality. In patient with chronic heart failure. N Engl J Med 1996; 334:1349-55.
5. Curtiss C, Cohn JN, Vrobel T, Franciosa JA. Role of renin-angiotensin system in systemic vasoconstriction of chronic congestive heart failure. Circulation 1978; 58:763-70.
6. Levine TB, Francis GS, Goldsmith SR, Simon A, Cohn JN. Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relationship to hemodynamic abnormalities. Am J Cardiol 1982; 49:1659-66.
7. Francis GS, Benedict C, Johnstone De, et al for the SOLVD Investigators. Comparison of neuro-

endocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. Circulation 1990; 82: 1724-9.

8. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart: A new era in the treatment of heart failure. Circulation 1996; 94:2285-96.
9. Doughty RN, Rodgers A, Sharpe N, et al. Effects of beta-blocker therapy in mortality in patients with heart failure. A systematic overview of randomized controlled trials. Eur Heart J 1997; 18: 560-5.
10. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: A meta-analysis of randomized clinical trials. J Am Coll Cardiol 1997; 30:27-34.
11. Lechat P, Packer M, Chalon S, et al. Clinical effects of β-adrenergic blockade in chronic heart failure: A meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation 1998; 98: 1184-91.
12. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311:819-23.
13. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990; 82:1730-6.
14. Reichenbach DD, Benditt EP. Catecholamines and cardiomyopathy: the pathogenesis and potential importance of myofibrillar degeneration. Hum Pathol 1970; 1:125-49.
15. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992; 20:248-54.
16. Jahns R, Boivin V, Siegmund C, et al. Autoantibodies activiating human β_1-adrenergic receptors are associated with reduced cardiac function in chronic heart failure. Circulation 1999; 99:649-54.
17. Podlowski S, Luther HP, Morwinski R, et al. Agonistic anti-β_1-adrenergic receptor autoantibodies from cardiomyopathy patients reduce the β_1-adrenergic receptor expression in neonatal rat cardiomyocytes. Circulation 1998; 98:2470-6.
18. Mann DL, Kent RL, Parsons B, et al. Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992; 85:790-804.
19. Bristow MR, Ginsburg R, Umans V, et al. β_1-and β_2 adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective β_1 down-regulation in heart failure. Circ Res 1986; 59:297-309.
20. Alshuld RA, Starliing, RC, Hamlin RL, et al. Response of failing canine and human heart cells to β_2-adrenergic stimulation. Circulation 1995; 92:1612-8.
21. Billman GE, Castillo LC, Hensley J, et al. β_2-adrenegic receptor antagonists protect against ventricular fibrillation: in vivo and in vitro evidence for enhanced sensitivity to β_2-adrenergic stimulation in animals susceptible to sudden death. Circulation 1997; 96:1914-22.
22. Bristow MR, Gilbert EM, Olsen S, et al. Long-term metoprolol therapy increases myocardial β-adrenergic receptor density relative to placebo controls. J Am Coll Cardiol 1993; 21:101A.
23. Bristow MR, Minobe WA, Raynolds MV, et al. Reduced β_1 receptor messenger RNA abundance in the failing human heart. J Clin Invest 1993; 92:2737-45.
24. Eichhorn EJ, McGhie AI, Bedotto JB, et al. Effects of bucindolol on neurohormonal activation in congestive heart failure. Am J Cardiol 1991; 67: 67-73.
25. Gilbert Em, Anderson JL, Deitchman D. Chronic β-blocker-vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: A double-blind, randomized study of bucindolol *versus* placebo. Am J Med 1990; 88:223-9.
26. Yoshikawa T, Handa S, Anzai T, et al. Early reduction of neurohumoral factors plays a key role in mediating the efficacy of b-blocker therapy for congestive heart failure. Am Heart J 1996; 131: 329-36.
27. Krum H, Gu A, Wilshire-Clement M, et al. Changes in plasma endothelin-1 levels reflect clinical response to b-blockade in chronic heart failure. Am Heart J 1996; 131:337-41.
28. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975; 37:1022-36.
29. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. J Am Coll Cardiol 1995; 25:1154-61.
30. CIBIS Investigators and Committees. A randomized trial of b-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994; 90:1765-73.
31. Packer M, Colucci WS, Sackner-Bernstein JD, 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; 194:2793-9.
32. Colucci WS, Packer M, Bristow MR, et al. Carve-

dilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 1996; 94:2800-6.

33. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease. Lancet 1997; 349:375-80.
34. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996; 94:2807-16.
35. Eichhorn EJ, Bedotto JB, Malloy CR, et al. Effect of beta-adrenergic blockade on myocardial function and energetics in congestive heart failure: Improvements in hemodynamic, contractile, and diastolic performance with bucindolol. Circulation 1990; 82:473-83.
36. Newton GE, Parker JD. Acute effects of β_1-selective and nonselective B-adrenergic receptor blockade on cardiac sympathetic activity in congestive heart. Circulation 1996;94:353-8.
37. Andersson B, Hamm C, Persson S, et al. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. J Am Coll Cardiol 1994;23:1397-483.
38. Bristow MR, O' Connell JB, Gilbert, EM, et al. Dose-response of chronic β-blocker treatment in heart failure from either idiopathic dilated of ischemic cardiomyopathy. Circulation 1994; 89: 1632-42.
39. Demopoulos L, Yeh M, Gentiluci M, et al. Nonselective β-adrenergic blockade with carvedilol does not hinder the benefits of exercise training in patients with congestive heart failure. Circulation 1997;95:1764-7.
40. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with heart failure. Circulation 1986; 73:503-10.
41. Pederson TR and the Norwegian Multicenter Study Group. Six-year follow-up of the Norwegian multicenter study on timolol after acute myocardial infarction. N Engl J Med 1985; 313:1055-8.
42. Kennedy HL, Brooks MM, Barker AH, et al. β-blocker therapy in the Cardiac Arrhythmia Suppression Trial. Am J Cardiol 1994; 74:674-80.
43. Krittayaphong R, Kangkagate C, Mahanonda N, Phankingthongkum R, Chaithiraphan S. Short term effects of atenolol in patient with dilated cardiomyopathy. J Med Assoc Thai 1998; 81:201-7.
44. Woodley SL, Gibert, EM, Anderson JL, et al. Beta-blockade with bucindolol in heart failure due to ischemic *vs* idiopathic dilated cardiomyopathy. Circulation 1991; 84:2426-41.
45. Doughty RN, MacMahon S, Sharpe N. Beta-blockers in heart failure: Promising or proved ? J Am Coll Cardilol 1994; 23:814-21.
46. Semplicini A, Pessina AC, Palatini P, et al. Orthostatic hypotension after first administration of prazosin in hypertensive patients: Role of plasma volume. Clin Exp Pharmacol Physiol 1981; 8:1-10.
47. Von Bahr C, Lindstrom B, Seideman P. Alpha-receptor function changes after the first dose of prazosin. Clin Pharmacol Ther 1982; 32:41-7.
48. Gaffney TE, Braunwald E. Importance of adrenergic nervous system in the support in circulatory function in patients with congestive heart failure. Am J Med 1963; 34:320-4.
49. Epstein SE, Braunwald E. The effect of beta-adrenergic blockade on patterns of urinary sodium excretion : Studies in normal subjects and in patients with heart disease. Ann Intern Med 1996: 75:27.
50. Dibona GF. Neural control of renal function : Role of renal alpha adenoceptors. J Cardiovasc Pharma col 1985; 7:S18-S23 (Suppl 8).
51. Eichhorn EJ, Bristow MR. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure. Am J Cardiol 1997; 79: 794-8.

การใช้ยากั้นบีตาในผู้ป่วยหัวใจล้มเหลว

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ระบบประสาทซิมพาเตติก และระบบเรนนิน เป็นตัวการสำคัญของการดำเนินโรค และความรุนแรงในผู้ป่วย chronic congestive heart failure การใช้ยา Beta-Blocker ในผู้ป่วยเหล่านี้เคยเป็นข้อห้ามใช้ แต่ในปัจจุบันพบว่ายาที่ไปยับยั้งอัลฟ่าและเบต้า-1 รีเซพเตอร์ น่าจะช่วยบรรเทาความรุนแรงและชะลอการเสื่อมถอยของหัวใจได้ การศึกษาในช่วงต้นๆ พบว่าการให้ Beta-Blocker ในผู้ป่วย mild to moderate heart failure ทำให้อาการดีขึ้น, เพิ่ม exercise capacity รวมทั้งลดขนาดของหัวใจ ข้อมูลการศึกษาที่มีต่อมาและหลักฐานในปัจจุบันที่มีอยู่เป็นจำนวนมากที่เป็นแบบ randomized, double-blind, placebo-controlled trials พบว่าการใช้ยา Beta-Blocker ระยะยาวในผู้ป่วย chronic heart failure ทำให้การทำงานของหัวใจดีขึ้น, ทำให้ NYHA ดีขึ้น, บรรเทาอาการ, ลดอัตราการตายและลดอัตราการเจ็บป่วยในโรงพยาบาล (20% ถึง 40%) จากประโยชน์ทั้งหลายเหล่านี้ทำให้มีการนำยามาพิจารณาใช้ในผู้ป่วยมากขึ้น การใช้ยาด้วยความระมัดระวัง เลือกกลุ่มผู้ป่วยให้เหมาะสม รวมทั้งการให้ขนาดยาและปรับขนาดยาตามที่แนะนำ จะมีประโยชน์อย่างสูงสุดต่อผู้ป่วยและช่วยหลีกเลี่ยงผลข้างเคียงที่จะเกิดจากยา จากประโยชน์ที่ได้กล่าวข้างต้นอาจทำให้ Beta-Blocker เป็นยาสำคัญตัวต่อไปในผู้ป่วย chronic congestive heart failure ใน standard regimen รองลงมาจาก ACE inhibitors, diuretics และ digoxin

คำสำคัญ : หัวใจล้มเหลว, การรักษา, Beta-blocker

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