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The Role of ß-Blockers in Congestive Heart Failure

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Introduction

Congestive heart failure (CHF) is a common medical disorder, affecting approximately 1% of the adult population.[1] The disease is associated with a poor prognosis, with a median survival after diagnosis of less than 5 years, as well as substantial morbidity. Despite the documented effect of angiotensin converting enzyme inhibitors (ACE I) on survival, the mortality remains very high.

Rationale for the use of ß-Blockers in CHF

In the last two decades, agents have become available which can improve the hemodynamic status of patients with heart failure, including vasodilators and inotropic agents. Unfortunately, the hemodynamic benefit is frequently not translated into clinical efficacy, and some of the vasodilators and inotropes are associated with increased mortality in CHF.[2] One explanation for the detrimental effect of some of these agents is the fact that there is neurohumoral activation in patients with CHF, with increased activity of the sympathetic and renin-angiotensin systems, possibly accounting for the progression of disease.[3] This activation may be worsened by some of the drugs used, and might explain their negative effects on mortality.[4] In support of this hypothesis is the beneficial effect of angiotensin converting enzyme inhibitors on survival. It is therefore plausible that agents which will antagonize the sympathetic nervous system, such as ß-blockers, will also exert a beneficial effect in these patients. Indeed, in a subgroup analysis of a large trial using propranolol post-myocardial infarction, the patients with worse ventricular function derived greatest absolute survival benefit with this therapy.[5]

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Early studies of ß-blockers in idiopathic dilated cardiomyopathy

ß-blockers have long been known to be negative inotropes and can precipitate or worsen CHF. Nevertheless, in the 1970's several small uncontrolled studies[6-8] of patients with idiopathic dilated cardiomyopathy (IDCM) using metoprolol showed improvements in ejection fraction (EF) and other markers of ventricular function. This improvement was maintained over weeks to months, and discontinuation of ß-blockers led to clinical worsening.[9] These results led to small randomized trials of ß-blockers (mostly metoprolol) in IDCM patients, demonstrating consistently improved ventricular function, symptoms and exercise tolerance.[10-11]

Metoprolol in dilated cardiomyopathy (MDC) trial[12]

The above results led to a multicenter randomized trial of approximately 400 patients with dilated cardiomyopathy who were clinically stable on ACE I, digoxin and diuretics. Patients were given test doses of 5 mg and then randomized to a cautious up-titration of metoprolol or placebo over a 6 week period, with a target dose of 100-150 mg daily. Follow-up was for 12-18 months and the primary endpoint was a combination of mortality and need for transplantation on the basis of predefined criteria. At the end of the trial, there was no significant difference in mortality (10.0% placebo, 11.9% metoprolol), but there was a significant decrease in need for transplantation from 10.0% in the placebo group to 1.0% in the treated patients ($p=0.001$). There was also an associated improvement in EF by 12% in the treated group compared to 6% in the placebo arm ($p<0.001$), especially in those with low baseline EF. Exercise time and symptoms were similarly slightly better on metoprolol.

Cardiac insufficiency bisoprolol study (CIBIS)[13]

Another large trial used a ß-1 selective agent, bisoprolol, in 640 patients on stable medical therapy (90% on ACE I), half of whom had ischemic cardiomyopathy. These patients were randomized to a slow up-titration of bisoprolol or placebo, and were followed for an average of 2 years. There was a trend towards lower overall mortality (16.6% vs. 20.9%, $p=0.2$) with treatment, with a statistically significant reduction in those patients who had no history of myocardial infarction (IDCM). Fewer patients on bisoprolol were admitted for CHF and more patients had symptomatic improvement with this treatment.

Combining the data from the metoprolol and bisoprolol studies suggests that slow up-titration of ß-blockers in CHF is well-tolerated in about 90% of patients, and leads to symptomatic improvements, and increases in EF of 5-10%. The effect on mortality is less clear, although there are encouraging trends in favour of treatment. The maximum benefits of therapy seem to be in patients with worse ventricular function and in the IDCM patients who were much more extensively studied than those with ischemic cardiomyopathy.

Newer ß-blocking agents: Bucindolol

Approximately 10% of patients in the above studies could not tolerate even small doses of ß-blockers due to worsening cardiac function. Recently, newer agents have become available that combine ß-blocking with vasodilating properties. Since vasodilation should lower afterload and improve cardiac performance, these drugs could theoretically improve the tolerability of ß-blockade in CHF patients. Bucindolol is an example of this class of ß-blocker, with an effective but as yet

undefined vasodilating property. It has been studied in a total of over 200 CHF patients and seems to be very well tolerated in over 95% of subjects, with dose-related increases in cardiac output compared to placebo.[14] It will therefore be used in a large multicenter randomized trial testing its effect on mortality in patients with moderately severe CHF, the BEST study.

Carvedilol

This agent is also a nonselective ß-blocker with potent alpha-blocking vasodilatory activity, which results in improvement in EF with a low incidence of side effects in non-blinded studies of patients with CHF.[15] It has been evaluated in 3 smaller[16-18] and two large-scale trials. In the smaller studies of approximately 50 patients each, the EF increased 5-10% compared with placebo, with improvement in CHF symptoms and some improvements in exercise capacity. The Australian-New Zealand Heart Failure Group[19] studied 415 stable ischemic CHF patients on ACE I, digoxin and diuretics followed for 6 months on carvedilol or placebo. There was a significant increase in EF, similar to that in smaller trials, but trends towards lower quality of life scores, despite a significant 40% decrease in hospitalizations due to CHF.

The most promising results with carvedilol, however, come from 4 substudies of the North American cooperative trials in carvedilol in CHF, presented in preliminary form at the 1995 American Heart Association meeting. These trials randomized a total of 1094 patients (half with IDCM, half NYHA III-IV) to carvedilol or placebo. Patients were entered into each substudy based on severity of CHF as measured by 6-minute walk tests: 10% had severe CHF, 55% had 'moderate' CHF, and one third had 'mild' CHF. Each subtrial had different primary endpoints, but the overall trial assessed all-cause mortality. All trials had secondary endpoints of EF change, need for CHF hospitalization, NYHA class changes, and global assessment of improvement or deterioration by patients and treating physicians. The 'mild' CHF trial assessed progression to symptomatic CHF, while one of the 'moderate' CHF trials (MOCHA) assessed the dose-response for carvedilol on exercise capacity and mortality. The other 'moderate' CHF trial (PRECISE) studied progression of CHF (such as need for medication changes), while the severe CHF group was followed for quality of life assessment.

The overall trial was terminated prematurely due to a significant progressive decrease in mortality in the carvedilol-treated patients: 3.0% vs. 7.8% at 400 days ($p<0.001$). In MOCHA, there was also an impressive and significant dose-response, with placebo mortality of 15.5%, compared to 1.1% with the highest doses of carvedilol. Secondary endpoints consistently showed more improvement with carvedilol, with better NYHA class and global assessments of quality of life, and trends towards lower CHF hospitalization. The EF improved 5-10% compared to placebo, but there was no significant difference in 6-minute walking distances. Carvedilol was well-tolerated, with only 10% of patients unable to tolerate test doses, and 8% discontinuation of active therapy (5.5% in placebo) due to side effects. Thus, carvedilol demonstrated a striking reduction in mortality of 67%, greater than any previous therapy in CHF, with acceptable tolerability.

Conclusions

Despite the fact that ß-blockers have the potential to acutely worsen ventricular dysfunction in CHF, the available literature suggests that they probably have the opposite effect on the chronic course of this disease, with improved symptoms and survival. Possible reasons for this benefit include reversing the chronic ß-receptor desensitization and down-regulation that occurs in CHF due to chronic sympathetic overstimulation.[20] Furthermore, ß-blockers may prevent catecholamine-induced oxidative myocyte damage, especially with carvedilol which has potent anti-oxidant effects.Additional trials are therefore planned to compare the newer vasodilating agents with older ß-blockers, in order to elucidate whether the vasodilatory or anti-oxidant effects of the newer drugs are essential to their clinical efficacy. One of these studies, COMET (Carvedilol Or Metoprolol European Trial) will enroll 3000 patients and compare the benefits of Carvedilol with Metoprolol therapy. The exact mechanisms of benefit with ß-blockers nevertheless remain to be defined and large-scale mortality trials will be needed to help confirm the true magnitude of benefit in patients with heart failure, and possibly help explain the mechanisms. ß-blockers will therefore likely become standard therapy for CHF, along with ACE Inhibitors, in slowing the neurohumorally-mediated progression of this condition.

MEDICAL MANAGEMENT OF HEART FAILURE

Therapy	Symptom Relief	Survival Benefit
ß-blockers	+	+
ACE inhibitors	+	+
Digitalis	+	neutral
Diuretics	+	?

+ = documented benefit
? = unknown effect

References

1. Kalan, K et al., The epidemiology of heart failure: the Framingham study. *J Amer. Coll. Cardiol.* 1993; 21(Suppl.A):6A-13A.
2. Packer, M et al., Effect of oral milrinone on mortality in severe chronic heart failure. *N. Eng. J Med* 1991;325:1468-75.
3. Packer, M. The neurohumoral hypothesis: a theory to explain the mechanism of disease progression in heart failure. [Editorial] *J Amer. Coll. Cardiol.* 1992;20:248-54.
4. Moe, G, Rouleau JL, Proulx G, Arnold M, Sestier F, for the PROFILE investigators Increased mortality with flosequinan in patients with failure is accompanied by increase in plasma norepinephrine. *Circulation* 1994;90: Abstr. I-380.
5. Chadda, K et al., Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503-10.
6. Waagstein, F et al., Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br. H J* 1975;37:1022-36.
7. Swedberg, K et al., Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. *Lancet* 1979;i:1374-7.
8. Swedberg, K et al., Beneficial effects of long-term beta-blockade in congestive cardiomyopathy. *Br. H J* 1980;44:117-33.
9. Swedberg, K et al., Adverse effects of beta-blockade withdrawal in patients with congestive cardiomyopathy. *Br. H J* 1980;44:134-42.
10. Anderson J, et al., A randomized trial of low-dose beta-blocker therapy for idiopathic dilated cardiomyopathy. Am. J Cardiol. 1985;55:471-5.
11. Engelmeier, R et al., Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. *Circulation* 1985;72:535-46.
12. Waagstein, F et al., Metoprolol in Dilated Cardiomyopathy. *Lancet* 1993;343:1441-6.
13. CIBIS. Cardiac Insufficiency Bisoprolol Study. *Circulation* 1994;90:1765-73.
14. Ikram, H. Therapeutic controversies with use of beta-adrenoceptor blockade in heart failure. *Amer. J Cardiol.* 1993;71:54C-58C.
15. Das Gupta, P et al., The effects of intravenous carvedilol, a new multi-action vasodilating beta-blocker in congestive heart failure. *J Cardiovasc. Pharm.* 1991;18(S4):S12-16.
16. Metra, M et al., Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical condition. *J Amer. Coll. Cardiol.* 1994;24:1678-87.
17. Olsen, S et al., Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. *J Amer. Coll. Cardiol.* 1995;25:1225-31.
18. Krum et al., Double-blind, placebo-controlled study of long-term efficacy of carvedilol in patients with severe heart failure. *Circulation* 1995;91:1499-1502.
19. Australian-New Zealand Heart Failure Research Collaborative Group. Effects of carvedilol, a vasodilator-beta-blocker in patients with congestive heart failure due to ischemic heart disease. *Circulation* 1995;92 212-8.
20. Bristow, M. Pathophysiological and pharmacological rationale for clinical management of chronic heart failure with beta-blocking agents. *Amer. J Card.* 1993;71:12C-22C.

Upcoming Scientific Meetings

19-22 June 96
CARDIOSTIM '96: 10th International Congress
Nice, France
(Centre Chirurgical Val d'Or)
Tel.: 33 1 41 12 07010

22 June 96
Prevention of Coronary Ischemic Events: Role of ACEI's
Glasgow, Scotland
(Sponsored Satellite Symposium to the 16th Scientific Meeting of the International Society of Hypertension)
Tel.: 908-423-5486

24-28 June 96
13th International Congress on Fibrinolysis and Thrombolysis
Barcelona, Spain
(FISP Services)
Tel.: 34 3 280 6582

13-17 July 96
66th Congress of the European Atherosclerosis Society
Florence, Italy
(Fondazione Giovanni Lorenzini Medical Science Foundation)
Tel.: 39 2 29006267

21-24 July 96
6th World Congress of the International Society of Cardiothoracic Surgeons (ISCTS) and 9th Annual Meeting of the ISCTS-Japan Chapter
Hiroshima, Japan
(Simul International, Inc.)
Tel.: 81 3 3586 8691

4-7 August 96
44th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand
Brisbane, Australia
(Kevin J Wickman Pty Ltd.)
Tel.: 61 3 859 6899

Abstracts of Interest

A population-based survey of the incidence of heart failure

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The contemporary incidence of heart failure in the UK is not known. A prospective survey of new cases of heart failure presenting to 82 general practitioners and a district general hospital serving a population of 155 000 is now in progress. Cases are identified from hospital admissions and through a daily open-access heart failure clinic to which GP's refer all new cases of suspected heart failure. Following a standardised interview, physical examination, ECG, CXR and cardiac ultrasound all cases are reviewed by a panel of 3 cardiologists who determine whether the definition of heart failure is met, and its aetiology. In 6 months, 61 new cases of heart failure have been identified in the district giving a crude incidence rate of 0.8 cases per 1000 population per annum. The rate was 0.2 cases/1000/p.a. in those aged 45-55 years, rising to 11.7 cases/1000/p.a. in those aged 85 years and over. 13 (21%) cases were identified through the heart failure clinic, the remainder being acute hospital admissions. The aetiologies were ischaemic heart disease (39%), atrial fibrillation alone (10%), hypertension (8%), cor pulmonale (3%), and alcohol (2%). In 38% of cases the aetiology could not be determined from the history, examination and above investigations. 120 new cases of heart failure per annum are expected in this population, the vast majority arising in the elderly. Most cases present acutely to hospital. In over a third of cases the aetiology cannot be determined from the non-invasive investigations used in this population based clinical survey.

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Hypertension and the Heart – Left Ventricular Hypertrophy and Heart Failure: New Approaches to Therapy

Results of Recent Clinical Trials in Hypertension with Newer Beta-Adrenergic Blocking Agents

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Beta-adrenergic blockers remain first-line therapies for the treatment of systemic hypertension. Among the beta blocker drugs there are those with beta1-selectivity, the newest one being bisoprolol which is also available in a very lose dose combination with hydrochlorothiazide. There are those having partial agonist effects and those with combination beta blocker-vasodilator activity, the most recent being carvedilol a nonselective beta blocker which has, in addition, modest alpha1-adrenergic blocking activity and unique antioxidant and antiproliferative actions. Carvedilol used once or twice daily has been shown to be more effective than placebo in reducing systolic and diastolic blood pressure, and as effective as other beta blockers, including labetalol, the calcium blocker nifedipine, and the ACE inhibitor captopril. It has been used in combination with diuretics and nifedipine to achieve greater blood pressure control than with either drug used alone. Carvedilol has also been shown to reduce microalbuminuria in hypertensive diabetic patients, and it can cause a slight improvement in plasma lipids in patients having hypertension and dyslipidemia. There are no long-term survival data with carvedilol in a general hypertensive population, but preliminary data suggest a survival advantage with the drug in patients surviving myocardial infarction and those with congestive heart failure.

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