

Beta-blockers in heart failure — the evidence from clinical trials

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There are good theoretical reasons for supposing that long-term treatment with a beta-blocker would improve symptoms and survival in patients with heart failure. A series of small studies have shown that beta-blockers improve haemodynamic parameters, but it is well known that these correlate poorly with symptoms. There is some evidence that exercise tolerance is also improved. Although there is so far no convincing evidence that

beta-blockers prolong survival in patients with heart failure the development of a new generation of these drugs with additional vasodilating properties makes further large studies essential.

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Introduction

Activation of the sympathetic system and an increase in circulating catecholamines is a proper and useful circulatory response to heart failure, and it is a common clinical experience that the introduction of a beta-blocker — for example, for the secondary prevention of myocardial infarction — may induce heart failure. However, we now accept that activation of the renin-angiotensin system — also entirely appropriate in mild or pre-clinical failure — can reach the point where vasoconstriction and sodium retention are totally inappropriate. The assumption is that the sympathetic system may also become inappropriately overactivated with excess vasoconstriction, and that treatment with a beta-blocker would protect the circulation from these excessive effects.

There are many possible ways in which excess sympathetic activation could be harmful, but it is not clear which, if any, are important.

First, Beta-1 receptors are downregulated in the failing heart, and the response to beta-agonist drugs is attenuated^[1]. In theory, long-term treatment with a beta-blocker can allow upregulation of receptors, and restore the heart to an appropriate response to beta stimulation.

Second, plasma noradrenaline levels are a marker of the severity of heart failure, and sympathetic activation can be detected before clinical heart failure is

apparent. In animal models high concentrations of catecholamines cause necrosis of myocardial cells and beta-blockers are protective but whether this applies to the failing human heart we do not know^[2]. Bucindolol treatment has been associated with a marked fall in plasma noradrenaline^[3] but whether this has a primary effect (by reducing spill-over from synaptic clefts or by increasing noradrenaline clearance) or a secondary effect due to improvements in heart failure is not clear.

Third, it has been proposed that beta-blockers improve ventricular function. Beta-blockers might be expected to have an anti-ischaemic effect and therefore improve systolic function, and possibly diastolic function also^[4].

Fourth, the post-infarction trials showed that at least in this clinical situation beta-blockers reduced sudden death. Sudden death and arrhythmias are common in patients with heart failure (reported in various series to be between 4% and 86% of deaths) and significant arrhythmias also occur: 25%–71% of patients in various studies have been shown to have ventricular tachycardia^[2]. Sub-group analysis of the BHAT propranolol post-infarction study has shown that the greatest reductions in fatality were among patients with mild or moderate heart failure^[5].

Finally, stimulation of the renin-angiotensin system in heart failure is in part due to increased sympathetic tone, and this might be inhibited by beta-blockers.

An improvement in heart failure with propranolol and alprenolol was first described by Waagstein in 1975^[6], but beta-blockers are by no means a standard way of treating heart failure. However, evidence is increasing that they have a useful role. With the

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Table 1 Double-blind studies of beta-blockers in heart failure

Study	Design	No. of patients	Aetiology	Drug	Effect on		
					Symptoms	ETT	EF
Ikram (1984) ^[8]	C	28	D	Acebutolol	±	—	—
Currie (1984) ^[9]	C	10	D/I	Metoprolol	±	—	—
Engleleir (1985) ^[10]	P/C	25	D	Metoprolol	+	+	+
Anderson (1985) ^[11]	P	50	D	Metoprolol	+	+	+
Pollock (1990) ^[12]	P	19	D/I	Bucindolol	+	+	+
Leung (1990) ^[13]	C	12	D	Labetolol	+	+	
Gilbert (1990) ^[3]	P	24	D	Bucindolol			+
Woodley (1991) ^[14]	P	50	D/I	Bucindolol	+	±	+
Fisher (1991) ^[15]	P	35	I	Metoprolol	+		+
Paolisso (1992) ^[16]	C	10	D/V	Metoprolol	+	+	+
Olsen (1992) ^[17]	P	54	D	Carvedilol		+	+
MDC (1993) ^[18]	P	380	D	Metoprolol		+	+
Wisnibaugh (1993) ^[19]	P	24	D/F	Nebivolol		—	+

C=Crossover; D=Dilated cardiomyopathy; ETT=Exercise tolerance; P=Parallel group; I=Ischaemic dilatation; EF=Ejection Fraction; +=positive effect; —=no effect; ±=doubtful effect.

Blank indicates not measured.

introduction of beta-blockers with vasodilating properties, and the realization that heart failure is common and carries a very poor prognosis, it is not surprising that the possible value of beta-blockers for the treatment of heart failure is attracting increasing attention. However, theoretical reasons why beta-blockers should be useful in heart failure are not sufficient for them to become routine clinical practice, nor are small studies which were not randomized and double-blind. It is essential to remember that haemodynamic parameters such as heart rate, blood pressure, cardiac output and ejection fraction correlate poorly with a patient's symptoms, and inducing haemodynamic improvement may well not improve exercise time or quality of life. Similarly, symptoms and survival are not well correlated, as was shown by the ability of drugs such as milrinone^[7] to improve exercise ability but to cause an excess of deaths.

Haemodynamic studies, which are usually short-term, are relatively easy to perform in patients with heart failure; a group of 20 to 30 patients is usually sufficient to give a significant result. Exercise testing is much more difficult: patients vary considerably over a period of weeks or months, with spontaneous improvement, and with changes in concomitant medication. Heart failure carries a poor prognosis and it must be expected that in a 3 month study several patients will die, making the statistical handling of data very difficult. Two hundred to 300 patients are likely to be needed for an exercise study to give a clear result. If we assume that a treatment such as a beta-blockers might reduce fatality in heart failure by one quarter, the number of patients needed in a trial will depend on their clinical state (the worse the risk, the less patients needed) but roughly 2000–3000 patients will have to be included. The problem has been made even more difficult by the clear demonstration that ACE inhibitors prolong survival: this means that any beta-blocker study now has to be

designed on the basis of all patients being on an ACE inhibitor. Even though ACE inhibitors have a completely different mode of action it may be unrealistic to suppose that the addition of a beta-blocker to an ACE inhibitor will lead to a further reduction in fatality or heart failure.

Trials of beta-blockers in heart failure

Table 1 lists the beta-blocker studies which were double-blind and placebo-controlled^[8–18]: there has been a variety of open studies but these can now be regarded as of mainly historical interest. Publications involving 10 or less patients, and those currently available only in abstract form, have been excluded. Metoprolol has been the most frequently studied drug, presumably because of the initial findings of Waagstein^[6]. Acebutolol and labetalol are represented once each, but then interest has clearly shifted to the vasodilating beta-blockers. There have been four studies of bucindolol, and each with carvedilol and nebivolol, and more studies with one each of these have been presented in abstract.

The overall pattern of these results seems to be that (where reported) symptoms and ejection fraction have improved. There seems to be a tendency suggesting that long-term treatment is more effective than short-term treatment. So far as it goes, all these drug studies seem to have comparable effects — bucindolol does not stand out as more effective than metoprolol — except that the single study of alprenolol suggested that this drug caused harm rather than benefit.

Improvement in ejection fraction and other haemodynamic parameters seems an almost universal finding^[19,20]. Metoprolol (in an open study, not included in Table 1^[21]) has been shown in patients with dilated cardiomyopathy to increase ejection fraction, decrease

left ventricular diastolic dimensions, reduce mitral regurgitation, decrease pulmonary capillary wedge pressure and (surprisingly) systemic vascular resistance and this was accompanied by a rise in blood pressure. Carvedilol (again in a short-term open study^[22]) decreased heart rate, blood pressure and systemic vascular resistance and increased ejection fraction. Bucindolol^[3] increased cardiac index, decreased pulmonary capillary wedge pressure and increased ejection fraction, but in another study^[12] decreased ejection fraction. Nebivolol increased stroke volume and although there were increases in systemic vascular resistance and pulmonary capillary wedge pressure, these were not significantly different from zero^[19].

Table 1 shows that in the majority of studies involving exercise time, this was improved. There are, however, exceptions with alprenolol causing a reduced exercise time, albeit in a study of short duration^[8]. Although one has to remember the possibility of publication bias, metoprolol seems consistently effective. What is perhaps surprising is that the results with bucindolol are not consistent, with improvement in two^[12,14], but not in a third^[3]. In a single study of nebivolol^[19], exercise time was not increased.

Effect of beta-blockers on mortality in heart failure

Only two trials (the Metoprolol in Dilated Cardiomyopathy (MDC) trial^[18] and the study of Xamoterol in severe heart failure^[23]) are anywhere near large enough to give information about the effect of a beta-blocker on mortality in patients with heart failure.

The Metoprolol in Dilated Cardiomyopathy Study was relatively small (383 patients) and was designed to study a combined endpoint of fatal plus nonfatal events. Patients could be in relatively mild failure (NYHA Class II–III, ejection fraction up to 40%) but about 80% were simultaneously treated with an ACE inhibitor. Metoprolol was initially given as 5 mg b.d. and increased slowly to 100–150 mg daily. The trial just failed to achieve a statistically significant reduction in its defined primary endpoint of all cause fatality plus a need for cardiac transplantation: there was a 34% reduction in this combination (95% CI –6 to +62%, $P=0.06$) with 23 deaths and two patients needing transplantation in the metoprolol group, compared with 19 deaths and 19 needing transplantation in the placebo group. The 'need for transplantation' as a surrogate for death adds a new complexity to the interpretation of clinical trials, but even so the results of this trial can hardly be claimed to be sufficiently promising to necessitate a widespread change in the clinical management of heart failure.

In the Xamoterol Study^[23] 516 patients with severe heart failure (NYHA III–IV) despite treatment with diuretics and ACE inhibitors were randomized in a double-blind fashion to treatment with Xamoterol 200 mg b.d. or placebo. There was some suggestion

of an improvement in symptoms but not in signs, and there was no improvement in exercise duration in the Xamoterol group. Xamoterol reduced heart rate and blood pressure but did not affect arrhythmias. On an intention to treat analysis there were 39 deaths in the Xamoterol group (9.1%) and six (3.7%) in the placebo group: this difference was statistically different and led to the premature discontinuation of the trial and the withdrawal of the drug.

Xamoterol is an unusual beta-blocker in being a partial agonist at low heart rates. It could be argued, therefore, that the increase in mortality seen in this study would be particular to Xamoterol and unlikely to be seen with any other beta-blocker. In the absence of further trials with other beta-blocking drugs, however, this is not necessarily a safe assumption to make.

Are beta-blockers effective in both ischaemic heart disease and dilated cardiomyopathy?

The neuroendocrine responses to heart failure are the same whatever the underlying cause, and it might therefore be assumed that a treatment effective in patients with ischaemic disease would also be effective in those with dilated cardiomyopathy. This is true in the case of angiotensin-converting enzyme inhibitors. On the other hand, the pathology of the heart, and presumably its metabolism, is different in the two circumstances with ischaemic hearts having a mixture of normal (albeit partly ischaemic) muscle and fibrosis, and cardiomyopathies having a generalized abnormality. The problem is further complicated by the simple fact that many patients clinically diagnosed as cardiomyopathy have underlying (or co-existing) coronary disease: detailed investigations including angiography might well not be practicable in a study large enough to show whether or not beta-blockers affect survival.

Given the undoubted beneficial effect on survival following myocardial infarction, and especially so in those with failure, one might have expected that beta-blockers would be particularly valuable when heart failure results from ischaemic disease. However, most published work has been in patients with dilated cardiomyopathy.

Table 1 shows that improvement seems equally likely whatever the underlying diagnosis, but in the only study that set out specifically to compare patients with ischaemic disease and cardiomyopathy, improvement was seen only in the latter^[14].

References

- [1] Bristow MR, Ginsburg R, Minobe W *et al.* Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *N Engl J Med* 1982; 307: 205–11.
- [2] Meinertz T, Hofmann T, Zehender M *et al.* Beta-blocking agents vs. antiarrhythmic interventions in heart failure complicated by arrhythmias. *J Cardio Pharmacol*; 16: (Suppl 5): S151–S157.

- [3] Gilbert EM, Anderson JL, Deitchman D *et al.* Long-term beta-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.
- [4] Clarkson P, Wheeldon NM, McDonald TM. Left ventricular diastolic dysfunction. *Quart J Med* 1994; 87: 142-8.
- [5] Chadda K, Goldstein S, Byrington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986; 73: 503-10.
- [6] 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.
- [7] Packer M, Carver JR, Rodeheffer RJ *et al.* For the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991; 325: 1468-75.
- [8] Ikram H, Fitzpatrick D. Double-blind trial of chronic oral beta blockade in congestive cardiomyopathy. *Lancet* 1981; ii: 490-2.
- [9] Currie PJ, Kelly MJ, McKenzie A *et al.* Oral beta-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. *J Am Coll Cardiol* 1984; 3: 203-9.
- [10] Engelmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. *Circulation* 1985; 72: 536-46.
- [11] Anderson JL, Lutz JR, Gilbert EM *et al.* A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. *Am J Cardiol* 1984; 55: 471-5.
- [12] Pollock SG, Lystash J, Tedesco C, Craddock G, Smucker ML. Usefulness of bucindolol in congestive heart failure. *Am J Cardiol* 1990; 66: 603-7.
- [13] Leung WH, Lau CP, Wong CK, Cheng CH, Tai YT, Lim SP. Improvement in exercise performance and hemodynamics by labetalol in patients with idiopathic dilated cardiomyopathy. *Am Heart J* 1990; 119: 884-90.
- [14] Woodley SL, Gilbert EM, Anderson JL *et al.* Beta blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation* 1991; 84: 2426-41.
- [15] Fisher ML, Gottlieb SS, Hamilton B *et al.* Beneficial effects of metoprolol in congestive heart failure associated with coronary heart disease. a randomized trial (abstr). *Circulation* 1991; 84 (Suppl II): II-312.
- [16] Paolisso G, Gambardella A, Marrazzo G *et al.* Metabolic and cardiovascular benefits deriving from beta-adrenergic blockade in chronic congestive heart failure. *Am Heart J* 1992; 123: 103-10.
- [17] Olsen SL, Yanowitz FG, Gilbert AM *et al.* Beta-blocker related improvement in submaximal exercise tolerance in heart failure from idiopathic dilated cardiomyopathy (abstr). *J Am Coll Cardiol* 1992; 19: 146.
- [18] Waagstein F, Bristow MR, Swedburg K *et al.* for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993; 342: 1441-56.
- [19] Wisenbaugh T, Katz I, Davis J *et al.* Long-term (3 month) effects of a new beta-blocker (Nebivolol) on cardiac performance in dilated cardiomyopathy. *J Am Coll Cardiol* 1993; 21: 1094-100.
- [20] Doughty RN, MacMahon S, Sharpe N. Beta-blockers in heart failure: promising or proved? *J Am Coll Cardiol* 1994; 23: 814-21.
- [21] Waagstein F, Caidahl K, Wallentin I, Bergh C-H, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. *Circulation* 1989; 80:551-63.
- [22] DasGupta P, Broadhurst P, Lahiri A. The effects of intravenous carvedilol, a new multiple action vasodilatory beta-blocker, in congestive heart failure. *J Cardiol Pharmacol* 1991; 18 (Suppl.4): S12-S16.
- [23] The Xamoterol in Severe Heart Failure Study Group. *Lancet* 1990; 336: 1-6.