β Adrenoceptor blockade in congestive heart failure: future perspectives

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The concept of using β blockers in the treatment of heart failure was introduced about 25 years ago. The initial reaction among cardiologists was one of scepticism or frank disbelief, first because β blockers were known to have a negative inotropic effect on cardiac muscle, and second because a failing heart was believed to be dependent on sympathetic activation, particularly during exercise.

β Blockers were introduced into cardiology for the treatment of angina pectoris and hypertension. Congestive heart failure was an early contraindication, which is still present in the datasheets for many drugs in this category. The rationale, indications, possible mechanisms, and advantages of β adrenoceptor blockade have been the subject of debate ever since.

β Adrenoceptor blockade has the potential to minimise any damage to myocytes brought about by long term stimulation as a consequence of activation of the sympathetic system. The response of other organs within the body to continuing sympathetic activity would also be diminished. β Adrenoceptor blockade is known to reduce sudden cardiac death in the context of ischaemic heart disease. A similar mechanism could be present in heart failure, which is a condition characterised by frequent abnormal rhythms of the heart. Any benefit might simply be attributable to the known slowing of the heart rate, which would result in improved diastolic coronary flow and an increased left ventricular filling time. These effects may be particularly important in the aging heart and in the presence of cardiomegaly, myocardial ischaemia, or functional mitral regurgitation. Alternatively, the advantage of β blockers might be the consequence of reduced occurrence and frequency of myocardial ischaemia. β Blockers could act beneficially in a situation somewhat similar to myocardial hibernation.

Glossary

BEST: Beta-blocker evaluation survival trial
CIBIS: Cardiac insufficiency bisoprolol study
COMET: Carvedilol or metoprolol European trial
COPERNICUS: Carvedilol prospective randomised cumulative survival trial
MDC: Metoprolol in dilated cardiomyopathy
MERIT-HF: Metoprolol randomized intervention trial in heart failure

Objectives of treatment

Many of the earlier clinical studies in heart failure were observational in nature. Later trials, which had the merit of being randomised and properly designed, were either short term or had haemodynamic variables or ejection fraction as end points. The ejection fraction is a particularly inappropriate measure of haemodynamic performance when the drug being studied has a major effect on heart rate, as an increase in ejection fraction of approximately 10% is entirely compatible with a reduction of heart rate of the same order of magnitude in the presence of constant cardiac output. To demonstrate efficacy of a drug in heart failure, it is necessary to show an impact on symptoms or prognosis. Surrogate end points such as haemodynamic variables are not sufficient.

The intended impact on symptoms should be manifest as an increased ability to exercise or as an increase in the quality of life, fewer symptoms at a submaximal level of exercise or an ability to undertake the tasks of everyday living without the more complex symptoms of heart failure such as fatigue and tiredness. The impact on prognosis is expected to prolong life.

In terms of benefit, importance should be given to delay in the progression of heart failure and in the occurrence of severe heart failure. Many patients would be grateful if it were possible to improve their quality of life, even if prognosis was not affected. In this scenario, the symptoms of heart failure would not progress and life would be of the same duration but terminated by a sudden event.

Current controversies

Three recent trials are of particular importance with regard to the role of β blockers in heart failure.¹⁻³ The results of two of the three trials, CIBIS¹ and MDC² trial, failed to show any benefit in terms of overall mortality. However, there are major difficulties in assessing trials in dilated cardiomyopathy in that the condition can only be diagnosed with certainty by coronary angiography. Consequently, many patients with the alleged diagnosis and global dysfunction of the heart have coronary heart disease rather than idiopathic dilated cardiomyopathy.

The most recent of the three trials used carvedilol.³ The study, which was the sum of four smaller trials, and which claimed to show a substantial reduction in mortality over six months, has given rise to considerable debate. Not least among the many points being raised

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is whether the apparent benefit relates to β adrenoceptor blockade or to other effects of carvedilol, such as inhibition of oxygen free radicals or effects caused by α adrenoceptor blockade resulting in peripheral vasodilation.

Five important new studies are being undertaken to evaluate β adrenoceptor blockade: the BEST study (bucindolol), CIBIS II (bisoprolol), MERIT-HF (metoprolol), COMET (carvedilol), and COPENHAGEN (carvedilol). Until the results of these trials are available the physician is left with a number of difficult decisions. Patients with heart failure should certainly be treated with diuretics and angiotensin converting enzyme inhibitors, provided there are no contraindications. A few, but only a few, selected patients may benefit from digoxin, and in some patients consideration should be given to the use of β blockers.

An awkward question facing the physician is which patients might benefit most from the

use of β blockers. The one subgroup of patients in which this treatment is worth consideration are those with tachycardia, small hearts, often hypertrophy, and a degree of mitral regurgitation. The use of β blockers can also be advocated in patients who have chest pain manifest as angina in association with symptoms suggestive of heart failure. This latter group is an appreciable proportion of the patients with heart failure who are currently receiving β blockers.

The next few years will demonstrate whether the somewhat limited indications for prescribing β blockers should be widened.

- 1 CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The cardiac insufficiency bisoprolol study (CIBIS). *Circulation* 1994;**90**: 1765-73.
- 2 Waagstein F, Bristow MR, Swedberg K, *et al*. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993;**342**:144-6.
- 3 Packer M, Bristow MR, Cohn JN, *et al*, for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;**334**:1349-55.