The treatment of heart failure—what next?

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- 1 Despite demonstrable benefits in terms of symptomatic relief and improvement in prognosis, even the best treatments of heart failure currently available fall short of being ideal. We review the basis for newer approaches to the treatment of heart failure and discuss some of the agents which capitalize on current understanding of the underlying patho-physiology.
- 2 Several drugs, old and new, are presently being investigated by major clinical trials. We also consider some of the difficulties related to the design and conduct of such trials and suggest how drugs might be better assessed in the future.

Keywords heart failure medical therapy

In recent years there have been considerable advances in the treatment of cardiac failure and in the understanding of the mechanisms underlying the syndrome. This paper reviews the salient features of the important clinical trials to date and the rationale behind the use of the drugs most recently developed for the treatment of heart failure. We shall also consider the prospects for possible new treatments and the design of future trials.

Although vasodilator therapy was for a long time thought likely to be of benefit in the treatment of heart failure, the modern era of treatment really began with the trials that demonstrated improved mortality with sustained therapy (Cohn *et al.*, 1986; Consensus Trial Study Group, 1987) even when used in addition to conventional therapy (Consensus Trial Study Group, 1987; The SOLVD Investigators, 1991). The first Veterans Administration Co-operative study (V-HeFT) showed a reduction in mortality of 38% in those treated with hydralazine and isosorbide combined compared with those taking prazosin. In the Co-operative North Scandinavian Enalapril Survival Study (Consensus) the total 1 year mortality was reduced by 31% in patients with severe heart failure (NYHA class IV) taking enalapril in addition to conventional therapy. It was subsequently established that angiotensin converting enzyme inhibition, when added to diuretics, could prevent or delay the progression of symptoms and was better than digoxin (The Captopril-Digoxin Multicenter Research Group, 1988). Most recently, the benefit has been demonstrated of starting an ACE inhibitor early after myocardial infarction in asymptomatic patients with reduced ejection fraction, irrespective of whether those patients had received thrombolysis (Pfeffer *et al.*, 1992). Giving an ACE inhibitor to asymptomatic patients with reduced ejection fraction and in the absence of other drugs has been shown to reduce progressive ventricular dilatation (Konstam *et al.*, 1992) and the incidence of heart failure

and the need for hospitalization (The SOLVD Investigators, 1992). Another trial showed delayed progression from NYHA class II and III to class IV in patients treated with captopril in addition to other therapy (Kleber *et al.*, 1992) and, after longer follow-up, a marked reduction in death due to pump failure (Kleber, 1991). The second V-HeFT study (Cohn *et al.*, 1991) has shown that ACE inhibition with enalapril had a greater effect in terms of improved mortality than the combination of hydralazine and isosorbide even though the latter treatment had a greater effect in terms of improving exercise tolerance.

Despite these developments, the fact remains that approximately 40% of the patients enrolled in the trials mentioned above died in the first 4 years after being recruited. Any new treatment for heart failure, whether to be used alone or in combination with established treatments, must better these results, should make the patient feel better and involve no extra unwanted effects or extra inconvenience for the patient.

The concept that afterload reduction was of paramount importance for the prevention of progression of heart failure has prompted the testing of many different vasodilators. However, it emerged that the long-term efficacy of vasodilator drugs was not related to their haemodynamic effects. For example, controlled trials of minoxidil (Franciosa *et al.*, 1984) and the calcium antagonist vasodilators verapamil (Ferlinz & Gallo, 1984), nifedipine (Elkayam *et al.*, 1990) and diltiazem (Goldstein *et al.*, 1991) showed that patients treated with these agents were at greater risk of developing worsening heart failure and of dying from cardiovascular causes than those treated with placebo. In the case of the calcium antagonists this appears at least in part due to negative inotropic effects. An alternative approach of manipulating haemodynamics using positive inotropic agents or so-called inodilators similarly seemed logical.

Unfortunately, the benefits in the short term of agents such as milrinone have not translated into improvements in long-term survival, with a 28% increase in deaths from all causes and a 34% increase in the risk of death from cardiovascular causes in one trial (Packer *et al.*, 1991a). However, pimobendan, a new phosphodiesterase inhibitor/calcium sensitizer has recently been shown to have favourable effects on symptoms and exercise capacity during a 12 week period, without penalties in terms of increased mortality or proarrhythmic effect (Kubo *et al.*, 1992; Remme *et al.*, 1992). Whether it will have the same neutral effect on mortality over longer periods remains to be seen.

The newer approaches to the treatment of heart failure take greater account of the neurohormonal and peripheral adaptive changes which may be regarded as the consequences of the ventricular dysfunction and associated haemodynamic impairment (Francis, 1990). There have been several important observations that have led to consideration of the pathophysiology of heart failure other than in terms of haemodynamic changes alone.

First, an attenuated myocardial response to catecholamines has been found as a result of down-regulation of β -receptors (Bristow *et al.*, 1982; Fowler *et al.*, 1986) in the face of sustained endogenous inotropic stimulation. Peripheral vessels display an amplified response to α -adrenergic stimuli, however. It is known that plasma noradrenaline levels are a guide to prognosis in patients with severe heart failure (or post-myocardial infarction) before treatment (Cohn *et al.*, 1984; Francis *et al.*, 1982). This activation of the sympathetic nervous system has consequences not only in terms of peripheral vasoconstriction and increased ventricular wall stress but also may have directly damaging effects on myocardial cells (Mann *et al.*, 1992). Treatment with ACE inhibitors has many effects but is known to reduce neuroendocrine activation as shown by reduced levels of noradrenaline and adrenaline (Carson *et al.*, 1992; Swedberg *et al.*, 1990a).

Secondly, the other means by which blood pressure is maintained when cardiac output falls involves the renin-angiotensin-aldosterone-vasopressin system (Brown *et al.*, 1970; Goldsmith *et al.*, 1983). High levels of renin and angiotensin II (pre-treatment) also appear to indicate a poor prognosis (Dzau *et al.*, 1981; Swedberg *et al.*, 1990b). Like high levels of noradrenaline, angiotensin II may have directly toxic effects on myocardial cells (Tan *et al.*, 1991). Elevated atrial natriuretic factor (ANF) is also indicative of poor prognosis (Gottlieb *et al.*, 1989; Richards *et al.*, 1986). Produced in response to atrial stretch it exerts central or ganglionic sympatho-inhibitory effects (Floras, 1990) and direct effects on renal glomerular and tubular function. However, the response to these effects, which cause vasodilation and counterbalance salt and water retention, tends to become progressively blunted (Cody *et al.*, 1986; Hirooka *et al.*, 1990).

Thirdly, the almost instant improvement in central haemodynamics brought about by cardiac transplantation does not necessarily result in immediate improvement in exercise tolerance (Sinoway *et al.*, 1988) though the marked impairment of arterial baroreflex control may recover within 2 weeks (Ellenbogen *et al.*, 1989). Clearly, peripheral adaptations are involved but the relative

importance of flow-dependent vasodilation mediated by EDRF (Drexler *et al.*, 1992; Ontkean *et al.*, 1991), the effects of endothelin (Stewart *et al.*, 1990), possible sodium and water retention in vessel walls and local renin-angiotensin systems causing hypertrophy or other structural changes (and therefore decreased compliance of vessels (Asmar *et al.*, 1988)) is uncertain. Furthermore, abnormalities of skeletal muscle ultrastructure and metabolism develop which may not be quickly reversible even with effective treatment of heart failure (Drexler *et al.*, 1987; Lindsay *et al.*, 1992; Massie *et al.*, 1988; Poole-Wilson *et al.*, 1988).

How do newer agents for the treatment of heart failure capitalize on the current understanding of the underlying pathophysiology? The appreciation of the profound importance of sympathetic nervous activation has led to attempts to counteract this directly, using new sympathetic inhibitors, and alternatively to assess the usefulness of directly acting vasodilator drugs in terms of their effects on levels of neurohormones as well as their haemodynamic effects.

Although β -adrenoceptor blockers have been shown to be of benefit in some patients, their negatively inotropic action carries with it a serious risk of worsening heart failure. However, bucindolol, a β_1 -adrenoceptor antagonist with β_2 -adrenoceptor agonist (and therefore peripheral vasodilating) activity and carvedilol, which combines β_1 -adrenoceptor antagonist activity with α -adrenergic antagonism could be beneficial if their desirable effects outweigh depression of myocardial function. Given the results of early trials (Anderson *et al.*, 1991), the results of larger studies of these agents are awaited with interest.

The prospect of successfully using calcium antagonists has been revived, these agents having previously fallen out of favour (Packer *et al.*, 1987). The new calcium antagonists, such as amlodipine, felodipine and nifedipine, when used at therapeutic doses, act selectively on peripheral arterioles. They have little detectable negative inotropic effect (Culling *et al.*, 1984; Thomas & Sheridan, 1990), but this can depend on contractility being carefully measured (Aroney *et al.*, 1989; Culling *et al.*, 1984; Joshi *et al.*, 1981) and may anyway be offset by the dominant vasodilating action (Aroney *et al.*, 1989). They can improve symptoms and exercise capability in patients with chronic heart failure (Dunselman *et al.*, 1989; Packer *et al.*, 1991b) and, crucially, decrease the activity of the sympathetic nervous system (Kassis & Amtorp, 1990) (although some studies of the use of felodipine in hypertension have reported elevation of neurohormones (Fagard *et al.*, 1987; Katzman *et al.*, 1986; Leenen & Holliwell, 1992)).

The presence of dopaminergic receptors in the circulation, activation of which causes arterial vasodilation (via DA_1 receptors), inhibition of renin and aldosterone release and inhibition of noradrenaline release from post-ganglionic sympathetic nerve endings (DA_2), can be exploited to treat heart failure (Brodde, 1990). Ibopamine, a pro-drug, can be taken orally to yield epinine which is active at DA_1 and DA_2 receptors. It has been found to be a good substitute for dopamine in patients stabilised on between 2–5 $\mu\text{g kg}^{-1} \text{ min}^{-1}$ of the latter (Dei Cas *et al.*, 1989). The main problem with this approach is that the dopamine receptors could

become down-regulated in the same way as β -adrenergic receptors with prolonged exposure and the efficacy of ibopamine could therefore decrease with time.

Flosequinan, an orally active quinolone, is a vasodilator which is active on both arteries and veins and therefore potentially offers beneficial effects not only on afterload alone but also on preload (of particular importance not only because of the long-established symptomatic benefits of preload reduction but also because increased left ventricular filling pressure has been correlated with raised adrenergic drive as reflected by elevated coronary sinus norepinephrine (Sandoval *et al.*, 1989)). It operates via the inositol triphosphate pathway (Yates, 1991) with only a modest increase in heart rate and without the potentially troublesome cough and adverse effects on renal function associated with the ACE inhibitors. It has been shown to have beneficial effects on symptoms and exercise tolerance when used alone (Packer *et al.*, 1990; Pitt, 1991) or in combination with ACE inhibitors (Elborn *et al.*, 1989). It has also been shown, by analysis of heart rate variability, to reduce sympathetic activity and augment parasympathetic tone (Binkley *et al.*, 1992). Some studies have demonstrated a positive inotropic action depending on the dosage (Perreault *et al.*, 1991), preparation (Weishaar *et al.*, 1991), and animal species tested (Greenberg *et al.*, 1990). Even using the same invasive technique for assessing changes in contractility in patients has yielded conflicting results (Burstein *et al.*, 1992; Starling, 1992a). There is agreement, however, that it has a positive lusitropic action (as assessed by LV diastolic chamber compliance (Starling, 1992b) and peak negative dP/dt (Burstein *et al.*, 1992)). Preliminary reports have shown it to be an effective and well-tolerated drug in patients with congestive heart failure who have been withdrawn from ACE inhibitors (Packer *et al.*, 1992). There is some evidence of a favourable effect of flosequinan on ventriculo-arterial coupling such that there is an increase in the mechanical efficiency of the left ventricle in patients with dilated cardiomyopathy (Starling, 1992b) (the more efficiently the heart transfers energy to the circulation, the lower the cost in terms of oxygen consumption). However, the technique used to establish this is relatively novel and not yet sufficiently widely used to be able to say whether or not the improvement in efficiency is common to other effective treatments for heart failure.

The principal clinical trials currently investigating treatments for heart failure are:

- i) DIG – the Digoxin Investigation Group will assess the effect of digoxin in addition to ACE inhibitor therapy. Approximately 10 000 patients with heart failure and ejection fractions less than 45% will need to be recruited and the results are not expected for another 4 years. The results of this trial, together with those from the V-HeFT III study (below), should go a long way to determine the modern usage of this still not fully understood drug;
- ii) FACET—which is investigating the effect of flosequinan in combination with ACE inhibitors (Massie *et al.*, 1992);
- iii) PRAISE—which is designed to investigate the effect of amlodipine versus placebo in those also taking an ACE inhibitor;
- iv) PRIME—investigating the effect of ibopamine

vs placebo in patients in NYHA grade IV;

- v) PROFILE—the Prospective Flosequinan Longevity Evaluation, which is investigating the long-term effect of this drug on mortality in approximately 3500 patients with congestive cardiac failure who are already on an ACE inhibitor;
- vi) REFLECT—assessing the applicability of flosequinan in patients who are symptomatic despite digoxin and diuretics (Pitt, 1992);
- vii) V-HeFT III—which will assess felodipine in combination with enalapril for the treatment of patients in NYHA grades II and III. This study, involving approximately 900 patients, includes randomization to digoxin or placebo. The results are expected within the next 2 years.

Other agents potentially of use in the treatment of heart failure which are actively being investigated at present include candoxatril, an inhibitor of ANF degradation (Elsner *et al.*, 1992a; Good *et al.*, 1992; Northridge *et al.*, 1990), a renin inhibitor (Friedrich *et al.*, 1992), a vasodilating prostacyclin analogue (Adams *et al.*, 1992; Steffen & de la Mata, 1991), an antagonist of the vasoconstrictor effects of neuropeptide Y (Xiang Ying Sun *et al.*, 1992), a quinolinone derivative acting on sarcolemmal ion channels (Feldman *et al.*, 1992) and urodilatin, which increases natriuresis and diuresis without haemodynamic effects (Elsner, 1992). The possibility of using leukotrienes (Elsner *et al.*, 1992b) and of favourably manipulating tumour necrosis factor (Levine *et al.*, 1990; McMurray *et al.*, 1991) (thought to be responsible for the debilitating loss of body weight in those with severe heart failure), the non-contractile elements of the heart (Weber & Brilla, 1991) or some means of promoting repair in a damaged heart are more distant prospects for therapy in heart failure.

With no shortage of agents to investigate, there is an immediate problem of how to design ethical trials which are likely to yield appropriate information about new agents. As has been pointed out before (Hampton & Cowley, 1991), in the light of the trials which showed the benefits of vasodilator therapy, especially ACE inhibitors, it is probably no longer ethical to conduct a study with mortality as an endpoint in which a new drug is compared with placebo, unless the design includes the comparison of new drug with placebo in addition to the established best therapy. If each new drug is thought likely to improve mortality by a similar percentage, then successively larger trials will be needed to demonstrate a difference. This time-consuming and increasingly costly process, for all the care taken in the design and execution and collaboration between centres, essentially means counting the numbers of deaths in each treatment group at the end of a given period.

There can also be problems in trying to assess objectively the symptomatic improvement in patients involved in clinical trials. A relatively convenient means of assessment involves some form of exercise testing, sometimes with the refinement of measurement of oxygen consumption at maximal effort. However, there can be marked differences between the amount of exercise a patient can manage on a treadmill compared with the amount of exercise he or she is prepared voluntarily to undertake in the course of daily life (which may be more

realistic indication of how much better the patient feels as a result of treatment (Hampton, 1991)). Measurements of calf blood flow at rest and after exercise have been shown to correlate with the patient's state and response to therapy as measured by exercise on a treadmill (Cowley *et al.*, 1986). This non-invasive method, which can be used even in those patients who are unable or unwilling to go on a treadmill or bicycle ergometer, could be more widely used.

A clearer understanding of the beneficial haemodynamic and neurohumoral responses to drugs would greatly improve the assessment of new agents. In this context, further work is needed to investigate the effects of heart failure treatment on ventriculo-arterial coupling. Vasodilators have been known for a long time to work in ways not adequately characterised by the concept of reduction in afterload (O'Rourke *et al.*, 1993). They can exert effects at least in part by reducing the amplitude and changing the timing of reflected pressure waves returning from the periphery so that these waves do not add to the work of the heart (Fitchett *et al.*, 1988; Latson

et al., 1988; Yaginuma *et al.*, 1986). Perhaps more effort should go into assessing the haemodynamic effects of drugs using these methods, load-independent methods of assessing contractility (Kass & Beyar, 1991) and other means of assessing ventriculo-arterial coupling (Binkley *et al.*, 1990; Parker & Jones, 1990; Sasayama & Asanoi, 1991) in the hope that better means of characterising drug action could limit the need for long clinical trials.

The tangled mechanisms responsible for the syndrome of heart failure continue to be unravelled. The prospects for patients with heart failure have been dramatically improved now that treatments capable of improving systems and exercise capacity have also been established to be effective in reducing mortality in the longer term. There is no room for complacency, however. Much work remains to be done in establishing whether newer drugs and combinations of drugs can deliver additional benefits and, ideally, we need also to develop ways of predicting earlier whether new treatments are likely to be consistently and sustainably effective.

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