Physiological rationale for co-treatment with diuretics in heart failure

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Contemporary treatment of heart failure should be based on an understanding of its pathophysiology. Only in recent years has the complex involvement of many systems in this syndrome become widely recognised. The systemic response to impaired left ventricular function generates a wide array of symptoms and physiological derangements that may contribute to the natural history of the syndrome. The challenge to clinical investigators, the pharmaceutical industry, and the treating physician is to identify and properly use a therapeutic regimen that can successfully counter the unwanted maladaptive responses to the cardiac disorder without interfering with the necessary adaptive responses. In this review I examine the rationale for polypharmacy in this syndrome.

Clinical syndrome

The clinical syndrome of heart failure has its origin in left ventricular dysfunction. This dysfunction may manifest itself predominantly in systole as a reduced wall motion and lowered ejection fraction, or in diastole as impaired filling characteristics of the left ventricle. The end result of systolic dysfunction usually is progressive dilatation and hypertrophy of the left ventricular chamber. The consequence of diastolic dysfunction is an increased end-diastolic pressure. The haemodynamic manifestations of these disorders are similar. Cardiac output may be normal or only modestly decreased at rest but the increase in cardiac output normally generated by exercise is attenuated and exercise is accompanied by an inordinate rise in left ventricular filling pressure. These cardiac manifestations of heart failure are hallmarks of the disease process. None the less, it is important to recognise that considerable left ventricular dysfunction may exist in the absence of symptoms of heart failure such as impaired exercise performance or quality of life. Thus the haemodynamic derangement of left ventricular dysfunction is not adequate to explain the clinical syndrome.

An inevitable accompaniment of the clinical syndrome of heart failure is an impairment in exercise performance. Clinically this is recognised by the patient's inability to carry out his or her normal activities without symptoms of fatigue or breathlessness. The degree of exercise intolerance experienced by the patient (the New York Heart Association classification) is often used to classify the severity of the syndrome. As this classification is based on historical information obtained by interviewing the patient, rather than by any objective measure of exercise performance, it is a rather imprecise and insensitive guide to the degree of functional impairment. More objective data can be obtained by performing laboratory exercise tests. Most of these tests are designed to impose a progressive increase in load over time until patients reach their maximal exercise capacity. Measurement of gas exchange during exercise can confirm that the anaerobic threshold has been surpassed and that the symptoms of dyspnoea and fatigue represent true maximal exercise performance. This documentation of maximal exercise capacity does not necessarily provide much insight into the limitation of activity in normal life, which usually consists of submaximal exercise performed intermittently throughout the day. Attempts to develop submaximal exercise tests with suitable end points to evaluate this impaired lifestyle related to reduced exercise capacity have not been very successful.

A third important manifestation of heart failure is sodium retention. Oedema and pulmonary congestion are prominent manifestations that usually alert the physician to the presence of heart failure. Indeed, the diagnosis is generally not made in the absence of fluid retention. Although sodium retention is a common manifestation of heart failure and in some instances may occur as an early sign of the disease, the syndrome of left ventricular dysfunction and impaired exercise capacity may exist without abnormal sodium retention. It is these non-oedematous patients with heart failure who represent the most troublesome diagnostic challenge to physicians confronted with non-specific complaints of fatigue. When oedema is present the physician appropriately gives a diuretic agent that usually relieves the congested state. In the past, however, many physicians assumed that diuresis had effectively treated heart failure and did not recognise that the progressive syndrome continued to exist in the absence of fluid retention.

Ventricular arrhythmias are also a common manifestation of the syndrome of heart failure. The mechanism of these ventricular arrhythmias is not completely understood but they seem to be directly related to the severity of cardiac dysfunction. Most of these ventricular arrhythmias in such patients are relatively asymptomatic, often presenting as an unexpected premature ventricular contractions on an electrocardiogram or as episodes of non-sustained ventricular tachycardia noted on Holter
monitoring. Although the significance of these ventricular arrhythmias is controversial, the high incidence of sudden death in these patients raises the possibility that the electrical instability of the heart is playing an important part in the natural history of the disease.

A fifth manifestation of heart failure is activation of neurohormonal mechanisms. Plasma noradrenaline (norepinephrine) is almost invariably raised in patients with heart failure, and is also increased in patients with left ventricular dysfunction even in the absence of the symptoms of heart failure. Plasma renin activity may be strikingly increased in patients with heart failure, and there are also increases in plasma arginine vasopressin and in plasma atrial natriuretic factor. The mechanism of activation of these neurohormonal mechanisms is not entirely understood, although haemodynamic abnormalities may play a key part. Because of the vasoconstrictor effect of the sympathetic nervous system, the renin-angiotensin system, and the vasopressin system, these increased hormonal concentrations are usually thought to be related to the vasoconstricted state of heart failure. Atrial natriuretic factor functions in the circulation at least in part as a vasodilator and is often viewed as a counter regulatory vasodilator mechanism in the syndrome of heart failure. As vasoconstriction is a hallmark of the syndrome, it is clear that the vasodilator effect of atrial peptide is inadequate to counteract the forces of vasoconstriction that exist in heart failure.

Determinants of survival

The severity of heart failure might best be characterised by the likelihood of dying. Recent trials have provided a data base from which one can assess the relation of the physiological variables already described to mortality. In most studies the function of the left ventricle, as assessed by the measurement of left ventricular ejection fraction, has served as the most powerful predictor of survival. This relation has been best delineated in the Veterans Administration heart failure trial (V-HeFT) in which a close correlation between the depression of left ventricular ejection fraction and the annual mortality has been noted. These data certainly suggest that the left ventricle is the culprit organ in heart failure and that preservation of left ventricular function might have a long-term salutary effect on the course of the syndrome.

Although exercise tolerance correlates poorly with left ventricular ejection fraction, peak exercise capacity measured by gas exchange during bicycle exercise in the V-HeFT trial was directly related to survival in heart failure. Thus for any given level of left ventricular ejection fraction poor exercise capacity was associated with a poorer prognosis than good exercise capacity. These findings raise the possibility that the left ventricle is not the sole target organ in heart failure and that other regulatory mechanisms are also critical to the natural history of the disease.

The presence of ventricular arrhythmias is associated with a poor prognosis, but the independent influence of the rhythm disturbance on mortality can only be evaluated by multivariate analysis taking into consideration the other univariate predictors of mortality. With this approach in the second trial (V-HeFT II), the presence of couplets or non-sustained ventricular tachycardia on a Holter monitor, found in 60% of the patients, was a significant independent prognostic marker.

Plasma noradrenaline concentration also is an independent predictor of survival. In previous studies from our laboratory a plasma noradrenaline concentration >600 pg/ml carried with it a significantly poorer prognosis than a plasma noradrenaline concentration <600 pg/ml. These findings have now been confirmed in the much larger V-HeFT II database. In that trial a plasma noradrenaline concentration <600 pg/ml was associated with a good prognosis, a plasma noradrenaline concentration from 600 to 900 pg/ml with an intermediate prognosis, and a plasma noradrenaline concentration of >900 with a poor prognosis. Whether this adverse long-term effect of heightened plasma noradrenaline merely identifies a patient population with more severe haemodynamic derangement or whether the activated sympathetic nervous system is an independent risk factor for premature death remains to be determined. None the less, the data linking the sympathetic nervous system to mortality in patients with heart failure has led to growing enthusiasm for the use of agents that inhibit the action of the sympathetic nervous system. $\beta$ Blockers have been advocated in an attempt to alter the prognosis of the disease.

Assessing the mortality in patients with heart failure represents one way to explore the progressive nature of the heart failure syndrome. Diseases that damage the ventricular myocardium do not necessarily produce progressive damage. Recently it has become clear that even in the absence of more direct myocardial damage the process of cardiac dilatation and hypertrophy may proceed. This progressive change in the left ventricle in the absence of further primary damage may best be viewed as a process of ventricular remodelling. It is this remodelling process that leads to dilatation of the chamber and progressive hypertrophy that may be an important risk factor in the development of pump failure, ventricular arrhythmias, and premature death. The peripheral vasculature also plays a part in this progressive process by imposing an increased impedance on left ventricular ejection. The vascular impedance in heart failure may initially be high because of heightened vasoconstrictor tone in the vasculature, but eventually some of the increased impedance may relate to structural changes in the vessel wall that may also be thought to represent a hypertrophy and remodelling process.

Thus the myocardium and the peripheral vasculature may be viewed as the main target organs in heart failure contributing to progression of the syndrome. The role of
endocrine factors, particularly local tissue endocrine mechanisms,\textsuperscript{31} cannot be discounted as contributing to both the myocardial and peripheral vascular changes over time.

**Regulatory and counter regulatory processes**

The complex physiological responses to left ventricular dysfunction may be viewed as regulatory or counter regulatory, depending on the clinical setting and the degree of the response. Thus vasoconstriction is compensatory because it supports arterial pressure in the face of a falling cardiac output; but it becomes counter regulatory when it results in an increased impedance that further depresses performance of the left ventricle. Left ventricular dilatation may be regulatory if it allows maintenance of a normal stroke volume with reduced wall motion, but it becomes counter regulatory if the dilatation leads to increased wall stress, inadequate myocardial perfusion, and metabolic or structural abnormalities that lead to progression of the pump failure.

The other physiological abnormalities found in heart failure may also be viewed as double edged swords capable of both supporting circulatory function and leading to progression of the circulatory deficiency. Hormonal stimulation, sodium retention, left ventricular hypertrophy, tachycardia, etc, can all be viewed as compensatory in some situations and deleterious in others.

**Therapeutic implications**

The multiple physiological mechanisms identified in heart failure encourage the use of combinations of agents that can inhibit or alter these mechanisms to influence the course of the disease. Diuretics are obvious candidates for treatment because of the common sodium retention in the syndrome. Indeed, most other drugs used to treat the syndrome may improve haemodynamics but usually do not eliminate the need for concomitant diuretic treatment. The loop diuretics, such as frusemide, are the most popular agents for use in heart failure and are often very effective in relieving the congestion and oedema. The problem with diuretic treatment in patients with heart failure is that it usually does not lead to an increase in cardiac output and may further activate neurohormonal mechanisms that can aggravate vasoconstriction in the syndrome. As loss of potassium is a common consequence of loop diuretic treatment, to give supplementary potassium or a potassium retaining diuretic is a prudent approach to management. Patients with heart failure often need very high doses of diuretic for adequate diuresis and it is these patients that giving a second diuretic, such as metolazone, can be most effective. Studies that have explored the long-term response of patients treated with diuretic alone have confirmed that to give digoxin or angiotensin converting enzyme (ACE) inhibitor with a diuretic reduces morbidity.\textsuperscript{32}

Vasodilators have become popular in the management of heart failure because of the haemodynamic evidence of vasoconstriction and the finding that acute doses of vasodilators can profoundly improve left ventricular function.\textsuperscript{33} This favourable haemodynamic response to vasodilators has been the stimulus to develop oral regimens that could be given chronically for long-term benefit.\textsuperscript{24} The view that the acute haemodynamic response to a vasodilator can be translated into long-term efficacy may be naïve. Improvement of exercise capacity is not temporally related to the improvement in haemodynamics induced by a vasodilator drug.\textsuperscript{25} Furthermore, some drugs that exert a potent vasodilator effect have not necessarily been associated with improved symptoms or exercise capacity.\textsuperscript{26} Thus the mechanism by which exercise capacity is improved seems to be independent of the haemodynamic response to the vasodilator drug in heart failure. This improvement of exercise tolerance may relate more to direct improvement in perfusion of skeletal muscle, to alterations in the structure or metabolic function of skeletal muscle, or to a subtle reconditioning process that may take months to achieve. None the less, several vasodilator regimens, including ACE inhibitors,\textsuperscript{27} oral nitrates,\textsuperscript{28} and the combination of hydralazine and isosorbide dinitrate,\textsuperscript{29} have been shown to improve peak oxygen consumption and maximal exercise capacity in patients with heart failure.

The vasodilator drugs have a clear place in the contemporary management of patients with heart failure. Newer vasodilator drugs are being developed in the hope that they might be effective in combination with other drugs in the management of the syndrome. The ACE inhibitors, although they exert a vasodilator effect, also have other metabolic and haemodynamic actions that may not result specifically from their vasodilator mechanism. Hydralazine and isosorbide dinitrate represent a potent vasodilator combination that is effective both in prolonging life and improving left ventricular function and exercise tolerance. As this generic drug combination is not manufactured and neither of these drugs is approved for use in heart failure, they have not been widely used in the treatment of heart failure because of the absence of a marketing effort. Consequently, other newer vasodilator drugs are currently being developed in the hope that a marketable drug could be used in the syndrome. Calcium antagonists that have been shown to be more vasoselective than previously marketed calcium antagonists are currently being studied in patients with heart failure. Felodipine and amlodipine are the most prominent examples of this new class of calcium antagonists. It is likely that most studies with these new agents would involve patients already receiving ACE inhibitors, in which case the calcium antagonist would serve as a combination vasodilator in association with an ACE inhibitor. Another new vasodilator compound, flosequinan, has
been shown to improve exercise performance and quality of life in patients treated with an ACE inhibitor, but the dose used in those trials has shown an adverse effect on survival.\(^6\)

An orally effective positive inotropic agent has long been sought by the pharmaceutical industry to replace or supplement digoxin in the management of heart failure. The failing left ventricle shows reduced ventricular wall motion, and agents with potent inotropic effects, such as dobutamine and phosphodiesterase inhibitors, can improve cardiac function in part by increasing contractility of the left ventricle. Despite the intuitive attractiveness of an agent that could improve the contractile behaviour of a depressed left ventricle, clinical trials with new orally effective inotropic agents, mostly phosphodiesterase inhibitors, have been disappointing.\(^4\) Despite the evidence that these drugs can strikingly augment cardiac performance when given acutely, long-term administration even with sustained haemodynamic efficacy, has not necessarily been associated with relief of symptoms or improved quality of life. Furthermore, one recent study has shown an adverse effect on survival of milrinone given to patients with severe congestive heart failure.\(^7\)

The failure of these early trials with positive inotropic drugs may relate more to the toxic side effects of these agents than to any flaw in the conceptual design of the trials. The search for an inotropic agent that is safer, perhaps by virtue of a different mechanism of action, is a high priority in the drug development industry. One such drug, pimobendan, seems to exert at least part of its effect by sensitising the contractile apparatus to calcium. In early trials this drug has improved haemodynamics and exercise tolerance as well as quality of life in patients with moderate to severe heart failure.\(^8\) Additional studies with this drug are necessary not only to confirm its efficacy but also to show if it is safe to give long term.

The multiple mechanisms involved in the development and progression of heart failure make polypharmacy a rational approach to management. The figure shows that the sites of action of the drugs currently used in the treatment of heart failure should be complementary in contributing to a favourable response to treatment.

**Methods of assessment**

One of the main problems of evaluating treatment for heart failure is the identification of the appropriate end point. Our growing insight into the syndrome has made it clear that not all physiological end points or clinical end points are equally deranged in patients with heart failure. Consequently, it would be imprudent to use a single end point as a guide to beneficial treatment. In many studies exercise tolerance has served as the main end point of treatment, but as this measurement is confined to peak exercise capacity and has proved remarkably insensitive to treatment it may not be its most useful marker. Quality of life may serve as a more appropriate end point, but this has needed a questionnaire that is aimed specifically at patients with heart failure. Such a questionnaire has been developed at the University of Minnesota and currently is in use in a number of centres to evaluate response to treatments.\(^9\) Preliminary trials suggest that such a patient based questionnaire can serve a useful purpose in establishing the efficacy of various treatments.\(^10\) Left ventricular function also may be a useful measurement, particularly because the prognosis of the disease seems to be so closely linked to the severity of left ventricular dysfunction. Furthermore, a sequential improvement in ejection fraction may be a marker for a favourable effect on long-term mortality.\(^11\) Ventricular arrhythmias could also serve as an end point, as the high incidence of non-sustained ventricular tachycardia makes the search for a drug that can reduce these arrhythmias attractive. The recent cardiac arrhythmia suppression trial (CAST) has made it clear that drugs that directly suppress the arrhythmia are not necessarily safe.\(^12\)

Mortality has emerged as the most persua-
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...end point for response to treatment in patients with heart failure because it is so easily measured and so non-controversial. The vasodilator combination of hydralazine and isosorbide dinitrate and the ACE inhibitor enalapril have been shown to prolong survival in patients with heart failure. Despite the favourable effect of these drugs on the course of the disease, progression of this syndrome was not halted by these agents. At the end of four years in the V-HeFT II trial more than 40% of patients had died even while receiving long-term enalapril treatment. Thus the natural history of this disease seems to be progressive and the present treatments have been ineffective in halting this progression. This poor long-term experience provides a window of opportunity for the development of new drugs that might more effectively inhibit the counter regulatory processes that lead to progression. Of particular promise in this area would be agents that would block growth and remodelling of the heart and the vasculature. Safe agents that could improve contractile force of the myocardium might also be attractive in altering the progression of the disease. The need for new agents is probably not necessarily mean that they will replace older agents. Diuretics, digoxin, vasodilators, and ACE inhibitors will probably continue to serve as the cornerstones for treatment of heart failure. β Adrenoceptor blockers are under intense evaluation for long-term efficacy in heart failure. Addition of new drugs to further inhibit the progressive process seems to be the likely strategy. Therefore, the polypharmacy that already exists today in this syndrome is likely to become more complex in the future as we gain further insight into the physiological mechanisms and pharmacological responses of these mechanisms to intervention.


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