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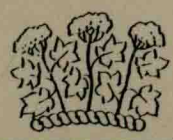
DIURETICS IN HEART FAILURE

TRENDS AND DEVELOPMENTS

EDITED BY

PHILIP A. POOLE-WILSON



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Diuretics in heart failure:
trends and developments

Edited by
Philip A. Poole-Wilson

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Diuretics in heart failure: trends and developments

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Introduction

In the last few years heart failure has re-emerged as a subject of considerable medical and scientific interest. This has occurred because of new understanding of the underlying pathophysiology, introduction of new non-invasive investigative techniques allowing more accurate diagnosis, the availability of new drugs (inotropes, vasodilators and angiotensin converting enzyme inhibitors) and the success of heart transplantation.

Heart failure is an important cause of morbidity, bed occupancy and time off work. The prognosis is poor. The survival at two years for all grades of heart failure is approximately 70% and for those with severe grades of heart failure (New York Heart Association classification grade III and IV) 30%. Although transplantation almost certainly extends the duration of life, only recently have trials begun to test this possibility when using newer drugs.

Medical therapy for heart failure has been directed towards symptoms. The primary objective has been to prevent or remove fluid overload and sodium retention. The secondary objective has been the alleviation of symptoms, particularly shortness of breath and fatigue.

The most effective group of drugs for the treatment of heart failure remains diuretics. The major problems with these drugs are the development of hypokalaemia and overuse leading to dehydration. To avoid hypokalaemia new preparations have become available which combine a loop diuretic with a potassium-sparing diuretic. In this symposium, German and British physicians exchanged ideas on the modern management of heart failure.

Philip A. Poole-Wilson
London
October 1985

Overview of heart failure therapy — a German view

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In heart failure an abnormality of cardiac function is responsible for the failure to supply the metabolizing tissues sufficiently. For maintenance of its pumping function, the heart depends on three principal compensatory mechanisms:

1. the Frank–Starling mechanism;
2. the release of catecholamines and
3. myocardial hypertrophy to increase the mass of contractile tissue.

In the treatment of heart failure it is important to remove the underlying cause first; for example, valvular disease, hypertension or arrhythmias. The second approach, the control of the congestive heart failure state, is the subject of this paper.

There are three pharmacological methods of improving cardiac function in congestive heart failure:

1. improvement of the heart's pumping function by restoring contractility towards normal;
2. control of excessive salt and water retention and
3. reduction of the heart's workload, including preload and afterload.

Acute heart failure

Until recently digitalis was the first choice in the treatment of acute heart failure in West Germany. However, since Bussmann *et al.* (1,2) of our group demonstrated the beneficial effects of nitroglycerin in pulmonary oedema in the early seventies the concept has completely changed and digitalis has now become the last choice in acute myocardial dysfunction.

As Fig. 1 shows, in seven patients with acute pulmonary oedema and right heart catheterization when the pulmonary oedema occurred, 1·6 mg nitroglycerin given sublingually led to a dramatic decrease in left ventricular filling pressure within 3–5 min and simultaneously, an increase in cardiac output. The patients' conditions improved promptly and pulmonary râles were no longer audible. Inotropic agents such as

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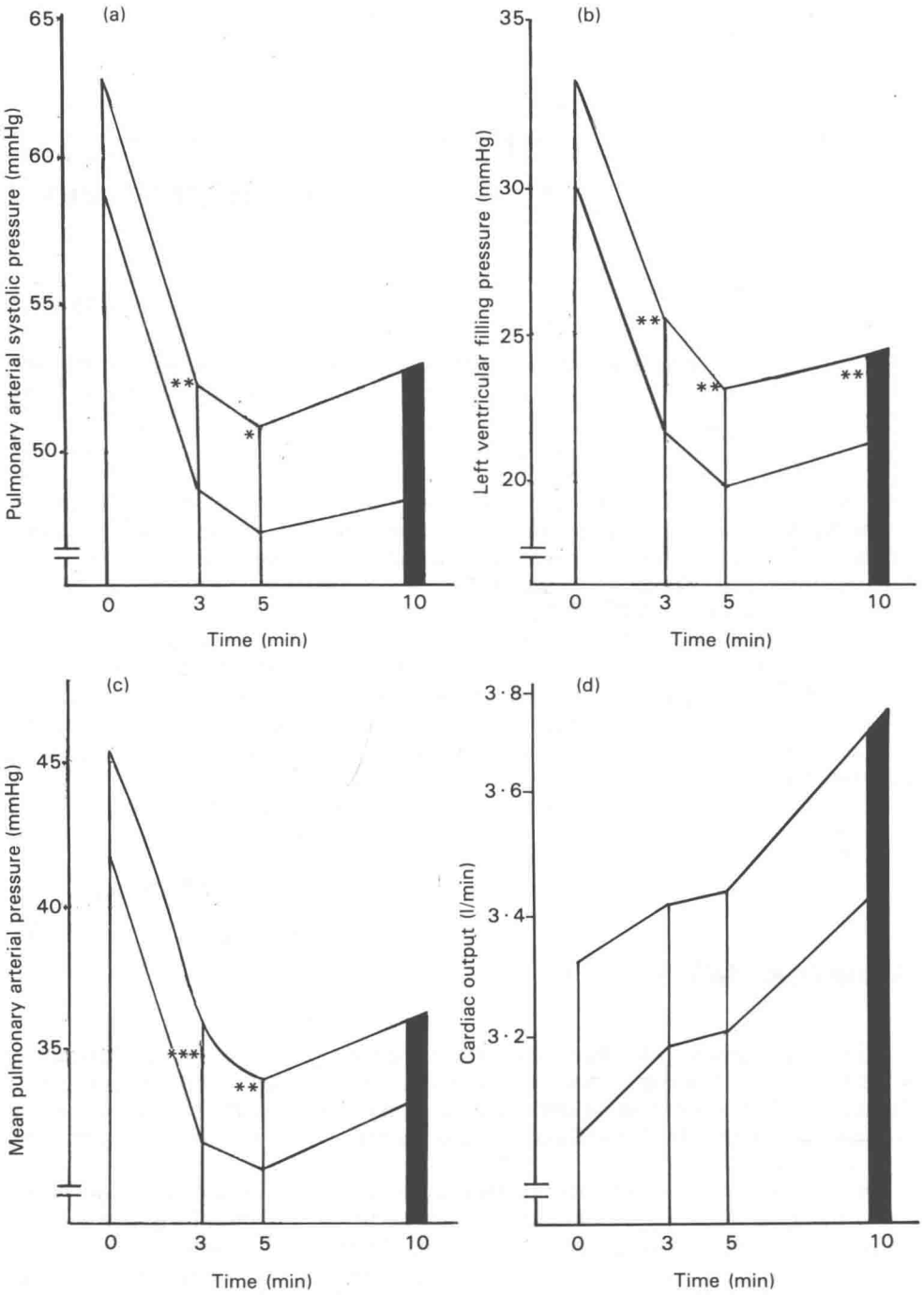

*Figure 1. Nitroglycerin given sublingually (1·6 mg) in seven patients with acute left heart failure and pulmonary oedema. Within 3–5 min (a) pulmonary arterial systolic pressure, (b) left ventricular filling pressure and (c) mean pulmonary arterial pressure decreased while (d) cardiac output increased significantly. *$p < 0·05$; **$p < 0·02–0·01$; ***$p < 0·005–0·001$.*

dopamine or dobutamine might be necessary in addition in markedly depressed cardiac output and low blood pressure. Diuretics should be given very cautiously, if at all.

Chronic heart failure

In chronic congestive heart failure the primary goal of treatment is improvement in the quality of life, with restoration of the patient's function and capacity to as near normal as possible. Before drug therapy is used simple adjustments in lifestyle should be considered. Such measures include:

weight reduction
salt reduction
fluid reduction and
a programme of regular dynamic exercise to avoid deconditioning.

Prolonged isometric exercise and drugs which may reduce cardiac contractility should be avoided.

In West Germany the preferred drug therapy still consists of digitalis and diuretics. The use of digitalis, however, will eventually decrease. If the patient is still symptomatic despite digitalis and diuretics, vasodilators are added to this classic concept. Positive inotropic agents, other than digitalis, are seldom used in chronic treatment.

Diuretics not only relieve the symptoms of congestion which result from excess sodium retention: they also reduce ventricular volume and wall stress (3). Since cardiac performance is dependent on filling pressure, over-aggressive use of diuretics may reduce cardiac output and further impair functional capacity. In patients with enlarged hearts and milder forms of heart failure, mild diuretics administered intermittently may be all that is necessary. In more severe degrees of heart failure, when the use of loop diuretics is necessary, dosage adjustment should be made weekly on the basis of body weight and physical examination. Maintenance of normal serum potassium is mandatory and can be achieved by the addition of potassium-retaining diuretics such as triamterene, amiloride or spironolactone.

There is probably no absolute contra-indication to the administration of vasodilator drugs in the patient with heart failure other than the presence of severe hypotension. Even when systolic pressure is less than 85 or 90 mmHg, cautious administration of vasodilator drugs may be appropriate.

Therapy may of course be initiated with any of the available vasodilators. If symptoms are predominantly related to shortness of breath and if venous pressure is elevated, a drug which mainly reduces preload, such as nitroglycerin or isosorbide dinitrate, should be considered. If, on the other hand, the patient complains predominantly of fatigue on exertion and if venous pressure is normal, an agent that effectively reduces impedance and increases cardiac output, such as hydralazine, should be administered.

Our findings with patients in classes II and III encouraged us in the early use of vasodilators. In a cross-over double-blind randomized trial over six months, the afterload-reducing vasodilator propyldazin—a drug very similar to hydralazine—significantly increased the patients' physical capacity by about 25% compared to placebo (4) (Fig. 2).

In patients with congestive heart failure class III and IV, digitalis, a drug with modest efficacy, is still employed, although its benefit-to-risk ratio in normal sinus rhythm is controversial. In these patients with end-stage disease the chronic efficacy of a vasodilator is still controversial.

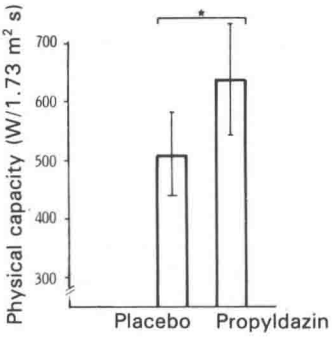

*Figure 2. In a double-blind cross-over study over six months, propyldazin significantly increased physical capacity by about 25% in patients with congestive heart failure NYHA class II and III. *p<0·05; n = 14; mean ± SEM.*

Some investigators have demonstrated the persistence of a salutary response to prazosin, nitrates and hydralazine (5–7), whereas others have reported tolerance (8–10). Most haemodynamic studies have not been placebo-controlled. We therefore compared, in a number of similar studies over 3 to 12 months, dihydralazine (200 mg/day), prazosin (20 mg/day) and captopril (50 mg/day) with placebo in patients with severe congestive heart failure (11). All patients had repetitive haemodynamic evaluations. Significant differences between placebo and medication in these patients with end-stage heart disease could be observed only with captopril, i.e.

vascular resistance at rest
pulmonary artery diastolic pressure at rest
cardiac index
stroke volume
diastolic pressure during exercise
cardiac index during exercise and
stroke volume during exercise.

Pulmonary artery diastolic pressure, for instance, decreased about 8% with prazosin, 15% with dihydralazine and 42% with captopril, and captopril alone was significant in comparison with placebo (Fig. 3). Cardiac index did not change significantly with dihydralazine and prazosin, but we saw a marked increase, greater than 40%, after six months with captopril, which was again significant in comparison to placebo (Fig. 4).

Tolerance and counter-regulatory effects may account for the unsatisfactory results with prazosin and dihydralazine. It is noteworthy that a large number of patients also improved with placebo, probably due to strict adjustments in lifestyle (Fig. 5).

Captopril counteracts the resultant adverse effects of congestive heart failure in a more rational way than other vasodilators. This might be the reason for its sustained beneficial effects even in end-stage disease of congestive heart failure.

Because of the modest efficacy of digitalis and its possible risks, considerable effort has been dedicated to the development of new orally effective inotropic drugs. These agents form at least two distinct classes:

drugs which work through beta-adrenergic receptors, e.g. pirbuterol, prenalterol and salbutamol, and
drugs which are non-adrenergic.

The efficacy of beta-agonists may wane with time because of a down-regulation of the beta-receptors during chronic stimulation.

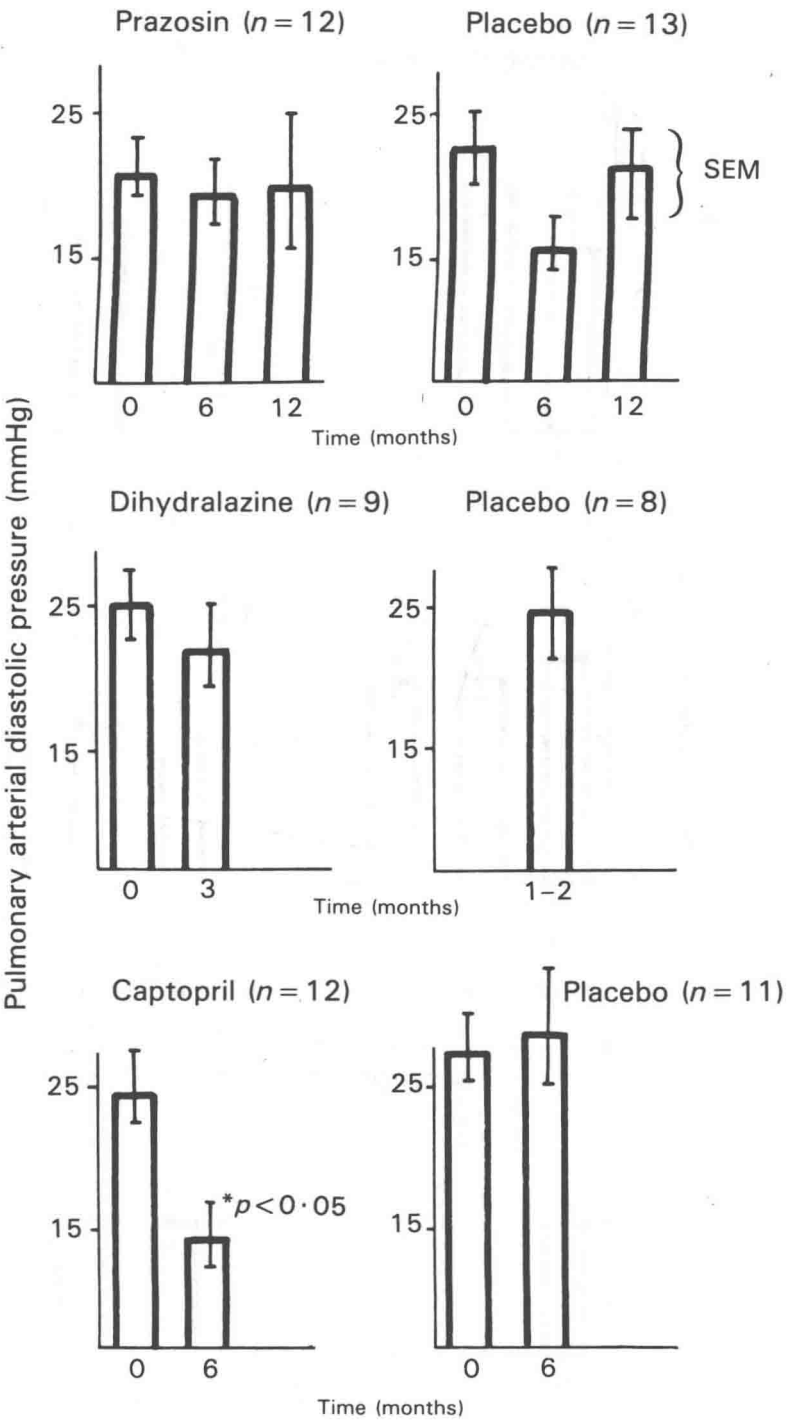

Figure 3. Placebo-controlled trials in severe congestive heart failure over 3–12 months. Pulmonary arterial diastolic pressure significantly decreased only with captopril.

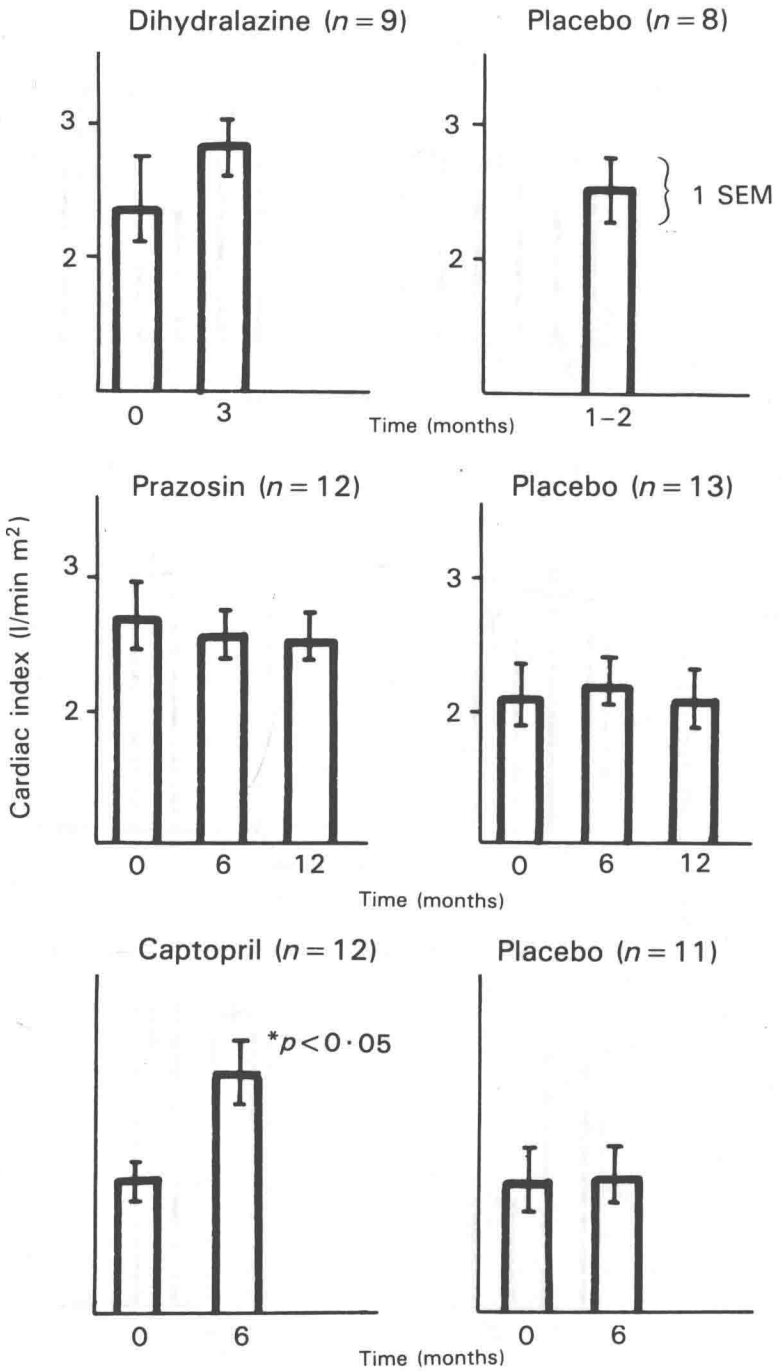

Figure 4. Placebo-controlled trials in severe congestive heart failure over 3–12 months. Cardiac index significantly increased only with captopril.

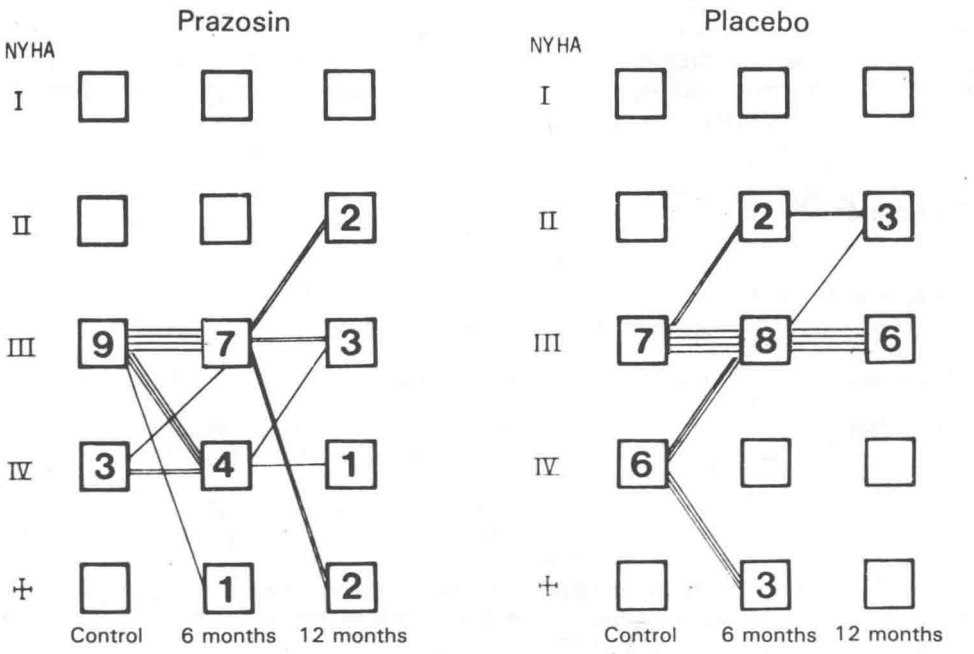

Figure 5. Placebo-controlled double-blind randomized trial with prazosin (20 mg/day) in severe congestive heart failure. An impressive improvement of symptoms can also be achieved with placebo (NS).

Some of the non-adrenergic drugs have an inhibiting effect on phosphodiesterase and may lead to increased cardiac levels of cyclic AMP. Others may increase the permeability of the myocardial cell to calcium, or may actually increase the sensitivity of the contractile apparatus to calcium. Agents currently being studied include amrinone, ARL 115, Forskolin, WIN 47203 and so on. Some of these new drugs have rather potent acute effects on increasing contractility but as yet proof of chronic efficacy has not been established.

Table 1 summarizes our therapeutic procedures in congestive heart failure. Patients with end-stage heart disease often require combinations of vasodilators, diuretics and digitalis, and intermittently some of these patients require administration of inotropic

Table 1

Pharmacological treatment of chronic congestive heart failure

Class I and II	Adjustment of life style (weight, salt, fluid, exercise)
Class II	Diuretics (intermittently) and/or vasodilators
Class III and IV	Diuretics ACE inhibitors Digitalis (?)
Class IV (end-stage)	Intermittently inotropic agents

drugs. In less severe degrees of heart failure, when functional capacity is only modestly impaired, it remains unclear if aggressive therapy with vasodilators and positive inotropic agents will alter the natural history of the disease. Until this information is available we must continue with our goal of improving symptomatology by the rational use of all our pharmacological tools.

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Overview of heart failure therapy — a British view

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The definition of heart failure

It is easy to recognize pulmonary oedema, and although heart disease is by no means the only cause of this it is usually easy to make a confident clinical diagnosis when heart failure is severe. When failure is moderate it can usually be recognized from the patient's description of breathlessness, orthopnoea, ankle swelling and sometimes abdominal discomfort due to hepatic distention, and from the physical signs of a raised jugular venous pressure, oedema, an enlarged liver, and moist sounds at the lung bases. In such patients there will usually be abnormal signs in the heart such as a displaced apex beat, and various murmurs or gallop sounds. The diagnosis becomes much more difficult when only mild heart failure is present for the patient may complain of breathlessness and fatigue, and there may be few abnormal signs and only circumstantial evidence that the symptoms are due to heart disease. The presence of other conditions, and particularly those associated with a high cardiac output (anaemia, thyrotoxicosis, pregnancy etc.) can make the diagnosis of heart failure very difficult; the most common cause of breathlessness and fatigue is a lack of physical fitness. Thus from a clinical standpoint 'heart failure' describes a spectrum of symptoms and signs extending from normality to a state that is life-threatening.

A physiological definition of heart failure is perhaps more precise, at least in theory. It would be acceptable to define heart failure as the state in which an increase in muscle fibre length (or filling pressure) no longer increases cardiac performance—that is, heart failure exists when Starling's curve becomes flat. Crudely this state can be inferred to exist when the heart's filling pressure is high, so it is possible to define heart failure—and certainly to assess its severity—by measuring the pulmonary capillary wedge pressure. Unfortunately such a definition, and such measurements, take no account of the state of contractility of the myocardium, and little useful information can be obtained from measurements of the cardiac output.

A loss of contractility would be a more acceptable definition of heart failure, and would take into account the metabolic state of the myocardial cells and the way cross-bridges form between actin and myosin. Unfortunately there is no simple way of

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