Focus on diastolic dysfunction: a new approach to heart failure therapy

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1 Although heart failure is commonly associated with depressed systolic function, there is increasing evidence that impaired diastolic performance is also universally present and might be a key determinant of symptoms, physical capacity and even survival in some subsets of patients.

2 Reduced diastolic distensibility increases cardiac filling pressure not only at rest, but even more during exercise when diastolic filling time is reduced. The increases in filling pressure and diastolic wall stress lead to pulmonary congestion and subendocardial ischaemia; it also triggers myocardial hypertrophy and a detrimental remodelling of the ventricular cavity. Perhaps even more importantly, impaired ventricular distensibility limits the use of the Frank-Starling mechanism, impairing systolic pump function and cardiac output adaptation during exercise. Therapies able to improve the distensibility of the ventricle are, therefore, desirable in heart failure.

3 Nitrates, angiotensin converting enzyme (ACE) inhibitors and diuretics may indirectly increase left ventricular chamber compliance by their effects on the right side of the heart. Cardiac glycosides do not improve myocardial relaxation and may even cause diastolic contracture at toxic doses. The new β_1 -adrenoceptor partial agonist, xamoterol, on the other hand, consistently lowers left ventricular filling pressure at rest and during exercise, and produces an increase in left ventricular dynamic compliance through the direct lusitropic effect of β_1 -adrenoceptor stimulation. These beneficial effects are maintained during prolonged therapy and also appear sufficient to slow the remodelling of the ventricular cavity. The improvement in symptoms and in exercise tolerance observed during xamoterol (Corwin, Carwin, Corwil, Xamtol, ICI 118,587) therapy might, therefore, be related to the improvement in left ventricular diastolic distensibility induced by this drug.

Keywords heart failure xamoterol β_1 -adrenoceptor partial agonist

Introduction

Heart failure therapy has generally been directed toward the improvement of the ejection performance of the ventricle by the use of positive inotropic drugs or by afterload reduction, as well as toward the correction of the consequences of impaired renal function (diuretics, angiotensin converting enzyme [ACE] inhibitors). The studies of Dougherty *et al.* (1984), Soufer *et al.* (1985), and more recently of Marantz *et al.* (1988), have

shown, however, that in approximately 40% of the patients with a definite diagnosis of congestive heart failure, left ventricular systolic function was well preserved. Further, in more than 20% of the patients with depressed systolic function, no evidence of congestive heart failure was present (Marantz *et al.*, 1988).

The discrepancy between the indices of systolic pump function and the presence or absence of

congestive heart failure can be explained by the other major component of cardiac function, namely, diastolic function (Grossman & Barry, 1980). Accordingly, optimal management of heart failure should also consider therapeutic interventions that specifically improve this phase of the cardiac cycle, i.e. lusitropic agents (Katz, 1988).

The purposes of this review are to analyse the mechanisms of impaired diastolic function, to examine the relationship between impaired diastolic function and heart failure, and to characterise the lusitropic effects of various therapeutic regimens currently used to treat heart failure.

Determinants of left ventricular diastolic function

The walls of the cardiac chambers, like all living biological material, exhibit complex physical behaviour such as plasticity, hysteresis and viscosity. They are made of highly heterogeneous materials (membranes, sarcomeres, nuclei, coronary vessels, valves etc.), and the characterisation of the physical properties of the myocardium from clinically available data, such as pressure and volume, is a complex, if not impossible task. Fortunately, for all practical purposes, the cardiologist needs to concern himself only with the main factors that determine the global distensibility of the ventricle (Table 1).

Passive physical properties of the ventricular walls

The passive distensibility of the ventricular walls may be altered by the destruction of the myocytes and their replacement by fibrotic tissue. This situation is frequent in all forms of ischaemic cardiomyopathy and also in idiopathic cardiomyopathy (Grossman & Barry, 1980). Another frequent cause of reduction in passive diastolic distensibility of the wall is myocardial hypertrophy, particularly the concentric form of hypertrophy, seen in pressure overload (Spotnitz & Sonnenblick, 1976; Grossman & Barry, 1980) in which new sarcomeres are added in parallel. In a few instances, the distensibility of the wall may be diminished by infiltration with various substances (amyloidosis, hypothyroidism).

The active relaxation process

Another factor that affects diastolic distensibility of the myocardium is the active relaxation process. Active tension is generated during systole when myoplasmic free calcium concentration is increased, thereby allowing the binding of calcium ions to troponin and the formation of actin-myosin cross-bridges. During diastole, several active, energy-dependent processes are necessary to reduce myoplasmic calcium concentration and to remove calcium from its troponin binding sites. Thus, during diastole, the calcium which

Table 1 Factors influencing the left ventricular diastolic pressure-volume relationship

Main factors

- * Passive physical properties of ventricular walls
 - Thickness of ventricular wall
 - Composition of ventricular wall (e.g. muscle, fibrosis, amyloid, etc.)
 - Viscous properties
 - Elastic recoil
- * Active relaxation process

<ul style="list-style-type: none"> – Sympathetic stimulation – Heart rate – Loading conditions – Metabolism 	and	<ul style="list-style-type: none"> rate of Ca^{++} repumping capacity of Ca^{++} sequestration total Ca^{++} load sensitivity of troponin to Ca^{++}
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- * Pericardial properties and mechanical interference between cardiac chambers

Accessory factors

- * Pleural pressures
- * Coronary perfusion pressure
- * Aortic root pressure
- * Mitral valve elasticity
- * Inertia, temperature, oedema
- * Activation sequence

entered through the slow channels during the plateau of the action potential, is extruded through a calcium pump and the sodium-calcium exchange mechanism. Simultaneously, calcium released from intracellular stores is actively re-pumped against a concentration gradient (Opie *et al.*, 1984).

These delicate biochemical processes are under the control of both neurohumoral and intracellular feedback. When the active relaxation process is impaired (Paulus *et al.*, 1982, 1985), troponin-calcium interactions and cross-bridge cycling persist during part or the whole of the diastolic period. In this case, left ventricular pressure decay is slowed and myocardial distensibility reduced. Among the multiple regulatory mechanisms of myocardial relaxation, three are particularly important from the practical viewpoint: the role of the β_1 -adrenoceptors and of the sympathetic nervous system, the energy supply essential to the active pumping process, and the effect of heart rate.

Regulation of myocardial relaxation by the sympathetic nervous system In addition to increasing the force and speed of contraction, the stimulation of the β_1 -adrenoceptors located on the myocytes by noradrenaline or any other full agonist, shortens the action potential and the mechanical systole, and accelerates the speed of relaxation. The relaxing effects of catecholamines are mediated through the intracellular messenger, cyclic adenosine monophosphate (cAMP), which triggers a cascade of enzyme phosphorylations in the sarcoplasmic reticulum (increased rate of calcium pumping), in the contractile apparatus (decreased sensitivity of troponin to calcium), and in receptor-operated channels of the sarcolemma (shortening of the action potential). These relaxing effects are enhanced or prolonged by agents that prevent the destruction of cAMP by the enzyme phosphodiesterase (Opie, 1984).

By enhancing both systolic and diastolic function, sympathetic stimulation plays a key role in the physiological cardiac adaptation to exercise and is a compensatory mechanism in myocardial dysfunction (myocardial infarction, cardiomyopathies etc.). Conversely, β_1 -adrenoceptor blockade or the myocardial denervation that may occur in areas adjacent to transmural myocardial necrosis (Barber *et al.*, 1983), will impair relaxation. It is also well known that, in the presence of a prolonged or excessive stimulation of the β_1 -adrenoceptor by catecholamines, down-regulation of these receptors occurs (Bristow *et al.*, 1986). Although no quantitative evaluation of relaxation has been provided in these studies, it is likely that β_1 -adrenoceptor

down-regulation results in depression of myocardial relaxation rate. Finally, the slower relaxation seen in the ageing heart might be caused by an age-related uncoupling of the β_1 -adrenoceptor.

Energy supply and active relaxation The movement of ions against concentration gradients through the sarcolemma, the sarcoplasmic reticulum or the mitochondrial membrane, is an energy-consuming process. Factors that prevent adequate high-energy phosphate synthesis therefore may depress relaxation, although other factors, such as intracellular pH, may sometimes interfere. Alterations in energy supply responsible for changes in intracellular calcium homeostasis and for impairments in relaxation are found in ischaemic heart disease. The most severe reductions in myocardial distensibility are observed immediately after the classical form of 'high-demand' angina pectoris (Mann *et al.*, 1979), but some degree of relaxation impairment is present in most patients with coronary artery disease, even in the absence of clinical signs of ischaemia (Rousseau *et al.*, 1980; Bonow *et al.*, 1981). It is now well established that myocardial ischaemia is not an 'all or none phenomenon' and that silent ischaemia with the use of anaerobic metabolism (Wisneski *et al.*, 1985) is common in patients with coronary stenoses.

Thus, in ischaemic heart disease, regional metabolism and energy production may be permanently abnormal because of chronic hypoperfusion, or because of incomplete recovery from previous ischaemic episodes ('hibernating myocardium') (Braunwald & Rutherford, 1986). Relaxation is impaired in these zones because of calcium overload in the cell, a decreased rate of calcium repumping by the sarcoplasmic reticulum or, even worse, by a reduced capacity of calcium sequestration by intracellular structures (Paulus *et al.*, 1982). Diastolic stiffness is increased, and if the area involved is sufficiently large, the stiffness of the whole ventricle is increased. This hypothesis is supported by the correlation observed between the amount of hypoperfused myocardium estimated by thallium scintigraphy, the alterations in diastolic function present at rest (De Kock *et al.*, 1986) or after pacing-induced angina (McKay *et al.*, 1984), and some metabolic markers of ischaemia such as lactate or alanine production (De Kock *et al.*, 1986).

Myocardial ischaemia might also play a role in the relaxation abnormalities of hypertensive or idiopathic hypertrophic cardiomyopathy (Bonow *et al.*, 1983), dilated cardiomyopathy (Grossman *et al.*, 1979), aortic stenosis (Peterson *et al.*,

1978) or chronic volume overload hypertrophy. Even in the absence of coronary stenosis, coronary vascular reserve is reduced in these diseases. Myocardial ischaemia may be present, particularly in the subendocardium, because of the increased diastolic wall stress and because of a mismatch between myocyte hypertrophy and microvasculature growth (Marcus *et al.*, 1987). Myocardial ischaemia related to vasospasm or thrombosis of the microvasculature has also been reported in some experimental models of heart failure.

Effects of heart rate on myocardial relaxation

An increase in frequency of stimulation, for example by atrial pacing, shortens the duration of the action potential and accelerates myocardial relaxation by mechanisms which are still poorly understood. During exercise, relaxation rate is normally improved by both β_1 -adrenoceptor stimulation and by the tachycardia. The change in relaxation when the heart rate rises is indispensable, since systole occupies a greater percentage of the cardiac cycle as heart rate increases.

In the normal heart, below 170 beats min^{-1} , the diastolic pressure-volume relationship is usually unaffected by this reduction in diastolic interval. Above 170 beats min^{-1} , completion of relaxation may no longer occur, causing an elevated ventricular pressure for any given volume (Weber *et al.*, 1986). When myocardial relaxation is already impaired at rest, this will occur at lower heart rates, and will cause an inappropriate rise in the left ventricular filling pressure during exercise, and incomplete filling of the ventricle.

Other factors that influence myocardial relaxation

Relaxation of the normal myocardium is load-dependent (Brutsaert *et al.*, 1980), an increase in systolic pressure tending to slow the relaxation rate and *vice versa*. There is some evidence that this load-dependency of relaxation is reduced in various cardiomyopathies. However, in the failing heart, the effects of afterload reduction on relaxation, such as with vasodilator therapy, may be difficult to separate from the effects of vasodilatation on myocardial ischaemia, recoil forces or pericardial restraints. The sequence of activation also has an influence, and this must be kept in mind in the presence of bundle branch block, a pacemaker or ventricular arrhythmias.

Role of the pericardium

The pericardium is the third clinically important factor that affects diastolic distensibility of the cardiac cavities. The syndromes of cardiac

tamponade or constrictive pericarditis are too well known to be discussed here. However, even in the absence of pericardial disease or fluid effusion, the pericardium, being a very stiff sac, may prevent the dilatation of a cardiac chamber and increase the mechanical interference between the ventricles and the atria, resulting in a typical 'upward shift' of the diastolic left ventricular pressure-volume relationship (Ross, 1979). During long-standing cardiac disease, the pericardium progressively enlarges and its restrictive role decreases but it never disappears completely.

Relationship between diastolic dysfunction and heart failure

As pointed out by Guyton *et al.* (1973) and Braunwald *et al.* (1976), 'There are only three basic physiological consequences of the different types and stages of heart failure: (1) decreased cardiac output with diminished perfusion of peripheral vascular beds, (2) elevated left atrial pressure with resultant pulmonary congestion and (3) elevated right atrial pressure with resultant systemic congestion. These changes may occur simultaneously, in any sequence, or in some instances only one or two of these may be evident . . . '.

According to these haemodynamic definitions, diastolic dysfunction causes heart failure by three mechanisms:

1. By increasing cardiac filling pressure at rest;
2. By preventing cardiac output to rise adequately during exertion;
3. By reducing cardiac output at rest.

The following paragraphs will examine in detail these mechanisms and the corresponding clinical situations.

Diastolic dysfunction causes heart failure as it increases the mean atrial pressure

The various forms of diastolic dysfunction already discussed have a common pathophysiological consequence: they all reduce left ventricular distensibility to some extent. During part or the whole of diastole, filling pressure has to be increased if the same ventricular volume is to be achieved. Accordingly, to preserve cardiac output in the presence of a reduction of the dynamic left ventricular compliance, pressure must increase in the left atrium and in the left ventricle.

Diastolic dysfunction and impaired exercise tolerance

Reduced exercise tolerance is the most common symptom of heart failure but the correlation

between objective measurements of physical capacity (such as maximal oxygen uptake) and the indices of systolic function is poor. Several mechanisms have been proposed to explain this lack of correlation, including metabolic, peripheral or respiratory factors.

Recently, changes in ventricular relaxation and filling on exercise have attracted interest, and there is now evidence accumulating to show that impaired diastolic filling might be one of the major determinants of the poor adaptation to exercise in many heart failure patients (Oldershaw *et al.*, 1983; Heo *et al.*, 1986; Soufer *et al.*, 1986; Balfour *et al.*, 1987; Higginbotham *et al.*, 1987; Pouleur *et al.*, 1987; Pouleur & Rousseau, 1988). Except at low exercise levels, the rising cardiac output in normal, untrained individuals is brought about largely by an increase in heart rate and in myocardial contractility. Though ejection time shortens, the positive inotropic effects of increased sympathetic activity and the reduction in peripheral resistance allow ejection rate to rise and end-systolic volume to decrease, so that stroke volume is maintained or slightly increased. Simultaneously, left ventricular filling time shortens, falling to just above 100 ms beat^{-1} at a rate of 150 min^{-1} (Oldershaw *et al.*, 1983). The maintenance of adequate ventricular filling under these conditions implies an ability to achieve mean filling rates during diastole considerably in excess of the rates during ejection (Oldershaw *et al.*, 1983). This situation is particularly critical in the ageing heart and in the heart with a reduced contractile reserve. These, in contrast to normal hearts, rely largely on the Frank-Starling mechanism to maintain their stroke volume during exercise (Higginbotham *et al.*, 1987).

Under these conditions, factors that influence the size of the ventricle in diastole control the maximal cardiac output. If the dynamic compliance of the ventricle is already abnormal at rest or adapts poorly during exercise, filling rates will be too low to achieve adequate filling and cardiac output will be prevented from rising normally despite large increases in left atrial and pulmonary capillary pressures. Even if the patient stops exercising because of poor skeletal muscle perfusion and lactacidaemia instead of dyspnoea, the primary determinant is still the diastolic function. Finally, with severe restriction of diastolic distensibility (constrictive pericarditis, restrictive cardiomyopathy), ventricular filling may even be impaired and cardiac output reduced at rest.

In summary, although many uncertainties remain regarding the underlying mechanisms, striking abnormalities of left ventricular filling

and exercise tolerance can be demonstrated at rest and on exercise in patients with left ventricular hypertrophy, ischaemic heart failure or other cardiomyopathies. In many patients, these abnormalities in diastolic function predict exercise tolerance better than indices of systolic function, suggesting that diastolic dynamic compliance and the ability to achieve rapid ventricular filling rate are important determinants of functional capacity. Finally, it is most important to realise that the measurements of left ventricular filling pressure during exercise are not themselves sufficient for proper assessment of the importance of diastolic function on exercise capacity. It is the actual ventricular volume at any given pressure that really matters.

Therapeutic implications

Practical conclusions may be drawn from the above data. Heart failure primarily caused by diastolic dysfunction exists and ranges in severity from the mild to the severe congestive form. In contrast, heart failure caused by pure systolic dysfunction probably does not exist: there is always some degree of diastolic dysfunction that contributes to the patient's symptomatology. This concept of diastolic heart failure and 'mixed' heart failure has therapeutic implications. In a randomised trial of digoxin vs placebo, only 14 of 25 patients improved clinically with digoxin (Lee *et al.*, 1982). Non-responders were characterised by less severe symptoms, smaller left ventricular dimensions and a higher mean ejection fraction. Thus, as expected, patients with relatively less systolic impairment do not benefit from pure inotropic support. Similarly, drugs like diuretics which reduce preload or afterload without simultaneously improving diastolic function might be of limited benefit. Thus, even when contractility is severely impaired, the cardiologist should consider interventions aimed at improving diastolic function, as well as inotropic support of the failing myocardium.

Katz coined the term 'lusitropic' to describe the effects of an agent on myocardial relaxation (Katz, 1988). As the interactions between inotropic and lusitropic effects may be variable, it is worth briefly reviewing the properties of the main substances used to treat heart failure.

β_1 -adrenoceptor agonists, partial agonists and antagonists

As discussed previously, β_1 -adrenoceptor full agonists like noradrenaline have positive inotropic and lusitropic effects. Moreover, catechol-

amines have the unique property among the positive inotropes of accelerating myocardial relaxation to a far greater degree than improving the velocity or the amplitude of contraction (Meerson, 1983).

Despite their unique pharmacological profile, full β_1 -adrenoceptor agonists are of limited value in treating heart failure. In fact, it could be postulated that high concentrations of catecholamines are detrimental in patients with severe cardiac failure by aggravating myocardial ischaemia, inducing down-regulation of the receptors and provoking arrhythmias related to ischaemia, cAMP or hypokalaemia. There is, therefore, a rationale for the use of β_1 -adrenoceptor antagonists in the management of cardiac failure, but, as expected, they are not well tolerated in the majority of heart failure patients because they reduce cardiac output, aggravate pulmonary congestion and induce bradycardia.

A more logical approach would be to treat heart failure with an agent combining the beneficial effects of the stimulants and blockers but free of their respective adverse effects. This agent should retain only some of the pharmaco-

logical properties of each, i.e. it ought to be a β_1 -adrenoceptor partial agonist (Ariens, 1979).

The amount of partial agonist activity of a compound used to treat heart failure is obviously of paramount importance. There is always some degree of sympathetic drive at rest and this resting sympathetic nervous system activity increases as the severity of heart failure progresses. The administration of a β_1 -adrenoceptor partial agonist with low partial agonist activity might depress relaxation. We therefore examined, in two groups of patients with coronary artery disease matched for cardiac function, the effects of the intravenous administration of two β -adrenoceptor partial agonists with different degrees of agonist activity (pindolol and xamoterol). As can be seen in Tables 2 and 3, the left ventricular function of these patients was nearly normal at rest, which suggests that resting sympathetic drive should have been normal. Despite this low sympathetic tone, pindolol acted as an antagonist as far as myocardial relaxation and diastolic function were concerned. Pindolol injection significantly increased left ventricular end-diastolic pressure and mean diastolic wall

Table 2 Effects of intravenous xamoterol administration on left ventricular systolic and diastolic function ($n = 9$). Data presented as means $\pm$ s.d.

	Before	After xamoterol (0.1 mg kg ⁻¹)	P value
Heart rate (beats min ⁻¹)	82 $\pm$ 12	88 $\pm$ 12	< 0.05
LVEDP (mm Hg)	12 $\pm$ 9	11 $\pm$ 10	NS
T ₁ (ms)	44 $\pm$ 8	36 $\pm$ 4	< 0.05
Mean diastolic stress (kdyn cm ⁻²)	32 $\pm$ 24	19 $\pm$ 14	< 0.05
EDVI (ml m ⁻²)	107 $\pm$ 14	103 $\pm$ 17	NS
ESVI (ml m ⁻²)	41 $\pm$ 12	36 $\pm$ 13	< 0.05
Ejection fraction (%)	62 $\pm$ 7	66 $\pm$ 7	< 0.05
Peak (+) dP/dt (mm Hg s ⁻¹)	1808 $\pm$ 365	2428 $\pm$ 641	< 0.05

LVEDP = left ventricular end-diastolic pressure; T₁ = time constant of early left ventricular isovolumic pressure fall; EDVI, ESVI = end-diastolic and end-systolic volume indices.

Table 3 Effects of intravenous pindolol administration on left ventricular systolic and diastolic function ($n = 9$). Data presented as means $\pm$ s.d.

	Before	After pindolol (1.4 mg)	P value
Heart rate (beats min ⁻¹)	78 $\pm$ 11	80 $\pm$ 10	NS
LVEDP (mm Hg)	13 $\pm$ 6	24 $\pm$ 10	< 0.05
T ₁ (ms)	49 $\pm$ 10	59 $\pm$ 16	< 0.005
Mean diastolic stress (kdyn cm ⁻²)	29 $\pm$ 11	75 $\pm$ 47	< 0.05
EDVI (ml m ⁻²)	122 $\pm$ 24	126 $\pm$ 23	NS
ESVI (ml m ⁻²)	49 $\pm$ 20	53 $\pm$ 26	NS
Ejection fraction (%)	61 $\pm$ 10	59 $\pm$ 13	NS
Peak (+) dP/dt (mm Hg s ⁻¹)	1606 $\pm$ 258	1532 $\pm$ 211	NS

stress, and prolonged the index of relaxation, T_1 (Table 3). In contrast, xamoterol administration improved relaxation and lowered mean diastolic wall stress (Table 2). Thus, the low partial agonist activity of pindolol resulted in a negative lusitropic effect under these experimental conditions, whereas the relatively high partial agonist activity of xamoterol (43%) induced positive lusitropic and inotropic effects.

Intrigued by these lusitropic properties of xamoterol, our group has been interested since 1982 in treating patients with this agent in the

long term. Figures 1, 2, 3 and 4, from previously published data (Rousseau *et al.*, 1985; Pouleur *et al.*, 1986, 1988a, c) illustrate the effects of chronic xamoterol treatment on the time-course of left ventricular pressure in three groups of patients: mild heart failure (New York Heart Association [NYHA] functional Class II, mainly diastolic dysfunction), moderate heart failure (NYHA Class III, systolic dysfunction, reflected by an angiographic ejection fraction $< 35\%$, and diastolic dysfunction), and severe heart failure (NYHA Class III despite full therapy including

Figure 1 Average left ventricular pressure tracings (sampling rate 2 ms, data presented are mean $\pm$ 1 s.d. for each point) in a group of eight patients with mild ischaemic heart failure (NYHA Class II). Left panel (a) = baseline data; right panel (b) = data during chronic (3 months) therapy with xamoterol. Left ventricular filling pressure and duration of systole were significantly reduced with xamoterol.

Figure 2 Average tracings of the first derivative of left ventricular pressure curves from Figure 1 ($\pm$ 1 s.d. for each point). Xamoterol (right panel b) increased $dP/dt_{\max}$ despite the reduction in filling pressure and improved the maximal rate of relaxation ($dP/dt_{\min}$).

Figure 3 Average left ventricular pressure tracings (sampling rate 2 ms, data presented as mean $\pm$ 1 s.d. for each point) in a group of eight patients with moderate ischaemic heart failure (NYHA Class III, ejection fraction < 35%). Left panel (a) = baseline data; right panel (b) = data during chronic (3 months) therapy with xamoterol.

Left ventricular filling pressure and duration of systole were significantly reduced with xamoterol.

Figure 4 Average left ventricular pressure tracings (sampling rate 2 ms, data presented as means $\pm$ 1 s.d. for each point) in a group of four patients with severe ischaemic heart failure treated with ACE inhibitors (NYHA Class III, ejection fraction < 30%). Left panel (a) = baseline data; right panel (b) = data during chronic (3 months) therapy with xamoterol.

ACE inhibitors, systolic and diastolic dysfunction).

In all three groups, the effects of xamoterol on ejection fraction were small (Rousseau *et al.*, 1985; Pouleur *et al.*, 1986, 1988a, c). However, the lusitropic effect remained clear during prolonged therapy and was significantly different from the changes in placebo groups. Left ventricular filling pressure was consistently lower, systole was shortened and relaxation rate was

faster. Furthermore, these changes were accompanied by a downward shift of the diastolic pressure-volume relationship, suggesting improved ventricular distensibility (Pouleur *et al.*, 1988c). These changes were different from those seen in placebo-treated patients and might have contributed to the prevention of long-term remodelling of the ventricular cavity (Pouleur *et al.*, 1988c).

Other studies have shown that left ventricular

filling pressure remains lower during exercise on xamoterol. The effects of xamoterol on diastolic function might therefore be an important mechanism underlying the improved exercise tolerance observed in heart failure patients in large-scale trials (Franciosa *et al.*, 1987).

Phosphodiesterase inhibitors

Since cAMP is believed to control the activity of phospholamban, the regulatory protein for sarcoplasmic reticulum calcium uptake, an improvement in relaxation might be expected to follow inhibition of the enzyme phosphodiesterase (PDE), which normally destroys intracellular cAMP. As many of these agents also have powerful veno- and arteriodilator properties, they can also improve ventricular distensibility by other mechanisms (pericardial restraint, afterload). Monrad *et al.* (1984) have shown that short-term administration of milrinone, a PDE inhibitor from the bipyridine family, indeed significantly improved ventricular diastolic relaxation and filling in patients with congestive heart failure. Careful analysis of their results also convinced these authors that their findings were consistent with a direct effect of milrinone on relaxation at the level of the myocardial cell.

PDE inhibitors from the benzimidazole family, such as sulmazole or pimobendan, have slightly more complex effects on relaxation, since they also seem to increase the sensitivity of the myofibrils to calcium. After pimobendan administration (1 mg) to conscious dogs, there was no change in the time-constant of relaxation, and the diastolic pressure-segment length relationship tended to shift upward (Pouleur *et al.*, 1988b), but in the clinical setting where preload and afterload also change, improvements in diastolic distensibility have been reported.

Digoxin

Little is known about the effects of cardiac glycosides on left ventricular distensibility in patients with heart failure. As digoxin exerts its positive inotropic action mainly by increasing intracellular calcium load, no improvement in relaxation is expected, but rather a deterioration. Diastolic contracture is one of the early signs of cardiac glycoside toxicity in isolated preparations. In open-chested dogs (Pouleur *et al.*, 1984), we compared the effects of dobutamine, a β -adrenoceptor full agonist, digoxin and xamoterol, on inotropic state and relaxation. No improvement in relaxation was seen with digoxin. Although this deserves further confirmation in patients, the data available so far suggest that

cardiac glycosides lack direct positive lusitropic effects. This might explain the absence of clinical benefit in many patients in sinus rhythm.

Other positive inotropic agents

Among the drugs presently under clinical investigation, one, DPI 201-106, has the peculiar profile of positive inotropic action with negative lusitropic action. Delayed relaxation appears to be related to an increased calcium influx via voltage-dependent channels or to increased sensitivity of the contractile proteins to calcium.

Vasodilators

Vasodilators, particularly those with a balanced action on the venous and arterial beds, produce important downward shifts of the diastolic pressure-volume relationship on acute dosing, that appear to be related mainly to pericardial effects. Indeed, no changes are seen if the pericardium is removed (Ross, 1979). Moreover, such downward shifts are more easily produced in the presence of an enlarged heart with depressed systolic function (Ludbrook *et al.*, 1982). The decrease in afterload during vasodilator therapy may itself also improve the relaxation rate (Brutsaert *et al.*, 1980). Moreover, as impaired diastolic function is frequently related to active or chronic ischaemia, it is possible that an improvement in the balance between oxygen supply and demand occurs during long-term vasodilator therapy, and that this plays a role in the improvement in diastolic distensibility.

In this perspective, calcium antagonists must also be considered. Clinical improvements accompanied by objective signs of increased diastolic distensibility or improved filling dynamics have been reported after administration of calcium antagonists in patients with hypertrophic cardiomyopathy (Lorell *et al.*, 1982) or with ischaemic heart disease (Bonow *et al.*, 1982). Whether these improvements are related to improvements in intracellular calcium homeostasis caused by a direct effect of these agents on the myocytes, or to an indirect action related to their vasodilator properties remains to be determined. However, the negative inotropic effect of calcium antagonists may have adverse consequences in heart failure patients (Packer *et al.*, 1987).

Diuretics and ACE inhibitors

Diuretics are perhaps the most commonly used drugs in the treatment of congestive heart failure. By reducing total blood volume, they decrease

cardiac filling pressure. Their widespread use shows the importance of the left ventricular filling pressure in causing symptoms of heart failure. Generally, however, diuretics will not improve cardiac output at rest nor its rise during exercise. Furthermore, in mild to moderate heart failure, they activate the renin-angiotensin system and this may be detrimental. ACE inhibitors are now widely used to treat heart failure but their direct effects on left ventricular diastolic function have been little investigated. Preliminary data from our laboratory suggest that, acutely, their action mimics that of vasodilators such as the nitrates.

In conclusion, the selection of optimal treatment in a patient with heart failure is difficult. Treatment of the underlying cause is seldom avail-

able. In the absence of such treatment, most would agree that the best therapy corrects the haemodynamic abnormalities responsible for the clinical symptoms without overshooting, improves functional capacity and quality of life, has no side-effects, and hopefully improves long-term prognosis. The therapeutic approach should be tailored to the individual haemodynamic disorder. In designing treatment, the physician should always remember that the heart needs to be filled before it can empty!

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