The pharmacology of xamoterol: a basis for modulation of the autonomic control of the heart

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1 Xamoterol (Corwin, Carwin, Corwil, Xamtol, ICI 118,587) is a β -adrenoceptor partial agonist which is of benefit in the chronic treatment of heart failure (e.g. The German and Austrian Xamoterol Study Group, 1988). These results contrast with those obtained with other β -adrenoceptor drugs, prenalterol and pirbuterol which were unsuccessful on chronic dosing (Currie *et al.*, 1984; Glover *et al.*, 1985).

2 Unlike prenalterol and pirbuterol, xamoterol has no significant agonist activity at the β_2 -adrenoceptor and has shown no tachyphylaxis in animals or man.

3 The overall action of xamoterol is to modulate sympathetic control of the heart such that at rest and at low levels of exercise the heart receives inotropic support whilst during more severe exercise, heart rate is reduced. In patients with left ventricular dysfunction these effects lead to an improvement in the relation between filling pressure and cardiac output at all levels of activity such that a given cardiac output is achieved with a lower filling pressure. It is suggested that this alteration in the pattern of cardiac activity over a long period of time results in a beneficial adaptation of the myocardium and is a possible explanation of the observed clinical improvement.

Keywords xamoterol partial agonist β_1 -adrenoceptor

Introduction

Xamoterol is a β_1 -adrenoceptor partial agonist which has been shown to be of benefit in the chronic treatment of heart failure (Blackwood & Marlow, 1988; The German and Austrian Xamoterol Study Group, 1988). These results are in contrast to those obtained with other drugs which also have significant agonist activity at β_2 -adrenoceptors. For example, both prenalterol and pirbuterol, though of benefit in acute studies, were unsuccessful on chronic dosing (Currie *et al.*, 1984; Glover *et al.*, 1985). The above differences in outcome, after chronic treatment for heart failure, are probably related to the different pharmacological profiles of the drugs.

The aim of this paper is to review those aspects of the cardiovascular pharmacology of xamoterol which are thought to be relevant to the clinical mode of action.

The approach taken to the definition and

measurement of agonism in this review is that taken by Ariens *et al.* (1964). The concentration of an agonist [A] is related to the effect E:

$$E/E_m = \frac{\alpha[A]}{K_A + [A]}$$

where E_m is the maximum possible effect from the tissue, α is the intrinsic activity of the drug A, and K_A is the dose required to give a response equal to $\alpha/2$, i.e. the ED_{50} . In this simple model, a partial agonist is defined as having a value of α greater than 0 and less than 1. Difficulties occur when precise physical meanings are given to these two parameters. For example, K could be equated with the dissociation constant of the drug receptor interaction, and should therefore have a value which is independent of the method of measurement. Even with a simple partial agonist like xamoterol, different values of K are obtained. As a convention, throughout this

paper values of K equated with the ED_{50} are called K_A and those from displacement of dose response curves K_B . α also is dependent upon species, tissue, and experimental conditions. A more general operational model, which includes the above as a special case, was proposed by Black & Leff (1983). Their admirable synthesis of previous models of drug receptor interaction analysed agonism in terms of parameters which are either tissue- or drug-dependent. Such an approach is necessary when the agonist activity of several drugs measured upon a variety of tissues, is being compared and when insight into the mode of action at a receptor level is required. The purpose here is not to analyse the action of a partial agonist at the receptor level, but rather to describe the effects of xamoterol on the sympathetic control of the heart. For this purpose, the parameters of intrinsic activity (α) and ED_{50} (K_A) and apparent dissociation constant K_B are sufficient.

Xamoterol (Figure 1) was selected from a series of 1[(amidoethyl)amino]-3-(4-hydroxyphenoxy)-2-propanols in which examination of the structure/activity relationships of the amide group on the heart and circulation of the dog showed that great variation in cardioselectivity and degree of agonism could be obtained

Figure 1 Structure of xamoterol, ($\pm$)-*N*-(2-(2-hydroxy-3-(4-hydroxy phenoxy) propylamino) ethyl morphine-4-carboxamide). Molecular weight of base is 339.4 and of the fumarate salt 794.9. Laboratory code number ICI 118,587. Proprietary name 'Corwin'®.

(Barlow *et al.*, 1981). The cardiovascular pharmacology of xamoterol in the dog is summarised in Table 1. Xamoterol has no significant agonist activity at the β_2 -adrenoceptor despite having effects at the β_1 -adrenoceptor, and was selected from the above series of compounds as the compound having the greatest agonist activity at the β_1 -adrenoceptor whilst having no measurable agonist activity at the β_2 -adrenoceptor. In this respect xamoterol is unique among those β -adrenoceptor drugs which have been used in the chronic treatment of heart failure. Both prenalterol and pirbuterol have significant β_2 -adrenoceptor agonist activity.

Occupancy of β -adrenoceptors by xamoterol

Xamoterol binds to both β_1 - and β_2 -adrenoceptors. Experiments performed both *in vitro* and *in vivo* in a variety of tissues (Nuttall & Snow, 1982; Cook *et al.*, 1984; Malta *et al.*, 1985) have shown that xamoterol is selective for the β_1 -adrenoceptor, the ratio of affinities for the two receptors ranging from approximately 10 to 100 depending upon the experimental conditions. For example, in the dog, the apparent dissociation constant (K_B) for xamoterol depends upon the agonist (Table 1). If it is assumed that the K_B against isoprenaline as a vasodilator, is a measure of the true affinity at β_2 -adrenoceptors, and against noradrenaline in the heart of β_1 -adrenoceptors, then the selectivity ratio is $\approx 71/3.0 \approx 23/1$. However, against isoprenaline in the two sites, heart and blood vessels, the ratio is only 8/1. These results point to the existence of functional β_2 -adrenoceptors in the heart as suggested by Carlsson *et al.* (1972).

Results so far obtained in man (Jennings *et al.*, 1984; Lof Dahl & Svedmyr, 1984; McCaffrey *et al.*, 1986) do not indicate any agonist activity at

Table 1 Summary of pharmacological properties of xamoterol in the dog. K_A and α are from agonist dose-response curves on heart rate and hind limb perfusion pressure. K_B from displacement of agonist dose-response curves by xamoterol

β_1	
Partial agonist activity	43%
ED_{50} , K_A	$2.3 \mu\text{g kg}^{-1}$
K_B (against noradrenaline)	$3.0 \mu\text{g kg}^{-1}$
K_B (against isoprenaline)	$8.7 \mu\text{g kg}^{-1}$
β_2	
Partial agonist activity	0%
K_B (against isoprenaline)	$71 \mu\text{g kg}^{-1}$
Orally active	Bioavailability 5%
Hydrophilic	log P-0.3 (octanol/water)
Renal excretion	
Terminal blood half-life 14 h

Figure 2 The relation between the percentage change in left ventricular dP/dt at a developed pressure of 40 mm Hg and the plasma concentration of xamoterol (ng ml⁻¹) in patients with ischaemic heart disease. The mean control level of left ventricular dP/dt was 27.3 ± 1.3 mm Hg s⁻¹ and the mean maximum was 37.5 ± 2.3 mm Hg s⁻¹. A (56 ng ml⁻¹) and B (175 ng ml⁻¹) are the trough and peak blood levels in patients with heart failure on chronic dosing at 200 mg twice daily. A theoretical β₂-occupancy curve based upon selectivity data obtained in the dog is shown (Pouleur *et al.*, 1987).

the β₂-adrenoceptor. Furthermore, at the oral dose (200 mg twice daily) used in the clinical efficacy trials, there is probably minimal occupation of β₂-adrenoceptors. For example, on the assumption that the concentration effect curves (Figure 2) are a reasonable indication of occupancy of the β₁-adrenoceptor, then the occupancy curve for the β₂-adrenoceptor would be expected to be displaced to the left, as indicated, and even at peak blood concentration only 30% of the β₂-adrenoceptors would be occupied. Lofdahl & Svedmyr (1984) observed in patients with stable intrinsic asthma that xamoterol had little or no β₂-adrenoceptor antagonist effect at a dose of 0.1 mg kg⁻¹ i.v. However, when xamoterol is given intravenously at doses in the region of 0.2 mg kg⁻¹, then the blood concentration may be sufficient to cause significant occupation of the β₂-adrenoceptors. From these results it may be concluded that xamoterol is having its major clinical effects through occupation of the β₁-adrenoceptor.

Agonist activity on the rate and force of contraction of the heart (β₁-adrenoceptor) and resistance to blood flow (β₂-adrenoceptor)

Experiments carried out in an anaesthetised dog preparation, depleted of catecholamines and in which cardiovascular reflexes were prevented from occurring, showed that xamoterol produces about 43% of the maximum increase in heart rate brought about by a full agonist (isoprenaline) with a K_A of 3.2 μg kg⁻¹ i.v. (Table 1, Figure 3) (Nuttall & Snow, 1982). In this series of experi-

ments no effects were observed on hind limb perfusion pressure and it was concluded that even though xamoterol occupied β₂-adrenoceptors, it had no measurable agonist activity on the smooth muscle of arterial resistance vessels.

The agonism of xamoterol on the heart may be measured either as chronotropic or inotropic effects. In this areflexic dog preparation, the relations between effects on rate and force brought about by either xamoterol or isoprenaline are the same (Figure 4). Furthermore, the K_A for both the chronotropic and inotropic effects of xamoterol are similar. These results support the conclusion of Furnival *et al.* (1971) that the β-adrenoceptors mediating rate and force in the sinoatrial node and the muscle of the left ventricle are also similar.

Direct evidence relating inotropic effects on the left ventricle to the blood concentration of xamoterol in man was obtained by Pouleur *et al.* (1987) in patients suffering from ischaemic heart disease (Figure 2). The K_A for this inotropic effect (3.7 ± 0.8 μg kg⁻¹ i.v.) is similar to that found in dogs. The magnitude of the inotropic effect in terms of left ventricular dP/dt_{max}, about 1000 mm Hg s⁻¹, is smaller than the 2000–3000 mm Hg s⁻¹ observed in healthy beagle dogs.

Chronic dosing with xamoterol in patients at 200 mg twice daily produces average peak and trough blood concentrations of 56 ng ml⁻¹ and 175 ng ml⁻¹ respectively, and therefore stimulant effects at rest between 75% and 100% of the partial agonist activity of xamoterol throughout the day. In animals, chronic dosing with xamoterol does not appear to induce receptor

Figure 3 Dose-response curves in a single dog relating heart rate to the dose of isoprenaline (■) and xamoterol (●). The partial agonist activity of xamoterol is calculated as the maximum change in heart rate caused by xamoterol as a percentage of the maximum caused by isoprenaline.

Figure 4 The effects of increasing intravenous doses of isoprenaline (●) and xamoterol (○) on heart rate and left ventricular dP/dt_{max} in an anaesthetised areflexic dog preparation.

down-regulation. Barnett & Maguire (1986) compared the effects of 6 days dosing with isoprenaline and xamoterol on the binding of iodopindolol to ventricular cell membranes in the rat. They concluded that maximal binding capacity was reduced by 43% by isoprenaline and not affected by xamoterol, and suggested that isoprenaline but not xamoterol also caused some uncoupling of the production of cyclic adenosine monophosphate (cAMP) from β -adrenoceptors. This lack of an effect may be related to both the level of partial agonist activity at β_1 -adrenoceptors and the absence of any β_2 -adrenoceptor activity.

Effects of xamoterol on autonomic control of the heart

The effect of xamoterol on the response of an areflexic dog heart to stimulation of the sympathetic nerves is shown in Figure 5. This result demonstrates not only the ability of xamoterol to antagonise the effects of noradrenaline, but also the failure of the sympathetic nerves, even at high rates of stimulation, to release sufficient noradrenaline to displace the required amount of xamoterol from the β_1 -adrenoceptor and achieve the control maximum response. Therefore, as the dose of xamoterol is increased, the range of the response of the heart to sympathetic nerve stimulation becomes increasingly narrowed (Figure 5). The overall effect is to stabilise both the inotropic and chronotropic responses of the heart to sympathetic nerve stimulation about a level determined by the partial agonist activity of xamoterol.

The direct effects of xamoterol on vagal efferent activity were examined in an anaesthetised dog preparation. Both vagi were sectioned and the distal end of the right vagus electrically stimulated. In three dogs, xamoterol ($50 \mu\text{g kg}^{-1}$) increased the control heart rate from 144 beats min^{-1} to 207 beats min^{-1} . Vagal stimulation was increased in a stepwise manner so as to obtain the slowest heart rate with a sinus rhythm. Xamoterol increased this slowest heart rate from 72 beats min^{-1} to 110 beats min^{-1} , and

Figure 5 Frequency response curves relating heart rate to the frequency of stimulation of the sympathetic nerves to the heart (right ansa subclavia) in the absence (●) and presence of 5 (○), 50 (▲) and 250 (■) $\mu\text{g kg}^{-1}$ of xamoterol. The rotation of the curves about a fixed point with increasing doses of xamoterol is characteristic of the interaction of a partial agonist (xamoterol) and full agonist (noradrenaline) and illustrates the stabilising or buffering action of xamoterol on the response of the heart to sympathetic stimulation.

the changes brought about by vagal stimulation were respectively $72 \text{ beats min}^{-1}$ and $110 \text{ beats min}^{-1}$. The frequency of stimulation required to produce a 50% reduction in heart rate was not altered by xamoterol. These changes in heart rate can be accounted for in terms of the known interaction of the vagal and sympathetic nerves at the sinoatrial node (Levy & Zieske, 1969). It was concluded from these experiments that xamoterol has no direct effects on the ability of the vagus to produce changes in heart rate and is unlikely to interfere with either the release or activity of acetylcholine at muscarinic receptor sites in the heart.

In contrast to effects in the areflexic dog, xamoterol has little or no effect upon heart rate in the conscious dog (Figure 6). However, the inotropic effects are similar. The dissociation of an effect on rate from that on force in the intact animal probably results from the lack of a vasodilating (β_2 -adrenoceptor) effect with xamoterol. Therefore, systolic blood pressure is increased and the baroreceptor reflexes, operating principally through the vagal nerves to the heart, preferentially slow heart rate. In general, the apparent ability of some β -adrenoceptor agonists to have differing effects on rate and force, e.g. noradrenaline and isoprenaline, resides in their opposing actions on the peripheral circulation and the consequent operation of baroreceptor reflexes, and not in the direct

Figure 6 The effects of increasing intravenous doses of xamoterol on heart rate and left ventricular dP/dt_{max} in five conscious dogs.

action of the compounds at the β -adrenoceptors in the sinoatrial node and muscle of the left ventricle (Linden & Snow, 1974).

A lack of a significant chronotropic response to xamoterol has also been observed in normal man at rest, but is present after atropine (Jennings *et al.*, 1984; Sasayama *et al.*, 1986).

The ability of xamoterol to modulate the response of the heart to sympathetic stimulation is central to an understanding of its pharmacological action in the intact animal. Thus, whether xamoterol acts to increase or decrease the response of the heart to sympathetic stimulation depends upon the ongoing level of endogenous sympathetic activity (Figure 5). Consequently, in the intact animal it is not sufficient just to consider the direct action of xamoterol on the heart, but also its interaction with sympathetic activity and secondary effects from cardiac reflexes. Therefore, the primary interaction between xamoterol and noradrenaline at the β_1 -adrenoceptor results in an alteration in the pattern of cardiac control at different levels of exercise. The cardiac output is achieved with a different combination of heart rate, stroke volume and end-diastolic volume. Evidence for this effect on cardiovascular control in normal dog and man and in patients with heart failure will now be considered.

Effects of xamoterol on the determinants of cardiac output at rest and during exercise

Measurements of the effects of xamoterol on the heart and circulation at rest and during exercise

Figure 7 Effects of xamoterol ($100 \mu\text{g kg}^{-1}$ i.v.) on heart rate, systolic blood pressure and cardiac index. Measurements were made before and at 2, 4, 6 and 8 h after xamoterol, at rest and at increasing work loads of 0.25, 0.5, and 0.75 of a previously measured maximum sustained work load. Supine measurements of heart rate and blood pressure were made at rest and are shown as ■. * $P < 0.05$; ** $P < 0.01$.

have been made in both man and dog (Detry *et al.*, 1983; Jennings *et al.*, 1984; Ohyagi *et al.*, 1984; Sato *et al.*, 1987). In man, Jennings *et al.* (1984) measured heart rate, blood pressure and cardiac output at rest and at three levels of exercise, before and at various times up to 6 h after xamoterol $100 \mu\text{g kg}^{-1}$ i.v. (Figure 7). At rest, xamoterol had no effect upon heart rate and diastolic blood pressure in either the sitting or the supine position; systolic blood pressure and cardiac index were increased, the latter by between 10% and 20%. During exercise, no significant effects were observed at 25% of the maximum sustained work capacity. At work rates of 50% and 75% of maximum, the only significant effects of xamoterol were a reduction in both heart rate and systolic blood pressure. All these effects were time dependent and present 6 h after dosing. Apart from the 10–20% increase at rest, xamoterol had little effect upon cardiac output at each level of exercise, but the manner in which a particular cardiac output was achieved in terms of heart rate and stroke volume was different (Figure 8). At rest and at low levels of exercise, the resultant effect on cardiac control is an increase in stroke volume, and at maximum exercise a reduction in heart rate.

This description of the control of cardiac output depends upon the fact that both rate and force are under separate control by cardiovascular reflexes (Furnival *et al.*, 1971) and on the assumption that they are matched in such a way that a particular cardiac output is achieved with a combination of heart rate, end-diastolic volume and systolic volume, which is optimal in terms of the mechanical efficiency of the heart. Such a mechanism is implicit in the following statement by Starling (1920) on cardiac control during exercise:

'In studying the reactions of the *isolated* heart, dilatation of the heart (Starling's Law) seems to be the only unfailing response of this organ to any increase in the demands made upon it. But the effect of throwing this organ into the circle of control by the central nervous system is that it is kept in rest or activity in an equable condition, and the dilatation, which was so marked a condition of its reaction when isolated, is reduced to such small dimensions in the intact heart reined in and controlled by the cardiac centres, and helped by the correlated changes in other organs, that it becomes imperceptible in the intact animal, and is not revealed, for instance, by any radiographic study of the heart during exercise'.

Figure 8 The effect of xamoterol on the relation between heart rate and cardiac index at rest and three levels of increasing exercise on a bicycle ergometer in normal subjects. Xamoterol alters the relation such that at rest and at low levels of exercise stroke volume is increased with little change in heart rate and during more severe exercise heart rate is decreased with no change in cardiac output. ○ xamoterol, ● placebo.

Figure 9 The effects of propranolol ($1.0 \text{ mg kg}^{-1} \text{ i.v.}$ ■) and xamoterol ($10 \text{ mg kg}^{-1} \text{ i.v.}$ ▲) on the relation between left ventricular dP/dt_{max} (inotropic changes) and left ventricular end-diastolic pressure (LVEDP) (Frank-Starling effect), at rest (lying and standing), and at three levels of exercise on a treadmill. Control measurements (●). Results are mean values from observations on 10 dogs. Xamoterol and propranolol alter in different ways the contribution of inotropism and Starling's law to the manner in which the cardiac output at a particular level of exercise is achieved.

The effects of pharmacological manipulation of this autonomic control of the heart during exercise in the dog are shown in Figure 9. These results, taken from Ohyagi *et al.* (1984), show that the relation between left ventricular end-diastolic pressure (an index of heart size) and left ventricular dP/dt_{max} (an index of the inotropic

response to sympathetic stimulation) is altered by both propranolol and xamoterol. Heart rate was increased at rest and decreased during maximum exercise by xamoterol, and decreased at all levels of activity by propranolol. Cardiac output was not measured in these experiments, but on the assumption that output was similar in the presence of placebo and each drug at corresponding levels of exercise, then it may be seen that the manner in which the output was achieved is quite different in the three situations.

In the normal dog, in the absence of any drug interference, autonomic control in terms of inotropism (left ventricular dP/dt_{max}) and chronotropism deals with the venous return from the exercising muscles and maintains end-diastolic volume (left ventricular end-diastolic pressure) relatively constant. Near complete removal of sympathetic control (propranolol) leaves the heart with only the Frank Starling mechanism and small increases in heart rate through vagal withdrawal, as a means of increasing output. In the presence of a β_1 -adrenoceptor partial agonist, normal sympathetic control is again altered (Figure 9). At rest, the inotropic state of the heart is increased, resulting in a reduction in left ventricular end-diastolic pressure and at the highest level of exercise these effects are reversed.

Thus, in the normal heart, xamoterol leads to a reduction in the range of the response of the

heart to sympathetic stimulation and even though maximum cardiac output may not be reduced, it is achieved with a slower heart rate and higher end-diastolic and stroke volumes (Figure 9).

In patients with left ventricular dysfunction, an important element of this reflex control of the heart is impaired, namely, the ability of the left ventricle to respond adequately to sympathetic stimulation. Both contraction and relaxation are impaired. Consequently, as the severity of exercise increases, the relations between heart rate, stroke volume and end-diastolic pressure become abnormal. In general, a given cardiac output is achieved with a greater heart rate, and a smaller stroke volume taken from a larger end-diastolic volume. In ischaemic heart disease, this mismatching of a high heart rate with a poor inotropic response and a consequent inability to shorten systole and preserve diastole, impairs coronary blood flow, exacerbates the ischaemia and further depresses left ventricular function. In these circumstances, the same directional changes produced by xamoterol in the normal heart have a beneficial effect and a more normal pattern of response is observed. This effect was

first demonstrated by Detry *et al.* (1983), who showed that both at rest and on exercise, pulmonary capillary wedge pressure was consistently reduced by xamoterol, despite the fall in maximum exercise heart rate. These findings are in contrast to those observed at rest and during submaximal exercise with the β -antagonists propranolol, practolol and atenolol, when decreases in cardiac output are associated with either no change or an increase in the filling pressure of the left ventricle (Epstein *et al.*, 1965; Parker *et al.*, 1968; Finegan *et al.*, 1972; Rousseau *et al.*, 1973; Reybrouck *et al.*, 1977; Bruce *et al.*, 1979).

This ability of xamoterol to cause a reduction in the filling pressure of the diseased left ventricle at rest and throughout all levels of exercise was confirmed by Detry *et al.* (1984) in patients with angina pectoris and by Sato *et al.* (1987) in patients with heart failure (Figure 10). The results obtained by Sato and colleagues provide an important link between the effects of xamoterol on the response of the heart to sympathetic stimulation and its mode of action in heart failure patients. They measured both plasma noradrenaline concentrations and

Figure 10 Observations of the effects of xamoterol made in 10 patients with heart failure (NYHA II–III) at rest and during supine exercise. The relations between plasma noradrenaline (NA) concentration (an index of sympathetic activity) and (a) heart rate, (b) pulmonary wedge pressure, (c) cardiac index and (d) systolic blood pressure are shown.

Figure 11 The resultant effect of xamoterol on the relation between cardiac index and pulmonary wedge pressure is shown. At all levels of physical activity the cardiac output is achieved at a lower wedge pressure in the presence of xamoterol.

haemodynamic changes, at rest and during three levels of exercise, and were therefore, able to examine the effects of xamoterol on the relation between an index of the stimulus and the response.

The changes produced by xamoterol were as expected. At low levels of stimulus, xamoterol added to the effects of noradrenaline and the nett effect was seen as an increase in heart rate, cardiac output and systolic blood pressure (Figure 10). During higher levels of stimulus, the effects of noradrenaline were attenuated. However, more noradrenaline was produced and the resultant cardiac output, during maximum exercise, was only slightly reduced.

Importantly, the filling pressures at all corresponding levels of either exercise or noradrenaline concentration were reduced. Therefore, when the relation between filling pressure and cardiac index was examined (Figure 11), it was seen that, both at rest and during exercise, the cardiac output was achieved at a lower filling pressure in the presence of xamoterol. It is important to realise that these effects at *maximal* exercise are achieved through a slowing of heart rate and a more normal matching of rate and force, and not through a direct inotropic effect of xamoterol upon the left ventricle. However, it must be remembered that the resting heart at the beginning of exercise is smaller when under the

inotropic stimulation of xamoterol and, consequently has a greater 'Starling' reserve.

Conclusions

In terms of cardiac control, left ventricular dysfunction may be defined as the inability of the left ventricle to respond to sympathetic stimulation. This blunting of the inotropic response of the left ventricle leads to an imbalance in the chronotropic and inotropic control of the heart at rest and in particular during exercise. The consequent inability of the diseased heart to shorten systole, an important part of the normal inotropic response as heart rate increases, results in a failure to maintain filling of the left ventricle, and in those patients with coronary artery disease to increase coronary blood flow adequately.

By providing inotropic support at rest and during low levels of exercise, and reducing the inappropriate tachycardia at higher levels, xamoterol tends to normalise the balance of inotropic and chronotropic control in the failing heart and the cardiac output is achieved with a more normal combination of heart rate, stroke volume and filling pressure. These changes are of particular benefit to the failing ischaemic heart on exercise, since they tend to improve the balance between energy supply and demand (Detry *et al.*, 1984; Molajo *et al.*, 1987).

Occupation of the β_1 -adrenoceptor by a partial agonist lacking β_2 -adrenoceptor agonism, leads to an alteration in the pattern of autonomic control of the heart on going from rest to exercise. This acute effect is of haemodynamic benefit to patients with left ventricular dysfunction.

The imposition of such an altered pattern of cardiac activity over a period of time, with associated changes in heart size and the preven-

tion of myocardial ischaemia, may cause beneficial adaptations, for example, changes in structure and β -adrenoceptors. Such changes could account for the observed improvement in the overall clinical condition of patients during long-term treatment with xamoterol (Blackwood & Marlow, 1988; The German and Austrian Xamoterol Study Group, 1988).

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