# The Development of β-Stimulant Drugs for the Treatment of Heart Failure

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## Introduction

Heart failure is a progressive disease of mixed aetiology which afflicts a large number of people in the Western World. In the U.S.A., for example, 250,000 new cases occur each year, with 200,000 deaths. Prognosis is poor, the survival rate being only 50% five years after initial diagnosis.

Heart failure may be caused by congenital defects or rheumatic fever, and these lesions may often be cured by surgery. More commonly the condition is caused by ischaemia or hypertension, and is often developed after a myocardial infarction. Though the patient presents with dyspnoea, fatigue, oedema, and often chest pain it is important to realise that these symptoms are caused by the failure of the heart to provide an adequate supply of blood to the tissues, and two types of treatment have been used to improve matters; vasodilators to reduce the resistance to blood flow, and cardiotonics to support the heart. The third type of treatment, diuretics, does not address the disease directly but will alleviate the symptoms. Only adrenergic cardiotonics will be considered in this paper.

## Adrenergic Cardiotonics

Adrenergic agonists have many effects which were very confusing until

Ahlquist[1], and later Lands[2], proposed the classification $\alpha$, $\beta_1$, $\beta_2$ as shown in fig. 1. This explained, very adequately, why noradrenaline (predominately $\alpha$– with some $\beta_1$) increases heart rate while causing vasoconstriction, adrenaline ($\alpha$ plus $\beta_1$ plus $\beta_2$) increases heart rate and causes some vasodilation, and isoprenaline (pure $\beta_1/\beta_2$ agonist) increases heart rate and causes profound vasodilation.

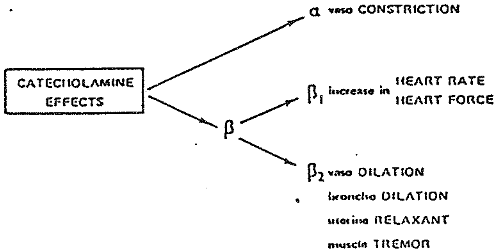
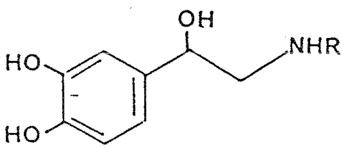



Fig. 1



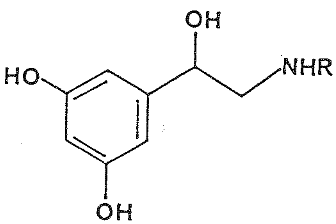

Noradrenaline R = H

Adrenaline R = Me

Isoprenaline R = $Pr^i$

Pure beta agonists could help heart failure patients either by their $\beta_1$ cardiotonic action, or $\beta_2$ vasodilation, and both have been investigated. The catecholamines themselves are rapidly and extensively metabolised, hence having a short duration of action after parenteral administration, and no oral bioavailability. Replacement of the catechol hydroxyl groups by chlorine atoms gave dichlorisoprenaline (DCI) which was an orally active partial agonist, and demonstrated the feasibility of producing a beta stimulant drug. Several groups tried to modify the catecholamine structure in order to reduce the most troublesome aspect of metabolism, the enzyme catechol–o–methyl–transferase (COMT) which selectively methylates the meta hydroxyl group.

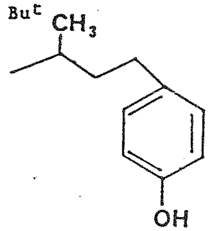
Mead Johnson workers mimicked the <u>meta</u> phenol group with methane sulphonamide, soterenol being a long lasting $\beta_1/\beta_2$ agonist[3]. The main reason for the research at this time was to produce a selective $\beta_2$-agonist as a bronchodilator for the treatment of asthma, and when orciprenaline ($\beta_1 + \beta_2$) was found to be resistant to COMT[4] further work was carried out to obtain terbutaline ($\beta_2$)[5] and then fenoterol (very $\beta_2$- selective)[6]. At Allen and Hanbury's laboratory modification of the <u>meta</u> phenol by insertion of a methylene group gave the $\beta_2$-selective agonist salbutamol (albuterol in USA)[7].

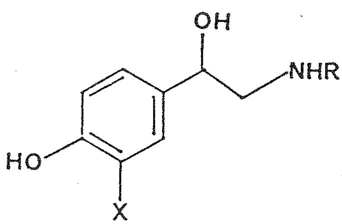



orciprenaline R = $Pr^i$

terbutaline R = $Bu^t$

fenoterol R =

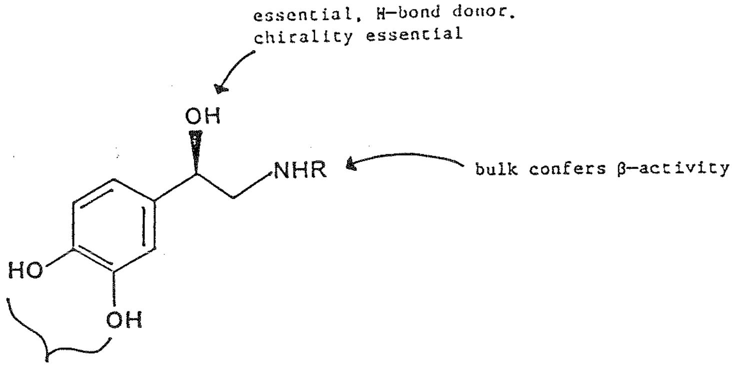



soterenol X = $NHSO_2$ Me, R = $Pr^i$

salbutamol X = $CH_2OH$, R = $Bu^t$

These early structures led to speculation about how catecholamines bind to $\beta$-receptors. Certain features were rapidly established, as illustrated in fig. 2, but the purpose of the catechol was not known. Subsequent synthesis of analogues replacing the methanol unit of salbutamol showed that acidic, basic, H-bond donating or accepting groups were all active, and probably the most likely common factor is that all could act as metal chelating groups[8,9]. This role is also supported by the activity of compounds such as quinterenol, which contains the powerful chelating system of 8-hydroxy quinoline (oxine). The 3-hydroxy-4-hydroxymethyl analogue of salbutamol is inactive, as is its soterenol counterpart.



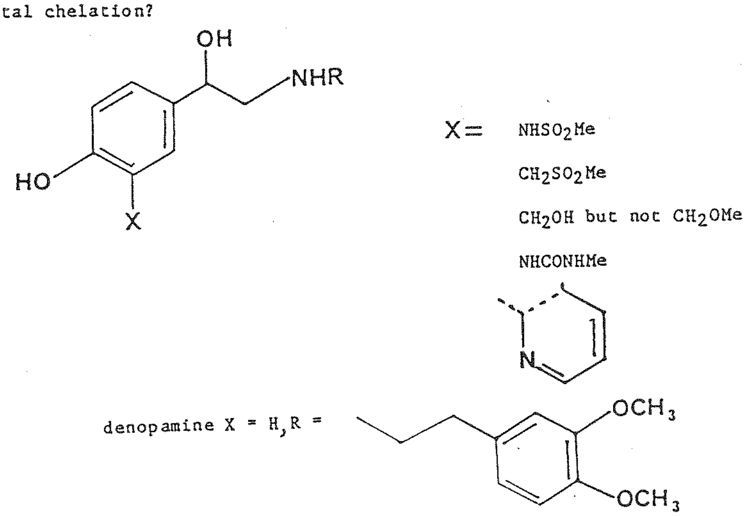

H-bond donor?

H-bond acceptor?

acidic binding?

metal chelation?

Fig. 2



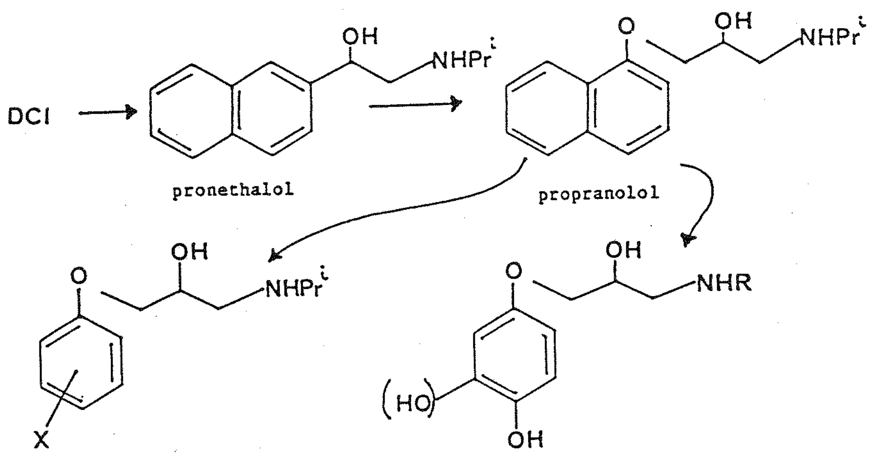
Removal of the meta group altogether gives part – or full agonists such as denopamine, which has a longer duration than the catecholamines. Denopamine has been used successfully in the treatment of heart failure acutely, but no trials relating to chronic dosing have been published[10,11].

Salbutamol[12] and its pyridine analogue pirbuterol[13] have been studied in heart failure, and had a beneficial effect acutely, which was probably largely due to vasodilation, leading to a reduction of afterload on the heart. Chronic dosing, however, failed to maintain this effect.

Aryloxypropanolamines

In the early 1960's J.W. Black, at the ICI laboratories, began the search for β-receptor antagonists as anti-ischaemic agents, and the group rapidly produced pronethalol, an analogue of DCI which possessed only a little of the agonist properties, but was a moderately potent β-antagonist. Pronethalol was effective in the treatment of angina pectoris[14] and hypertension, and this initiated widespread research activity throughout the World.

The first breakthrough came with the discovery of propranolol, a potent β-antagonist with no agonist properties[15]. The synthesis of monocyclic ring analogues followed, and this has lead to pure antagonists, partial agonists, and full agonists. During this period the possibilities for $\beta_1/\beta_2$ selectivity have also been discovered and exploited, and almost all combinations of agonism, antagonism, and selectivity have now been realised[8,16,17].




X = 2 — oxprenolol

X = 4 — NHAc practolol

X = 4 — $CH_2CONH_2$ atenolol

X = 4 — $CH_2CH_2OMe$ metoprolol

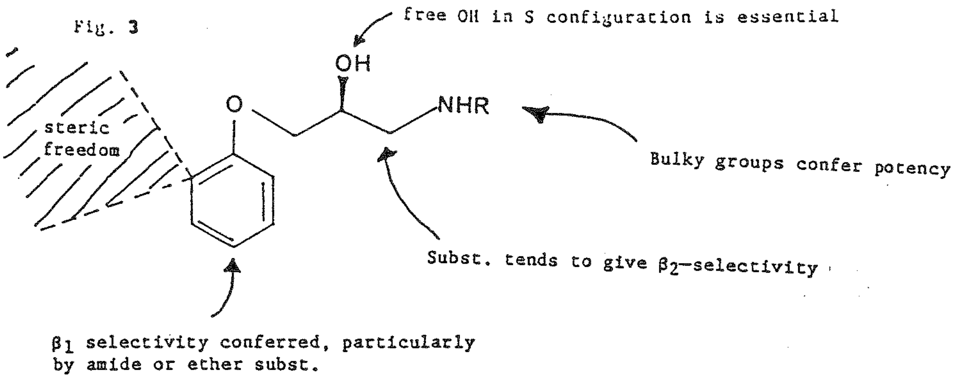
catechols are full agonists

phenols are partial agonists

β—antagonists, oxprenolol and practolol show a little agonism, all except oxprenolol are $\beta_1$—selective.

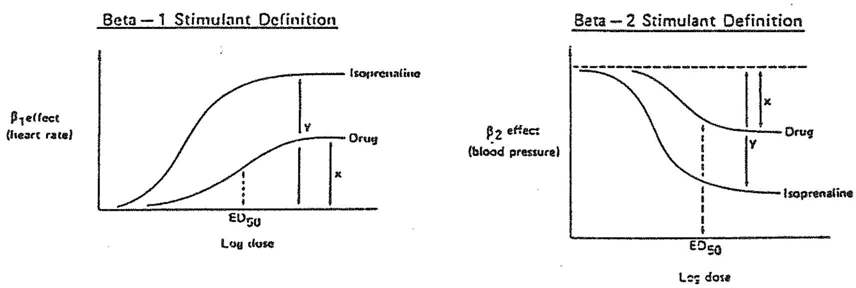
There is insufficient space here to discuss the S.A.R. of β—antagonists in detail, but results are shown schematically in fig. 3. This is also a convenient point at which to define precisely the S.A.R. parameters which will be used in the subsequent discussion, which will centre on aryloxy-propanolamine partial agonists. As an example, the results from a denervated anaesthetised dog model are shown in fig. 4.

Fig. 3




The benzene ring may be replaced by a variety of (aromatic) heterocycles.

Fig. 4

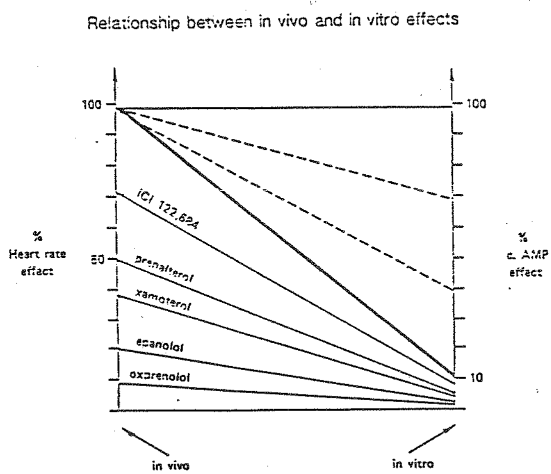



in both cases % agonism = $\frac{x}{y} \times 100$

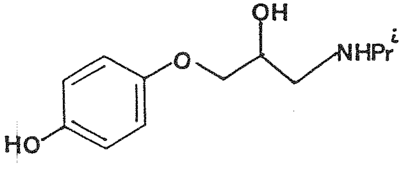
Selectivity = $\beta_2\ ED_{50}/\beta_1\ ED_{50}$

The difference between percentage agonism demonstrated in the above test and that observed in the biochemical situation where cAMP production is measured cannot be overemphasised. Thus (fig. 5) while isoprenaline is a full agonist in both systems other compounds which are, perhaps, 50% agonists <u>in vivo</u> will only show 5% in vitro, because, by definition, partial agonists need to occupy ALL receptors to achieve their maximum response while full agonists may only need to occupy 5 – 10% of the receptors to produce enough cAMP to achieve a full biological response. Compounds such as practolol are thus very weak agonists indeed. Some work in man with an ICI drug ICI 89406 suggests that drugs with around 30% agonism in the above test show neither a rise or fall in cardiac rate/force, and only compounds with more agonism than this will be cardiotonic in normal daily life[18].

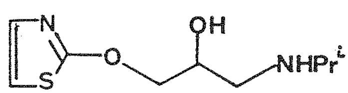
Fig. 5




Partial agonism is exhibited by a number of different aryloxypropanolamine structures, which may be classified as phenols, non-phenols, or heterocycles. Prenalterol was the first partial agonist to be used for treating heart failure. It has around 50% agonism on both $\beta_1$ and $\beta_2$ receptors and shows marked haemodynamic benefit when dosed acutely to patients with moderate




prenalterol

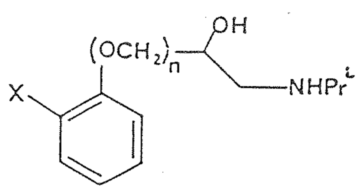



Tazolol

or severe degrees of failure[19]. Over medium-term treatment these effects are maintained, and subjective improvement is noted[20], but beyond one month benefit is not maintained[21]. In some trials ventricular tachyarrhythmias were noted, and some toxic effects were also found in animal studies; the oral dosage form of penalterol has been withdrawn. Some heterocyclic analogues of prenalterol e.g. tazolol, have very similar animal pharmacology to prenalterol, but none have progressed beyond initial volunteer studies.

Non-phenolic aryloxypropanolamines show varying degrees of agonism. The nature of an <u>ortho</u> substitutent, in particular, has a considerable effect on the amount of agonism, with large groups destroying it altogether. Two attempts have been made to quantify this effect; in the first[22], calculation of the energy of various conformations of the oxypropanolamine chain of the simple series shown (A) suggested the presence of two low energy states. The major state was the expected all-trans conformation, with a minor gauche conformer present in some cases. Correlation of the prevalence of this gauche conformer with the degree of agonism gave a straight line plot, suggesting that it was this isomer which was responsible for agonism.

Unfortunately when this work was extended to the corresponding arylethanolamine series (B) there was no evidence for a minor conformer.

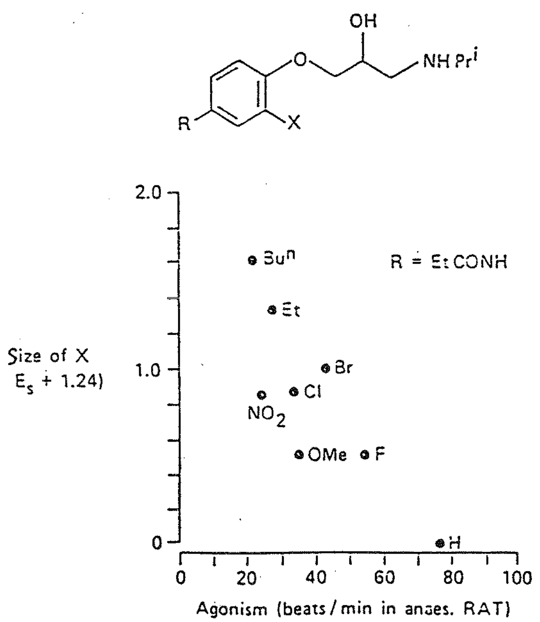



A; n= 1

B; n= 0

The second attempt[23] at quantifying the effect was to correlate Taft's steric parameter Es with degree of agonism. Again, in series A a straight line was obtained, and this carried through to series B, and also to a number of other aryl–oxypropanolamine series. This result suggests that bulky ortho substituents prevent the molecule adopting the mode of receptor binding necessary for agonism.

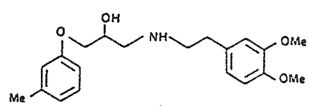
Effect of o Subst. on Degree of Agonism




All the early work on β–(ant)agonists supported the view that the nature of the aryl ring determined most of the properties of the molecule – potency, selectivity, and degree of agonism. The demonstration of $\beta_1$–selective antagonism in bevantolol[24] and tolamolol[25], both of which contained aryl substituents which are not normally associated with cardioselectivity, prompted ICI workers to investigate the nature of the side–chain more thoroughly[26,27]. Ethers, thioethers, and more particularly amides and ureas were found to be markedly selective for $\beta_1$–receptors or, more accurately, to be selective <u>against</u> $\beta_2$–receptors as $\beta_1$–potency is no greater than with non-selective analogues.

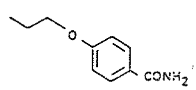
With the above background the ICI group decided to develop a partial agonist for the treatment of heart failure. The profile aimed for was a long acting $\beta_1$–selective partial agonist having about 50% of the agonism of isoprenaline. The reasons for this profile were two fold: partial agonism would mean that at times when sympathetic tone is low, i.e. resting, walking, the drug would act as an agonist, providing cardiac support, while during exercise it would be an antagonist, preventing overstimulation of the heart. A partial agonist would, therefore, have a stabilising effect.

Cardioselectivity was seen to be essential, for the reasons shown in fig. 6. $\beta_2$ vasodilator effects cause reflex tachycardia which exacerbates the direct tachycardia caused by $\beta_1$–stimulation. The reflex effect of the blood pressure rise due to $\beta_1$–myocardial stimulation is vagally mediated bradycardia, which counteracts the direct tachycardia, thus providing a drug which will stimulate cardiac force with little effect on heart rate.

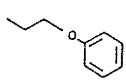



bevantolol

o tolyl




tolamolol



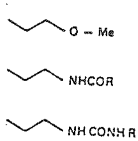
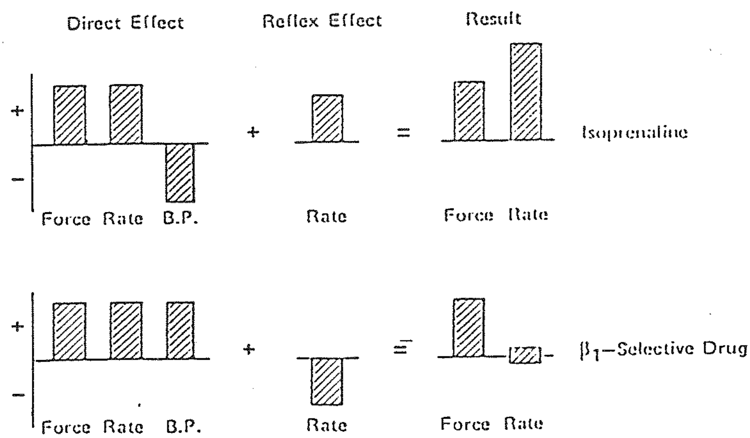



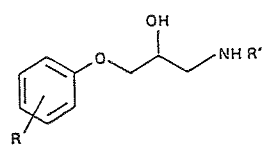
Fig. 6

## Effect of Cardioselectivity on Heart Rate



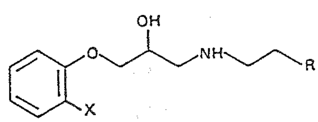

The acylaminoalkyl series provided a versatile means of achieving the target profile. Variation of the amidic group provided compounds with agonism ranging from 30–90%[28] (see table) and this effect was so notable in the phenol series that non-phenols were also examined. With an unsubstituted benzene

### Effect of Acylaminoalkyl Substitution – on AGONISM




| R | R' | Agonism % in dog * |
|---|---|---|
| 4–$NHCOCH_3$ | $Pr^i$ | 15 (practolol) |
| 2–CN | $Pr^i$ | 16 (kö 1313) |
| 4–OH | $Pr^i$ | 56 (prenalterol) |
| 4–OH | $CH_2CH_2NHCONMe_2$ | 29 |
| 4–OH | $CH_2CH_2NHCOCH_2Ph$ | 40 |
| 4–OH | $CH_2CH_2NHCONHPh$ | 50 |
| 4–OH | $CH_2CH_2NHSO_2Ph$ | 55 |
| 4–OH | $CH_2CH_2NHCONH$/\/OH | 69 |
| 4–OH | $CH_2CH_2NHCONHCH_2Ph$ | 80 |
| 4–OH | $CH_2CH_2NHSO_2NHPh$ | 92 |
| 4–OH | $CH_2CH_2NHCONH_2$ | 92 |

### Agonism in Non – Phenols




| X | R | Degree of agonism * |
|---|---|---|
| H | NHCONHPh | 21% |
| H | NHCON O | 33% |
| H | $NHSO_2NHPh$ | 52% |
| H | $NHCONH_2$ | 61% |
| H | $NHCONHCH_2Ph$ | 70% |
| F | $NHCONHCH_2Ph$ | 60% |
| H | NHCONHCH(Me)Ph | 30% |

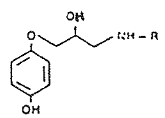
* isoprenaline = 100%

ring agonism of up to 70% could still be realised. With these non-phenols bulky <u>ortho</u> substituents still had the same effect as that described earlier for series A, allowing for "fine tuning" of the degree of agonism, and with groups larger than Cl or $CH_3$ almost all agonism is lost.

Most of the compounds in the table are moderately $\beta_1$-selective, having a $\beta_1/\beta_2$ ratio of around 3–5 (prenalterol 0.9, isoprenaline 0.3); when a primary or secondary urea group is present this still applies, but further substitution causes complete loss of $\beta_2$-activity (as an agonist) and it was from this series that the development candidate was selected.

Xamoterol is a potent, long acting, 43% partial agonist with a selectivity of several hundred to one for $\beta_1$ vs $\beta_2$ receptors[29]. This profile has been confirmed in healthy volunteers[30], the drug having an i.v. $ED_{50}$ of 5μg/kg (4μg/kg in dog) and 40–50% agonism. Effective treatment is achieved by dosing 200mg b.d. The cardiostablising effect of partial agonism was also confirmed (fig. 7).

Effect of Acylaminoalkyl Substitution - on SELECTIVITY




| R | Selectivity ratio $\beta_1/\beta_2$ | |
|---|---|---|
| NH $SO_2$ Ph | 0.7 | |
| NH CO $CH_2$ Ph | 3.2 | |
| NH CO NH $CH_2$ Ph | 4.3 | |
| NH CO N(Me)(Me) | > 40 | |
| NH CO N(Me)(CH₂CH₂OMe) | > 250 | |
| NH CON O | > 250 | = xamoterol (43% agonism) |
| N(Me) CON(Me)(Me) | poorly active | |

In heart failure patients none of the theoretical problems which could occur due to β-stimulation have been seen. Thus there is minimal, or no, tachycardia, no increase (in fact a decrease) in arrhythmias[31], no worsening of ischaemia[32] and, very importantly, no tolerance has been observed up to three years' dosing[33]. Xamoterol may be co-prescribed safely with diuretics, cardiac glycosides or ACE inhibitors[33].

On the positive side xamoterol increases cardiac output at rest, reduces exercise heart rate, and increases exercise workload and duration[34–8]. It reduces angina of effort[37] and is effective in postural hypotension[39]. Perhaps most important, it improves clinical signs and symptoms and 'quality of life'[33,36,37].

Fig. 7 Xamoterol in Volunteers

1. Cardiotonic at rest
2. No effect during moderate exercise
3. Beta antagonist during severe exercise

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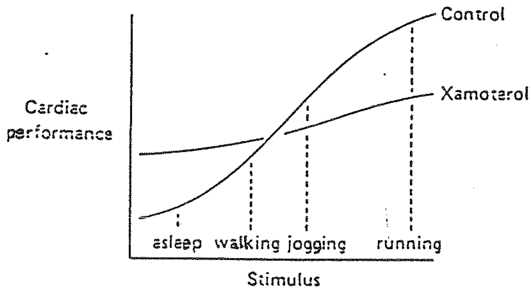

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