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Effects of xamoterol on resting and exercise haemodynamics in patients with chronic heart failure

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1 A bicycle exercise test was used to investigate functional capability and haemodynamics in 30 patients with heart failure (13 NYHA Class II, 17 Class III), before and after i.v. xamoterol (Corwin, Carwin, Corwil, Xamtol, ICI 118,587) 0.2 mg kg^{-1}.

2 Resting heart rate fell from 78 to 74 beats min^{-1} ($P < 0.05$) and cardiac index rose from 2.5 to 2.8 l min^{-1} m^{-2} ($P < 0.001$) after xamoterol. Blood pressure fell slightly, and systemic vascular resistance was reduced. Stroke work index improved and double product decreased. There were no changes in pulmonary artery wedge pressure, ejection fraction or plasma noradrenaline concentrations.

3 On exercise, xamoterol produced a considerable reduction in heart rate increase, improved stroke volume and left ventricular stroke index and lowered double product. Exercise duration increased by 10%, but this did not quite achieve statistical significance.

4 These results are consistent with the concept that a β_1-partial adrenoceptor agonist with the level of intrinsic sympathomimetic activity (43%) of xamoterol provides moderate inotropic support at rest, and protects the heart against overstimulation on exercise, when sympathetic drive is high.

5 Reduction of double product on exercise implies a lowered oxygen demand, which could be of considerable importance in patients with ischaemic heart disease.

Keywords xamoterol heart failure β_1-adrenoceptor partial agonist

Introduction

In patients with heart failure due to ischaemia or cardiomyopathy, the basic underlying abnormality is impaired left ventricular function. Reflex activation of the sympathetic nervous system occurs in these patients as a normal compensatory mechanism, with catecholamines providing natural inotropic support to the failing heart (Chidsey *et al.*, 1965; Thomas & Marks, 1978; Francis *et al.*, 1982; Levine *et al.*, 1982; Cohn *et al.*, 1984). The degree of activation reflects the severity of the heart failure (Thomas & Marks, 1978) and catecholamine levels can be used as a prognostic index (Cohn *et al.*, 1984). However, chronic sympathetic drive to the failing heart can have deleterious effects, causing β-adrenoceptor down-regulation (Mukherjee *et al.*, 1975; Mickey *et al.*, 1976; Tse *et al.*, 1979; Su *et al.*, 1980; Bobik *et al.*, 1981; Colucci *et al.*, 1981; Bristow *et al.*, 1982). This resultant loss of β-adrenoceptor function and density due to chronic receptor stimulation subsequently deprives the heart of its main compensatory mechanism. Therapeutic regimens leaving β-adrenoceptor stimulation unchecked or enhancing it, as is in the mechanism of action of many modern inotropes, may account for the observations of progressive heart failure despite medical therapy, the development of tachyphylaxis to many inotropic agents and explain, at least in part, why no inotrope has been shown to improve prognosis. Conversely, β-adrenoceptor antagonists which block β-adrenoceptor stimulation and perhaps protect or restore β-adrenoceptor function have been used successfully in the treatment of some patients with severe heart failure (Swedberg *et al.*, 1980a, b). However, removing catecholamine

support to the failing heart with pure β-adrenoceptor antagonists is potentially hazardous.

The pharmacological properties of xamoterol provide a unique opportunity to influence the degree of cardiac response to variations in sympathetic tone. Xamoterol has approximately 43% of the intrinsic sympathomimetic activity of the full agonist isoprenaline (Nuttall & Snow, 1982). It provides constant mild stimulation which enhances cardiac performance when sympathetic tone is relatively low, as in patients with mild to moderate heart failure at rest. At high levels of sympathetic tone, occurring on exercise in patients with all grades of heart failure and even at rest in patients with severe heart failure, xamoterol protects from overstimulation. Therefore, it should be possible with this compound to modulate the cardiac responses to variations in sympathetic tone and to provide a degree of agonist support and antagonist protection to the failing heart.

This study was designed to investigate these concepts by examining the acute effects of intravenous xamoterol at rest and on exercise in patients with mild to moderate heart failure.

Methods

The study group consisted of 30 patients (27 male, 3 female) with chronic heart failure and dyspnoea as the limiting symptom on exercise. The mean age of the group was 60 ± 2 years (± s.e. mean) and the clinical diagnosis was ischaemic heart disease in 24 patients (18 with a previous myocardial infarct) and congestive cardiomyopathy in six patients. Thirteen patients were in New York Heart Association (NYHA) Class II and 17 were in NYHA Class III. The mean duration of symptomatic dyspnoea was 22.4 ± 3 months (± s.e. mean, range 3 to 96 months). All except two patients were on diuretics. In addition, 12 patients were receiving digoxin, 16 vasodilators and two angiotensin converting enzyme (ACE) inhibitors. The study had hospital ethics committee approval and all patients gave informed consent prior to entry.

Study protocol

All patients underwent a symptom-limited bicycle ergometer exercise test 1 to 2 weeks prior to the haemodynamic study to determine individual exercise capacity. The initial workload of 25 watts was maintained for 3 min and the workload then increased by 25 watt increments every 3 min. On the morning of the study, a thermodilution Swan-Ganz catheter was inserted via the right subclavian vein and positioned in the pulmonary artery under fluoroscopy. An intra-arterial cannula was inserted percutaneously into the right brachial artery. The following haemodynamic parameters were monitored throughout the study: right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and brachial artery pressure (SBP, systolic; DBP, diastolic). Thermodilution cardiac output was determined in triplicate.

The following haemodynamic functions were derived from these direct haemodynamic measurements using conventional formulae; cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and double product (DP).

Left ventricular ejection fractions were measured using technetium 99^m gated blood pool scanning.

All measurements, both at rest and during exercise, were made with the patient in a semi-recumbent position at 25° from the vertical. Resting haemodynamic data were recorded 1 h after insertion of the catheters. The patients then carried out a symptom-limited bicycle exercise test at an initial workload of 25 watts increasing by 25 watt increments every 3 min. Haemodynamic parameters were recorded at the end of each stage and cardiac output was determined during the last minute of each stage. Radionuclide left ventricular scans were obtained during the last 2 min of each 3 min exercise period.

Four hours after this initial haemodynamic exercise test and when resting haemodynamic indices had returned to baseline, intravenous xamoterol was given in a dose of 0.2 mg kg^{-1} and resting haemodynamic data recorded 15 min later. The exercise test was then repeated using the same protocol and haemodynamic measurements made as above.

Blood for determination of plasma noradrenaline concentrations was taken at rest and at maximum exercise both before and after intravenous xamoterol.

Statistical methods

The results were analysed using Student's *t*-test for paired observations. All results are expressed as means ± s.e. mean and a P value of < 0.05 was considered indicative of a statistically significant difference.

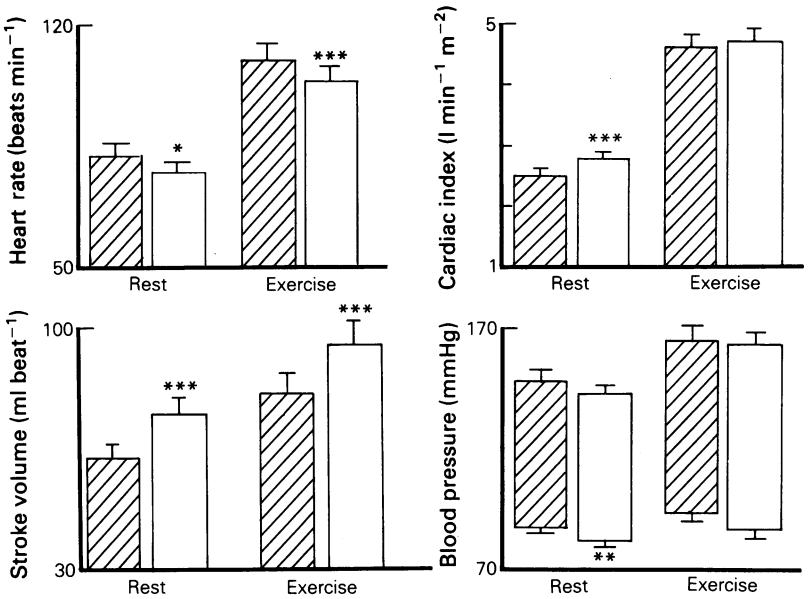

Figure 1 Effects (mean ± s.e. mean) of i.v. xamoterol on heart rate, cardiac index, stroke volume and blood pressure. ▨ pre-xamoterol, □ post-xamoterol. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Results

The effects of intravenous xamoterol on resting and exercise haemodynamics are shown in Figures 1, 2 and 3 and Tables 1 and 2.

Resting haemodynamics

Xamoterol caused a small fall in resting heart rate from 78 ± 3 to 74 ± 2 beats min^{-1} ($P < 0.05$). There was a significant improvement in resting cardiac index from 2.5 ± 0.15 to 2.8 ± 0.14 l min^{-1} m^{-2} ($P < 0.001$). This was due to an increase in stroke volume from 62 ± 4 to 75 ± 5 ml beat^{-1} ($P < 0.001$). Left ventricular stroke work index was significantly improved from 42.4 ± 3.6 to 47.7 ± 3.9 g m beat^{-1} m^{-2} ($P < 0.01$). There was a small fall in both systolic and diastolic blood pressures with only the diastolic change being significant (from 87 ± 2 to 81 ± 2 mmHg, $P < 0.01$). Systemic vascular resistance was significantly reduced from 1990 ± 141 to 1669 ± 112 dyn s^{-1} cm^5 ($P < 0.01$). Similarly, pulmonary vascular resistance fell from 428 ± 45 to 375 ± 34 dyn s^{-1} cm^5 ($P < 0.05$). Resting double product was lowered by approximately 10% due to small falls in both heart rate and systolic blood pressure. There was no significant change in pulmonary artery wedge pressure, which was initially 13.7 ± 1.5 mmHg. The mean resting ejection fraction was 35.2 ± 2.9% and this was unchanged following xamoterol.

Exercise haemodynamics

Intravenous xamoterol caused a significant attenuation in the expected increases in exercise heart rate. The mean exercise heart rate before treatment was 112 ± 4 beats min^{-1} and following xamoterol was 97 ± 3 beats min^{-1} ($P < 0.001$). However, the increase in cardiac output on exercise was unimpaired, due to maintenance on exercise of the improved stroke volume seen at rest. At maximal exercise, stroke volume rose significantly from 81 ± 6 to 97 ± 7 ml beat^{-1} ($P < 0.001$). Similarly, normal blood pressure responses to exercise occurred, and there were no significant changes in systemic vascular resistance, pulmonary artery wedge pressure or ejection fraction.

Exercise double product was significantly reduced (from 1864 ± 92 to 1599 ± 76 mmHg min^{-1} × 10) accompanied by a 10% increase in exercise time, although this change did not reach statistical significance ($P = 0.06$).

Noradrenaline levels

There was no significant change in resting (450 ± 46 pg ml^{-1} compared with 499 ± 54 pg ml^{-1}) or

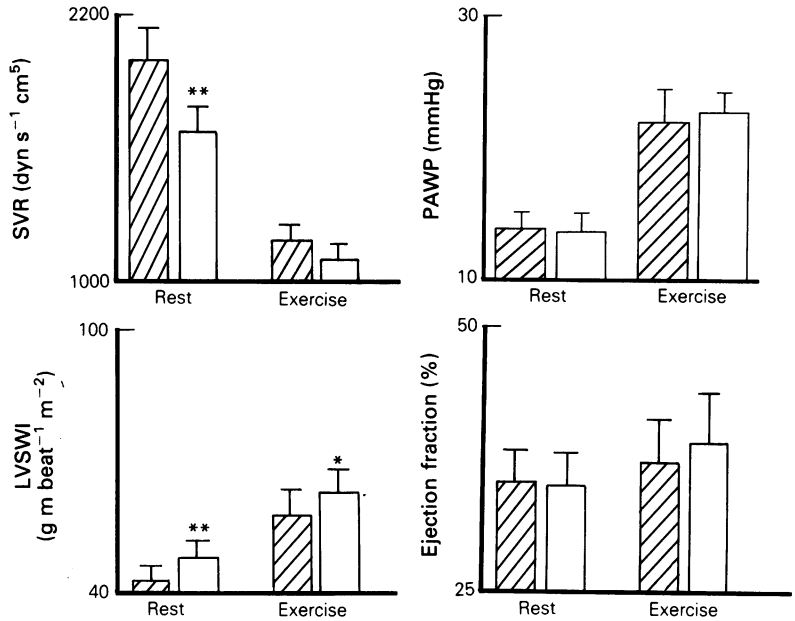

Figure 2 Effects (mean ± s.e. mean) of i.v. xamoterol on systemic vascular resistance, pulmonary artery wedge pressure, left ventricular stroke work index and ejection fraction. ▨ pre-xamoterol, □ post-xamoterol. $*P < 0.05$, $**P < 0.01$.

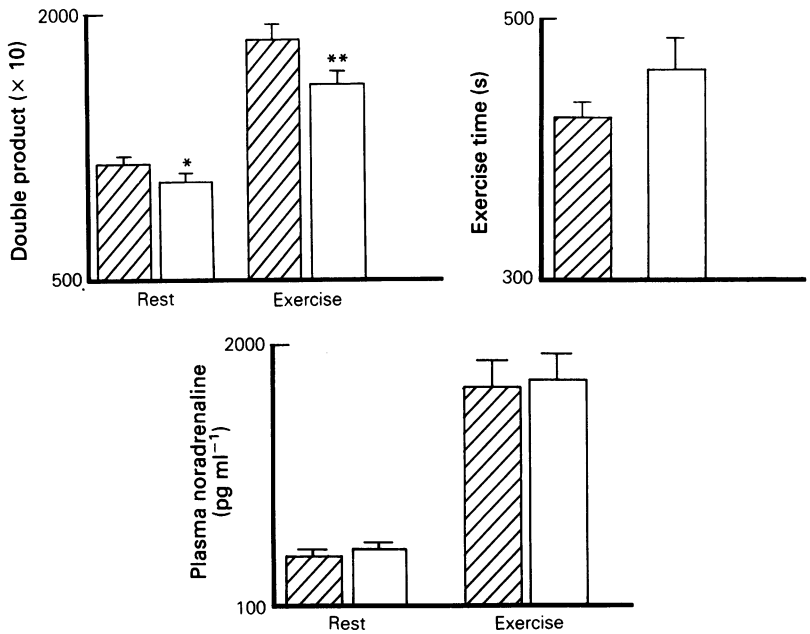

Figure 3 Effects (mean ± s.e. mean) of i.v. xamoterol on double product, exercise time and plasma noradrenaline, ▨ pre-xamoterol, □ post-xamoterol. $*P < 0.05$, $**P < 0.01$.

Table 1 Effects of intravenous xamoterol on resting haemodynamics

	Pre	*Post*	P *value*
HR (beats min^{-1})	78 ± 3	74 ± 2	< 0.05
CI (l min^{-1} m^{-2})	2.51 ± 0.15	2.80 ± 0.14	< 0.001
SV (ml $beat^{-1}$)	62 ± 4	75 ± 5	< 0.001
SBP (mmHg)	148 ± 4	142 ± 4	
DBP (mmHg)	87 ± 2	81 ± 2	< 0.01
PAWP (mmHg)	13.7 ± 1.5	13.5 ± 1.5	
SVR (dyn s^{-1} cm^5)	1990 ± 141	1669 ± 112	< 0.01
PVR (dyn s^{-1} cm^5)	428 ± 45	375 ± 34	< 0.05
LVSWI (g m $beat^{-1}$ m^{-2})	42.4 ± 3.6	47.7 ± 3.9	< 0.01
DP (mmHg min^{-1} × 10)	1146 ± 46	1051 ± 41	< 0.05
EF (%)	35.2 ± 2.9	35.0 ± 3.0	

Table 2 Effects of intravenous xamoterol on exercise haemodynamics

	Pre	*Post*	P *value*
HR (beats min^{-1})	112 ± 4	97 ± 3	< 0.001
CI (l min^{-1} m^{-2})	4.61 ± 0.27	4.70 ± 0.27	
SV (ml $beat^{-1}$)	81 ± 6	95 ± 7	< 0.001
SBP (mmHg)	166 ± 6	164 ± 5	
DBP (mmHg)	93 ± 2	88 ± 3	
PAWP (mmHg)	22 ± 2	23 ± 2	
SVR (dyn s^{-1} cm^5)	1178 ± 78	1095 ± 65	
PVR (dyn s^{-1} cm^5)	392 ± 51	401 ± 44	
LVSWI (g m $beat^{-1}$ m^{-2})	56.6 ± 5.6	62.3 ± 5.3	< 0.05
DP (mmHg min^{-1} × 10)	1864 ± 92	1599 ± 76	< 0.01
EF (%)	37.0 ± 4.0	39.2 ± 4.5	

maximal exercise (1671 ± 198 pg ml^{-1} compared with 1727 ± 201 pg ml^{-1}) levels of noradrenaline before and after the administration of intravenous xamoterol.

Discussion

Xamoterol improves cardiac performance at rest and on exercise. The positive inotropic effects at rest are consistent with the drug acting predominantly as a β-adrenoceptor agonist when sympathetic tone is relatively low. The main effects seen were an increase in cardiac output due to enhanced stroke volume, and an improvement in left ventricular stroke work index. Xamoterol has no direct vasodilator properties (Nuttall & Snow, 1982; McCaffrey *et al.*, 1988) and the observed fall in systemic vascular resistance was probably secondary and occurred reflexly due to the higher cardiac output. This may also account for the small fall in resting diastolic blood pressure.

The reduction in exercise heart rate is consistent with xamoterol acting mainly as a β-adrenoceptor antagonist when sympathetic tone is increased. However, the beneficial effects on heart rate were not associated with any concomitant reduction in cardiac output or blood pressure response to exercise. The ability to exercise at lower heart rates but with unimpaired increases in cardiac index and arterial pressure was due to a maintenance of the improvement in stroke volume seen at rest. At any given heart rate, stroke volume was greater following xamoterol (Figure 4). Also, left ventricular stroke work index was higher at any given filling pressure (Figure 5). The attenuation in exercise heart rate, allowing patients to exercise longer and with lower double products, is of particular importance in patients with heart failure due to ischaemic heart disease.

The degree of observed change following xamoterol, especially regarding the effects on heart rate, are dependent on the background level of sympathetic drive. In patients with mild heart failure and relatively low sympathetic activity, the β-adrenoceptor agonist property is more in evidence, and will result in an increase in resting heart rate. In other patients with more severe heart failure and greater degrees of left ventricular impairment, sympathetic tone will be higher and the β-adrenoceptor antagonist

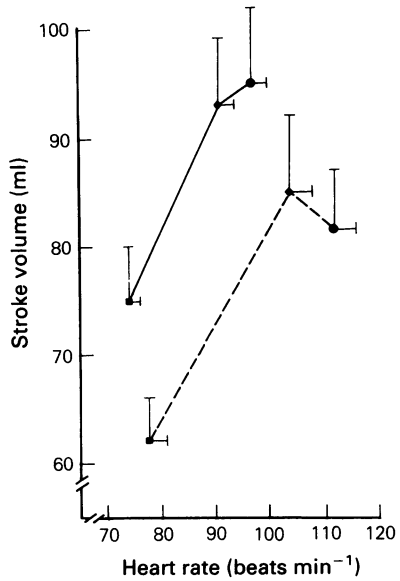

Figure 4 Stroke volume *vs* heart rate: effects of i.v. xamoterol (mean ± s.e. mean) --- pre-xamoterol, —— post-xamoterol, ■ rest, ◆ 50 watts, ● maximum exercise.

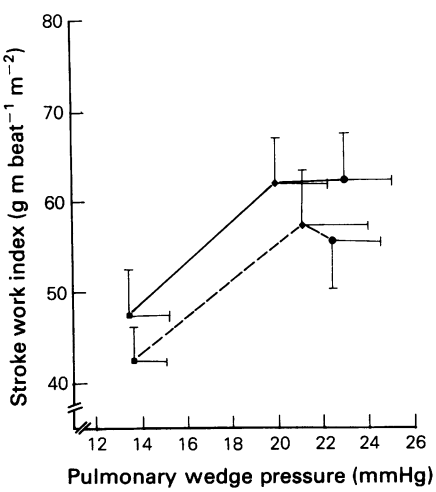

Figure 5 Left ventricular stroke work index *vs* pulmonary artery wedge pressure: effects of acute i.v. xamoterol (mean ± s.e. mean). --- pre-xamoterol, —— post-xamoterol, ■ rest, ◆ 50 watts, ● maximum exercise.

property will predominate, leading to a reduction in heart rate. The crossover point between agonist and antagonist effects has been shown to occur at a plasma noradrenaline concentration of between 400 and 500 pg ml^{-1} (Sato *et al.*, 1987). The mean plasma noradrenaline level in the study reported here was 450 ± 46 pg ml^{-1} (± s.e. mean) falling midway in this transition zone, and there was a small fall in resting heart rate. A number of other studies have reported the effects of intravenous xamoterol on resting and exercise haemodynamics (Detry *et al.*, 1983, 1984; Rousseau *et al.*, 1983; Ikaheimo & Takkunen, 1984; Simonsen, 1984; Molajo & Bennett, 1985; Amende *et al.*, 1986; Bhatia *et al.*, 1986; Watanabe *et al.*, 1986; Kayanakis & Snow, 1987; Sato *et al.*, 1987). Although these studies contained small numbers of patients with varying degrees of left ventricular impairment, and ejection fractions ranging from 9 to 74%, consistent, significant changes were apparent. Resting heart rate was unaltered or increased by approximately 10%. This was accompanied by similar changes in systolic blood pressure. Resting cardiac output was improved by up to 40%, although generally the level was between 15 and 20% as observed in this investigation. This was due to improved stroke volume and was associated with a 15 to 20% reflex fall in systemic vascular resistance. Whether left ventricular stroke work index or left ventricular dP/dt_{max} was used as an index of contractility, this was improved following intravenous xamoterol. In this study, left ventricular stroke work index increased by 11% and in other studies, left ventricular dP/dt_{max} improved by 17 to 46% (Rousseau *et al.*, 1983; Ikaheimo & Takkunen, 1984; Simonsen, 1984; Amende *et al.*, 1986). Pulmonary artery wedge pressure was reduced by up to one-third. No change was observed in resting pulmonary artery wedge pressure in this study; this may be a result of the relatively large doses of oral diuretics received by this group of patients.

The acute effects of xamoterol on exercise haemodynamics are less well documented (Detry *et al.*, 1983, 1984; Watanabe *et al.*, 1986; Sato *et al.*, 1987). However, in four other studies, exercise heart rate was uniformly lowered by 10 to 15%, as in this study. Only one investigation (Detry *et al.*, 1983) has demonstrated a small although significant reduction in exercise cardiac output and systolic blood pressure. Overall, despite the reduction in heart rate, exercise cardiac output and blood pressure levels are unimpaired. Double product is reduced due to the attenuation in exercise heart rate.

This haemodynamic profile of acute improvements in cardiac function at rest and on exercise with intravenous xamoterol is potentially of major benefit in the treatment of patients with heart failure. However, it is essential that these improvements are maintained on long-term treatment and that tachyphylaxis, as seen with other inotropic regimens, does not occur. To

date, some chronic effects of oral xamoterol have been described which show long-term improvements in functional class (Watanabe *et al.*, 1986), exercise tolerance (Ikaheimo & Takkunen, 1984; Molajo & Bennett, 1985; Watanabe *et al.*, 1986; Kayanakis & Snow, 1987), cardiac output (Kayanakis & Snow, 1987), pulmonary artery wedge pressure and ejection fraction (Watanabe *et al.*, 1986). No tachyphylaxis has been described, and there may be a long-term beneficial adaptation in cardiac function (Watanabe *et al.*, 1986).

In conclusion, xamoterol produces acute improvements in left ventricular function and haemodynamics at rest and on exercise due to a combination of agonist and antagonist effects at the β_1-adrenoceptor. At rest, when sympathetic tone is relatively low, it acts primarily as an agonist, enhancing cardiac performance. On exercise, when sympathetic tone is high, its antagonist action reduces heart rate. In the long-term, these beneficial effects are maintained, and tachyphylaxis, plaguing many other therapeutic regimens in heart failure, does not appear to occur. The ability to modulate the cardiac responses to variations in sympathetic tone is of major therapeutic importance in treating patients with heart failure, particularly in the light of knowledge regarding β-adrenoceptor function.

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