Improvement of Left Ventricular Contractility and Relaxation With the β_1-Adrenergic Receptor Partial Agonist Xamoterol at Rest and During Exercise in Patients With Postinfarction Left Ventricular Dysfunction

A Placebo-Controlled Randomized Trial

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A new cardioselective β_1-adrenergic receptor agonist xamoterol (Corwin) has been developed for the treatment of heart failure. To study the acute hemodynamic effects of xamoterol, 24 patients, 39–70 years old, with mild-to-moderate postinfarction left ventricular dysfunction entered a double-blind, between-patient comparison of a single 5-minute intravenous infusion of xamoterol (0.2 mg/kg) and placebo. The acute hemodynamic effects of xamoterol were measured at rest and during two multistaged symptom-limited supine bicycle exercise tests (Ex-T), a control Ex-T followed by an Ex-T with either xamoterol or placebo. Compared with placebo, xamoterol significantly increased left ventricular contractility (V_{max} and positive [+] dP/dt) and enhanced relaxation (dP/dt− and time constant relaxation) at rest and at the 25% and 50% levels of maximum exercise. The heart rate, the frequency and time to onset of anginal symptoms, the magnitude of exercise-induced ST segment depression, the left ventricular end-diastolic and peak systolic pressures, the mean pulmonary artery pressures, the cardiac index, the left ventricular stroke-work index, and the epinephrine and norepinephrine plasma levels at rest and during exercise did not differ significantly between placebo and xamoterol groups. Thus, xamoterol can be a useful addition for the treatment of left ventricular dysfunction because of long-term ischemic heart disease. (*Circulation* 1990;81(suppl III):III-99–III-106)

Xamoterol (Corwin; ICI 118.587) is a cardioselective β_1-adrenergic receptor partial agonist.[1–21] The overall effect of a partial agonist at any one time depends on the prevailing level of sympathetic activity. Xamoterol not only stimulates the heart effectively but not excessively when intrinsic sympathetic activity is low, but it also acts as a β-antagonist when sympathetic tone is high.[2,3,11,14–16,21] Previous studies demonstrated positive inotropism in animals,[1–3,12] normal volunteers,[4,13,14] patients with myocardial ischemia and regional wall-motion abnormalities,[5–9,16,19] and individuals with mild-to-moderate congestive heart failure.[10,18,20–22]

This inherent action of the drug would be beneficial in the treatment of patients with ischemic heart disease and compromised left ventricular (LV) function. The purpose of the present double-blind, randomized study was to assess the acute effects of xamoterol on hemodynamic variables at rest and during supine exercise in patients with angina pectoris and LV dysfunction because of a previous myocardial infarction.

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Methods

Patient Selection

Twenty-four men were studied (mean age, 58.3 years; range, 39–70 years). The criteria for inclusion were 1) stable angina pectoris of New York Heart Association (NYHA) class II or III, 2) LV dysfunction because of previous myocardial infarction, which had not occurred within 3 months of the study, 3) stable sinus rhythm, 4) ability to perform a symptom-limited exercise test, and 5) no clinical signs of heart failure at rest. Eighteen patients were classified according to NYHA functional class II and six

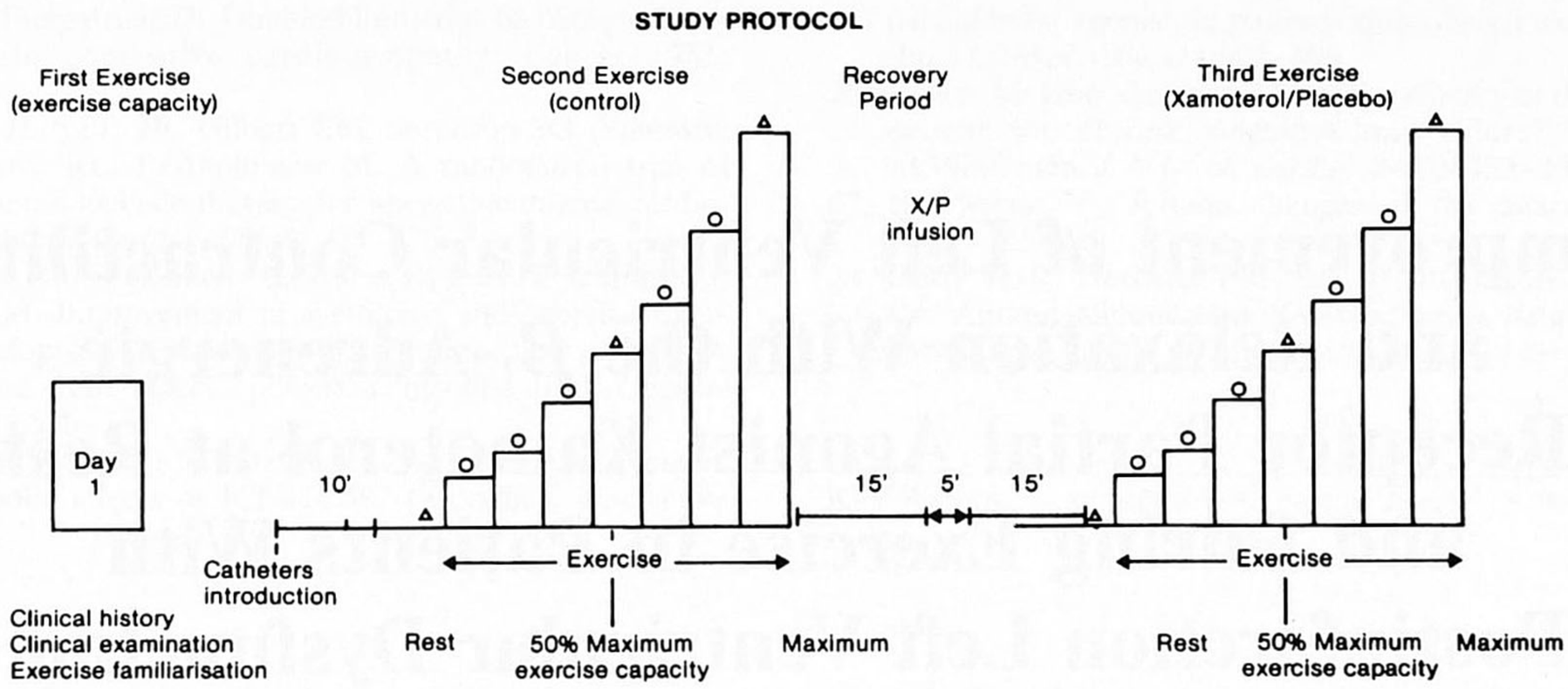

FIGURE 1. *Design of the study.* (○), *Measurement of left ventricular pressures and derivatives* (V_{max}, V_{ce}, *[+] dP/dt, [−] dP/dt,* T_1), *heart rate, mean pulmonary artery pressure, and changes of ST segment;* (△), *measurements of* ○, *cardiac output, and plasma levels of catecholamines.*

patients according to class III. The previous myocardial infarction site was located in the anterolateral wall in 19 patients, in the inferior posterior wall in seven patients, and in the anterolateral posterior wall in three patients.

All patients were catheterized for evaluation of a revascularization procedure (bypass surgery or percutaneous transluminal coronary angioplasty) because of unsatisfactory response to pharmacological treatment. Any patient receiving a β-blocker had it withdrawn at least 72 hours before the study, and other cardioactive medication (e.g., calcium antagonists, diuretics, and vasodilators) with the exception of short-acting nitrates were withdrawn 48 hours before the study. LV ejection fraction as assessed by left ventriculography was in the range of 18–57% (mean, 48%). Coronary artery disease was defined as a 70% diameter reduction of one or more major coronary arteries. Coronary angiography disclosed one-vessel disease in six patients, two-vessel disease in nine patients, and three-vessel disease in nine patients. The study was carefully explained to all patients, and all gave their informed consent.

Protocol

The design of this study was a double-blind, randomized, between-group comparison of a single intravenous infusion of xamoterol 0.2 mg/kg and placebo.

One day before the study, all patients performed a continuous multistage bicycle exercise test in the semisupine position (30°) to determine their symptom-limited exercise capacity and to familiarize them with the exercise procedure (Figure 1).

All three exercise procedures, the first (1 day before the study), the second (control), and the third (xamoterol/placebo) (on the day of the study), were performed according to the following protocol: The initial workload was 10 W for 1 minute, and this was increased every minute in 10-W increments to maximal exercise capacity determined by the onset of limiting symptoms such as angina pectoris, dyspnea, or exhaustion. Each patient served as his own control because the results obtained during the control exercise were compared with those obtained during xamoterol or placebo exercise. The maximal exercise capacity was individualized per patient but was similar in the control and randomized treatment exercise test.

On the study day, patients were brought to the laboratory in the fasting state. Before the study, a thermodilution catheter was inserted through the forearm vein into the pulmonary artery to monitor pulmonary artery pressure and to measure cardiac output by means of the thermodilution technique. Through the brachial artery, a micromanometer-tipped 8F pigtail catheter (Millar Instruments, Inc., Houston, Texas) was advanced into the LV. Zero reference was taken at the midaxillary level while the patient was in the supine position. The electrocardiogram was monitored continuously throughout the exercise procedure. ST segment changes at rest and during exercise were calculated from the X, Y, and Z leads by an earlier described method with use of an automated computer system.[23]

After introduction of the catheter and attachment of the electrodes for recording of electrocardiograms, the patients were allowed to rest for 10 minutes. Resting hemodynamic variables were then measured (Figure 1), and arterial blood was withdrawn to determine plasma epinephrine and norepinephrine levels. A supine multistage bicycle exercise test was performed, and during the last 20 seconds of each stage, all hemodynamic variables were collected and calculated on-line except for the cardiac output CO and catecholamine levels, which were measured (besides at rest) at the 50% level of the maximum predetermined exercise level and at maximum exercise.

After completion of the control exercise, patients were allowed to rest for at least 15 minutes or until recovery of the majority of the measured hemodynamic variables to precontrol exercise levels. Then,

either 0.2 mg/kg xamoterol or an equivalent volume of placebo was administered as an intravenous infusion in saline for 5 minutes. Fifteen minutes after the end of infusion of placebo or xamoterol, all hemodynamic variables, catecholamine levels, and xamoterol levels were measured, and the exercise procedure was repeated including the same measurements. After completion of the posttreatment exercise test, the patient underwent LV angiography and coronary angiography.

Analysis of Left Ventricular Pressure-Derived Indexes

LV pressure was digitized at 250 samples/sec. Peak LV pressure, minimal diastolic and end-diastolic LV pressures, peak positive (LVPK [+]dP/dt) and peak negative (LVPK [−]dP/dt) pressures expressed as the instantaneous first derivative of the rate of increase or decay of LV pressure, the relation between dP/dt pressure and total pressure linearly extrapolated to pressure equals zero (V_{max}) (LVV_{max} TOTP), and the peak velocity of contractile element (V_{ce}) ($LVPKV_{ce}$) were computed on-line after data acquisition of 20 seconds.

For off-line analysis of LV pressure relaxation, an updated version of the beat-to-beat program described previously[24] was used with the following definitions: 1) pressure at the beginning of isovolumic relaxation (P_b) is the pressure at the point at which dP/dt is minimal (maximum −dP/dt) and 2) pressure at the end of isovolumic relaxation (P_e) is the pressure less than or equal to the previous end-diastolic pressure but no less than 1 mm Hg. Although it is possible that the latter definition can result in P_e being measured just after mitral valve opening, estimation of the time constants by more stringent criteria such as end-diastolic pressure plus 10 mm Hg did not result in a significantly better estimation and failed to measure pressure during high heart rates. Two techniques were implemented for the off-line beat-to-beat calculation of the relaxation parameters.[25,26] All required a minimum of eight samples (over 32 msec) between P_b and P_e. No other computations were attempted.

Semilogarithmic model. The semilogarithmic model used was $P(t)=P_o e^{-t/T}$, where P is pressure, P_o is equivalent to P_b when a true exponential decay is present starting from the time of peak −dP/dt, and the P_o and T parameters were estimated from a linear least-squares fit on ln, in $P=(-t/T)+\ln \cdot P_o$. Additionally, a biexponential fit for isovolumic relaxation was determined, characterized by the two exponential time constants, the fit for the first 40 msec (T_1) and the fit after the first 40 msec (T_2).[26]

Hemodynamic Measurements

Pulmonary artery pressures were recorded directly and expressed as systolic, diastolic, and mean pressures. Cardiac output (CO) was determined by thermodilution. The following hemodynamic variables were calculated: cardiac index (CI)=CO/body surface area (l/min/m^2), stroke-volume index (SVI)=CI/HR (ml/beats/m^2), and stroke-work index (SWI)=SVI · (LVSP−LVEDP) · 0.0136 (g-m/m^2), where HR is heart rate, LVSP is left ventricular systolic pressure, and LVEDP is left ventricular end-diastolic pressure.

Catecholamine Measurements

Epinephrine and norepinephrine were measured in duplicate with the radioenzymatic technique of Peuler and Johnson[27] with slight modifications. Normal basal values in our laboratory are as follows: epinephrine, 10–110 pg/ml; norepinephrine, 100–500 pg/ml.

Statistical Analysis

The data assessed at rest and at 25%, 50%, 75%, and 100% of maximal exercise have been analyzed by a repeated-measures three-way analysis of covariance. The repeated factor in the analysis was the level of exercise, and the analysis allowed for the effects of patients and treatments. The covariate was the pretreatment response at each level of exercise. Five exercise levels were used, that is, rest, 25%, 50%, 75%, and 100% of maximum exercise.

Where a significant treatment by exercise interaction was found (*F* test), the effect of treatment was examined at each level of exercise. Because this required five significance tests for each variable, there was a danger of declaring one or more false-positive results. For a treatment effect to be considered significant, the *p* value had to be less than 0.05.

The data of CI, SVI, SWI, and catecholamines were collected at three levels of exercise only: at rest and at 50% and 100% of maximum exercise. They have been analyzed separately at each level of exercise by a one-way analysis of covariance. This allowed for the effects of treatment, and the covariate was the pretreatment response at the appropriate level of exercise. The significance of the treatment effect was assessed by the *F* test.

Results

No complications occurred because of the study, and the drug caused no side effects. The effects of xamoterol on hemodynamic variables, ST segment changes, isovolumic systolic and diastolic LV indexes, and epinephrine and norepinephrine plasma levels are tabulated in Tables 1–4 and are shown in Figures 2–5.

For LVPK +dP/dt, there were significant treatment effects at rest ($p<0.001$), at 25% ($p<0.001$), and at 50% ($p<0.05$) maximum exercise. In each case, the least-square mean was raised in the xamoterol group as compared with the placebo group. For $LVPKV_{ce}$, there were significant treatment effects at 25% ($p<0.001$) and 50% ($p<0.006$) maximum exercise. The least-square mean was raised in the xamoterol group as compared with the placebo group in both cases. For LVV_{max} TOTP, there were significant treatment effects at rest ($p<0.05$) and at 25% ($p<0.001$) and 50% maximum exercise ($p<0.001$). In each case, the least-square mean was raised in the xamoterol group as compared with the placebo group. For LVPK −dP/dt, there were significant treatment effects at rest ($p<0.0001$) and at 25%

TABLE 1. Comparison of Hemodynamic Variables and ST Segment Changes at Rest and at Different Levels of Exercise Between Xamoterol or Placebo in 24 Randomized Patients With Postinfarction Left Ventricular Dysfunction

	Heart rate (beats/min)		LV end-diastolic pressure (mm Hg)		LV systolic peak pressure (mm Hg)		Mean pulmonary pressure (mm Hg)		ST segment change (mm)	
Exercise level	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol
Rest	75±3	83±3	13±1	12±1	140±4	146±4	13±1	14±1	−0.1±0.1	−0.2±0.1
25%	93±2	99±2	21±2	18±2	148±2	148±2	23±1	23±2	−0.2±0.1	−0.2±0.1
50%	100±2	101±2	22±2	20±2	152±2	147±2	29±2	26±2	−0.4±0.2	−0.5±0.2
75%	110±2	106±2	22±1	21±1	155±2	154±3	28±1	27±2	−0.6±0.2	−0.7±0.2
100%	120±3	119±3	26±2	26±2	155±3	159±3	33±2	36±2	−0.8±0.3	−0.8±0.3

LV, left ventricular.

maximum exercise ($p<0.01$). In both cases, the least-square mean was raised in the xamoterol group as compared with the placebo group. For T_1, there were significant treatment effects at rest ($p<0.005$) and at 50% maximum exercise ($p<0.01$). At rest and 50% maximum exercise, the least-square mean was lowered in the xamoterol group as compared with the placebo group.

The HR at rest was raised in the xamoterol group as compared with the placebo group; however, this difference was not statistically significant. For LV end-diastolic and peak systolic pressure, mean pulmonary artery pressure, CI, SVI, and LVSWI, and norepinephrine and epinephrine levels, there was no significant treatment by exercise interaction. Also, for the frequency and time to onset of anginal symptoms during exercise (513 vs. 495 seconds) and exercise-induced ST segment changes, there was no significant interaction.

Discussion

In recent years, the clinical indications for β-adrenergic receptor partial agonists have been largely determined by their degree of agonism. Drugs with low agonist activity are efficient antianginal drugs, but in patients with LV dysfunction, these drugs can provoke dyspnea because of their negative inotropic effect.[28,29] Drugs with a high agonist activity are effective in the treatment of cardiac failure.[30,31] Because of their positive inotropic effect, however, they will increase myocardial oxygen consumption, which can impair myocardial metabolism and produce deleterious effects. To reduce these unwanted effects while retaining the anti-ischemic and hemodynamic benefits, an intermediate approach has been the development of a β_1-partial agonist that stabilizes β_1-adrenergic receptor activity at about half maximum, thereby avoiding the adverse hemodynamic consequences of inadequate or excessive endogenous stimulation.[3] Xamoterol, a β_1-selective adrenergic receptor partial agonist, has one effect that varies with the level of sympathetic tone; it is agonistic at low and antagonistic at high exercise levels.[1–16,18,19,21] Therefore, xamoterol would be beneficial in the treatment of patients with effort angina and mildly-to-moderately compromised LV function such as

TABLE 2. Comparison of Left Ventricular Pressure-Derived Isovolumic Systolic and Diastolic Variables at Rest and at Different Levels of Exercise Between Xamoterol and Placebo in 24 Randomized Patients With Postinfarction Left Ventricular Dysfunction

	$LVPKV_{ce}$ (sec)		LVV_{max} (sec)		+dP/dt (mm Hg/sec)		−dP/dt (mm Hg/sec)		T_1 (msec)	
Exercise level	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol
Rest	43±2	48±2	51±3	61±3*	1568±85	2083±85‡	1631±56	1949±56‡	54±2	45±2†
25%	36±2	48±2‡	56±2	68±2‡	1874±98	2368±98‡	1822±83	2141±83‡	45±2	40±2†
50%	37±2	46±2†	59±2	72±2‡	2104±85	2376±85†,‡	1997±78	2097±78	44±2	38±2†
75%	42±2	49±3*	66±3	70±3	2459±71	2523±78	2178±54	2317±60	38±1	36±1
100%	45±3	44±3	73±4	73±4	2833±121	2622±121	2443±111	2376±111	37±3	41±3

$LVPKV_{ce}$, peak velocity of the contractile element; LVV_{max}, V_{max} derived from total pressure, maximal velocity of the contractile element (dP/dt/P linearly extrapolated to P=0); +/−dP/dt, rate of change of pressure; T_1, time constant of relaxation (calculated for the first 40 msec).

*$p<0.05$, †$p<0.01$, ‡$p<0.001$.

TABLE 3. Comparison of Left Ventricular Ejection Variables at Rest and at Different Levels of Exercise Between Xamoterol and Placebo in 24 Randomized Patients With Postinfarction Left Ventricular Dysfunction

	Cardiac index (l/min/m²)		Stroke volume index (ml/m²)		Left ventricular stroke work index (g-m/m²)	
Exercise level	Placebo	Xamoterol	Placebo	Xamoterol	Placebo	Xamoterol
Rest	2.9±0.1	3.1±0.1	38±2	37±2	66±3	68±3
50%	4.7±0.2	4.7±0.2	46±2	45±2	75±4	76±4
100%	5.4±0.2	5.3±0.2	44±2	45±2	79±2	80±2

TABLE 4. Comparison of Plasma Norepinephrine and Epinephrine Levels

	Norepinephrine (ng/ml)		Epinephrine (ng/ml)	
Exercise level	Placebo	Xamoterol	Placebo	Xamoterol
Rest	0.27±0.02	0.29±0.02	0.07±0.01	0.07±0.01
50%	0.5±0.07	0.42±0.07	0.13±0.02	0.09±0.02
100%	0.81±0.09	0.93±0.09	0.21±0.03	0.18±0.03

Values (mean±SD) were measured at rest and during different levels of exercise in 24 patients (randomized between placebo and xamoterol groups) who had postinfarction left ventricular dysfunction.

occurs in patients with long-term postinfarction angina.

It seems that xamoterol does not affect LV function in the immediate postinfarction period in patients with mild-to-moderate heart failure.[17] This might be due to the altered sensitivity and density of β_1-adrenergic receptors of the heart in association with increased levels of circulating catecholamines in the immediate postinfarction period.[32] Furthermore, xamoterol can be harmful to patients with poor LV function who depend on high levels of sympathetic nervous system activity.[33–36] In these cases, xamoterol acts primarily as an antagonist[10,18,20] and might depress LV function even further.

Our randomized study was performed in patients who had sustained myocardial infarction more than 3 months previously. They all had effort angina and mild-to-moderate LV dysfunction. We demonstrated that xamoterol acted as an agonist at rest, that is, it was positive inotropic, and it enhanced relaxation. This effect was also demonstrable, although to a lesser degree, during low and moderate levels of exercise, and this effect virtually had disappeared at the 75% level of exercise. No significant antagonistic effect could be demonstrated at maximum exercise. This confirms earlier reports that also showed an agonistic effect at rest[1,4,5–7,9,10,13–16,18,19,21] and during mild-to-moderate levels of exercise[9,16,18,21] in humans. Because preload and afterload did not significantly change, the increase in the isovolumic pressure-derived indexes of contractility (i.e., V_{max}, PKV_{ce}, and +dP/dt) can only reflect a positive inotropic effect. Other investigators,[9,15,16,19] however, demonstrated an antagonistic effect of xamoterol at higher levels of exercise. This is probably because, in these studies, the maximum exercise level was higher than in our study. It was shown that an antagonistic effect only became apparent at the highest

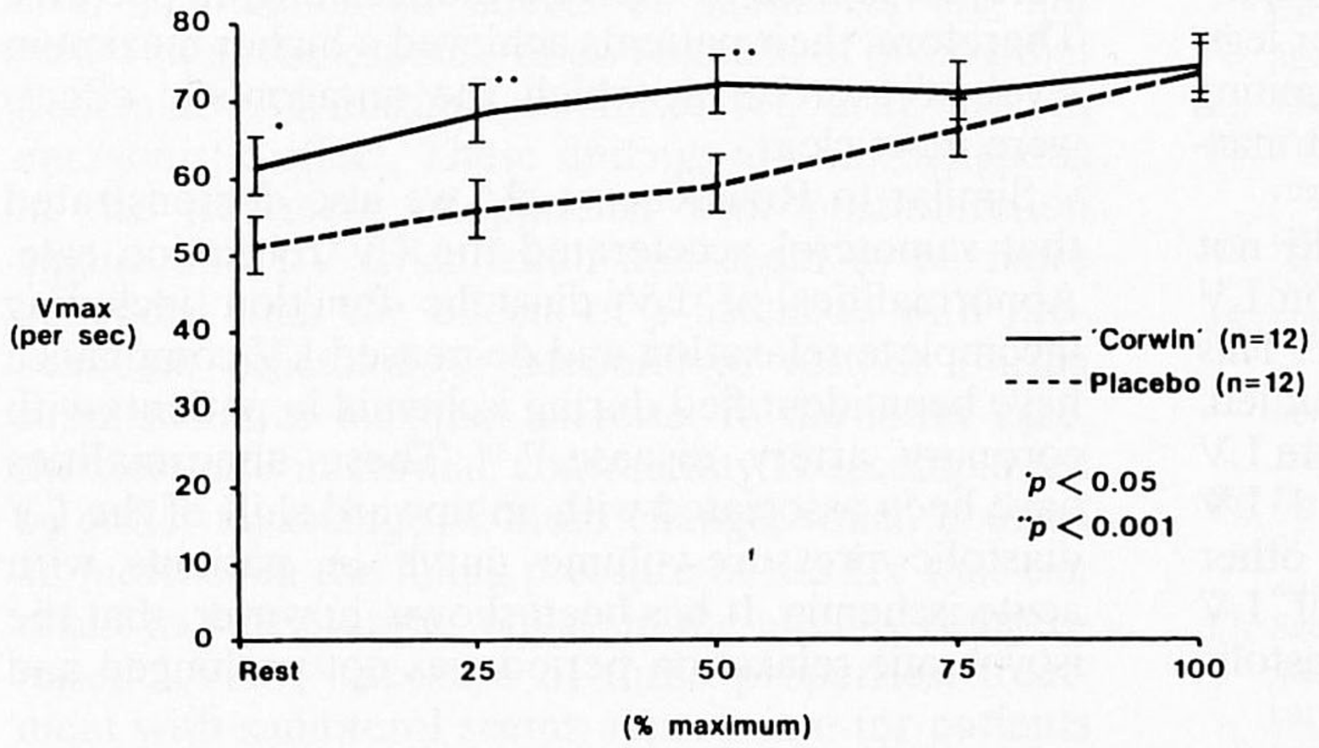

FIGURE 2. *Graph showing effects of xamoterol on V_{max} at rest and during various levels of exercise. Between-group comparison of xamoterol (—) and placebo (- - -). Values are given as least-square means. Standard error bars are given for each mean.*

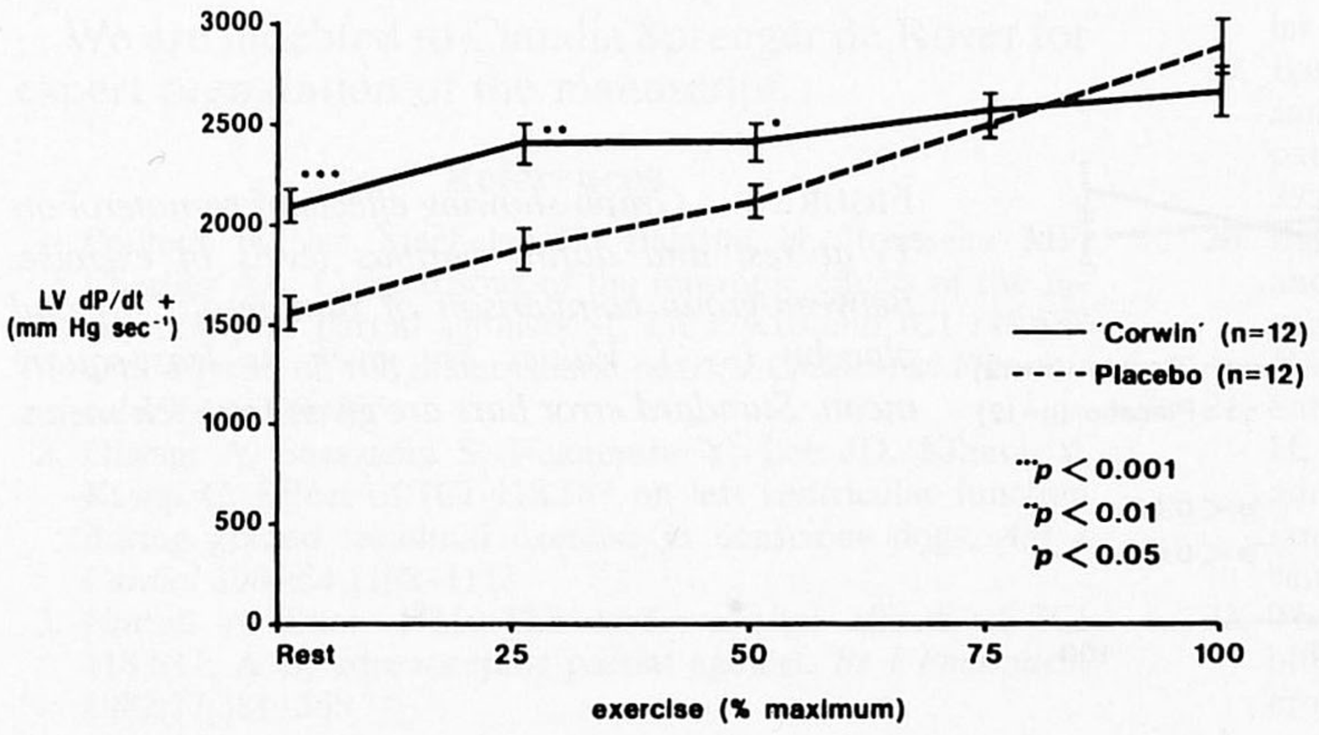

FIGURE 3. *Graph showing effects of xamoterol on +dP/dt at rest and during various levels of exercise. Between-group comparison of xamoterol (—) and placebo (- - -). Values are given as least-square mean. Standard error bars are given for each mean.*

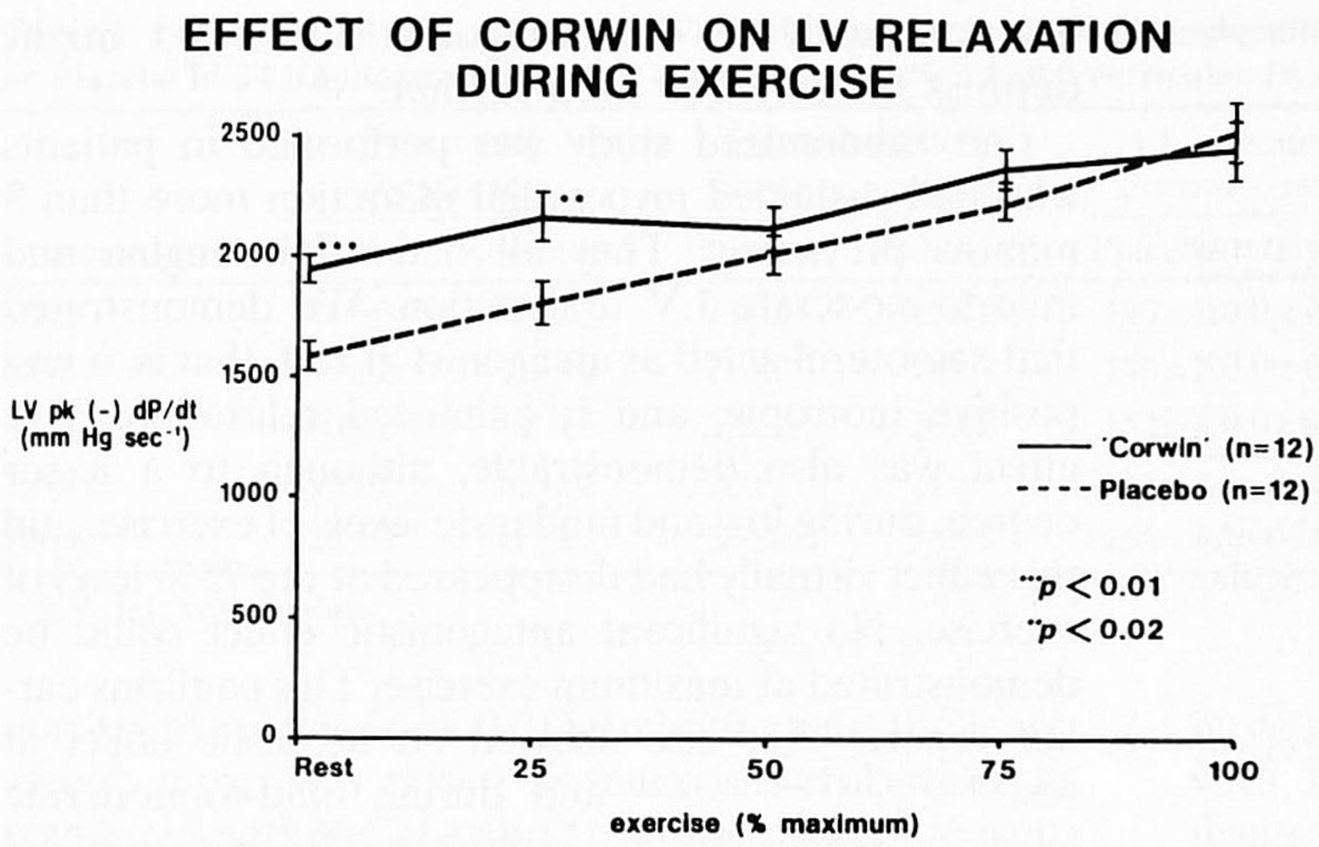

FIGURE 4. *Graph showing effects of xamoterol on −dP/dt at rest and during various levels of exercise. Between-group comparison of xamoterol (—) and placebo (- - -). Values are given as least-square mean. Standard error bars are given for each mean.*

levels of exercise, at HRs of 130–150 beats/min.[15,16,19,21] In our study, the maximum heart rate achieved was about 120 beats/min, even though we also used a maximum symptom-limited exercise test. There are two reasons for the apparent difference in achieved maximum HR. First, our study group consisted of patients with exercise-limiting effort angina and (not as in the other studies of patients without angina) with mild-to-moderate functional cardiac impairment, or volunteers. Second, our patients performed a supine exercise test, not the upright exercise bicycle test in the other studies.[15,16,19] In the supine position, the exercise capacity is often limited by muscle fatigue of the upper legs, even before chest pain or dyspnea becomes the limiting factor, and thus, the cardiovascular system is not maximally tested.

Unlike most other studies,[1,5,7,18,21] we could not demonstrate a significant effect of xamoterol on LV end-diastolic pressure at rest or during exercise. This might be explained by differences in patients studied. Our patients appeared to have mild-to-moderate LV dysfunction and normal or slightly increased LV end-diastolic pressures. This is in contrast to other patients studied who had higher degrees of LV dysfunction and higher baseline LV end-diastolic pressures. Also, the position of the patient during supine exercise, which increases filling pressures, might have attenuated the potential beneficial effect of xamoterol on LV end-diastolic pressure. In contrast with Sato et al,[21] we could not demonstrate a difference in effect of xamoterol on the levels of plasma norepinephrine or demonstrate the dual agonist-antagonist effect in relation to plasma norepinephrine level with a cross-over point at 400–500 pg/ml. This is explained by the fact that they studied patients with mild-to-moderate LV dysfunction who were not limited by exercise-induced angina pectoris. Therefore, their patients achieved a higher maximum level of exercise at which the antagonistic effects were most clear.

Similar to Rousseau et al,[6] we also demonstrated that xamoterol accelerated the LV relaxation rate. Abnormalities of LV diastolic function including incomplete relaxation and decreased LV compliance have been identified during ischemia in patients with coronary artery disease.[37,38] These abnormalities have been associated with an upward shift of the LV diastolic pressure-volume curve in patients with acute ischemia. It has been shown, however, that the isovolumic relaxation period was not prolonged and

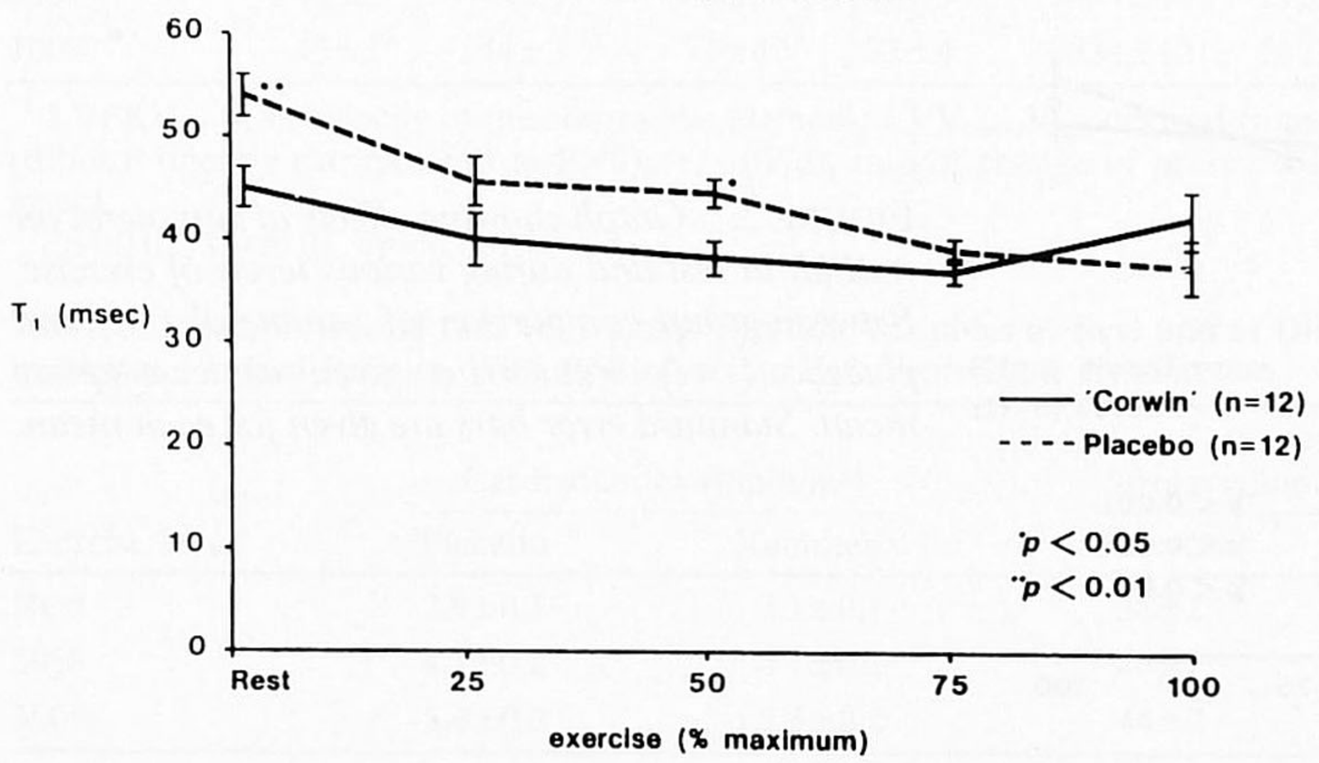

FIGURE 5. *Graph showing effects of xamoterol on T_1 at rest and during various levels of exercise. Between-group comparison of xamoterol (—) and placebo (- - -). Values are given as least-square mean. Standard error bars are given for each mean.*

the filling period was not abbreviated because of the early opening of the mitral valve at higher levels of LV pressure caused by compensatory action of the left atrium with an increase in left atrial pressure. Xamoterol might exert a beneficial effect by direct improvement of LV relaxation or indirectly by augmentation of the force of the atrial contraction.[39] Enhancement of relaxation in patients with postinfarction angina can be beneficial and can improve coronary perfusion, particularly in the subendocardial layers.

Although xamoterol had positive inotropic effects and enhanced relaxation at rest and during exercise, xamoterol did not significantly influence preload, afterload, or LVSWI, and also did not affect the magnitude of exercise-induced ST segment depression or the frequency and time to onset of anginal symptoms during exercise. In our study, xamoterol improved LV systolic and diastolic function. These effects were achieved without the induction of increased myocardial ischemia because the extent of exercise-induced ischemia appeared similar in both the placebo and xamoterol groups.

Thus, from this study and other reports,[4–7,9,13–16,18,19,21] it is evident that xamoterol exerts a moderately strong inotropic effect and accelerates relaxation at rest, which is maintained during mild-to-moderate exercise and virtually disappears at submaximal exercise. The beneficial effects of xamoterol are not achieved at the expense of an increase of myocardial ischemia.[6] At maximal exercise, the drug has an antagonistic effect. These findings are advantageous in the treatment of patients with postinfarction angina and LV dysfunction and seem to be more beneficial than the effects of β-blockade with propranolol, practolol, or atenolol at rest or during submaximal or maximal exercise. In the latter case, the decrease in cardiac contractility is accompanied by either no change or more change, which is often an increase in the filling pressure of the LV that can result in a deleterious effect on the already compromised LV.[40–45] Because of these properties, treatment with xamoterol seems appropriate for patients with postinfarction LV dysfunction.

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KEY WORDS • β_1-adrenergic receptor partial agonist • left ventricular dysfunction • left ventricular contractility • left ventricular relaxation