Long-term effects of xamoterol on left ventricular diastolic function and late remodeling: a study in patients with anterior myocardial infarction and single-vessel disease

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ABSTRACT The purpose of the study was to examine whether the prolonged administration of the β1-adrenoceptor partial agonist xamoterol could improve left ventricular diastolic function and affect the global remodeling process of the left ventricle after anterior myocardial infarction. In 22 patients with anterior myocardial infarction and single-vessel disease, left ventricular angiography (+ Millar) was performed under basal conditions 1 to 2 months after the acute myocardial infarction. Eight patients were then treated for 3 months with placebo and 14 were treated with xamoterol (200 mg bid) and a second left ventricular angiographic study was performed. Angiograms were digitized frame by frame to derive the diastolic pressure-volume relationship and to compute wall stress. An index of elastic myocardial stiffness was computed at a constant stress of 30 kdynes/cm² before and after treatment. To evaluate changes in left ventricular shape, segmental areas in anterior and inferior segments were computed and compared at end-diastole and end-systole. After xamoterol, left ventricular end-diastolic pressure and mean diastolic wall stress decreased (from 24 ± 5 to 15 ± 5 mm Hg and from 57 ± 32 to 38 ± 22 kdynes/cm², respectively; both p < .01 vs baseline and vs placebo). These changes were accompanied by a downward shift in the diastolic pressure-volume relationship and by a decrease in the index of myocardial stiffness from 526 ± 270 to 371 ± 194 kdynes/cm² (p < .02). Left ventricular shape was not significantly altered by xamoterol but a significant remodeling of the left ventricular silhouette was evident at end-systole, as indicated by an improvement in the ratio (anterior segmental area/inferior segmental area) from 1.14 to 1.02 (median values; p < .025 vs baseline and vs placebo). It is concluded that impaired diastolic function after myocardial infarction is not entirely caused by fibrotic scar tissue but also by some active alterations in the function of viable myocardial areas that can be improved by therapy with xamoterol. Further studies are needed to determine whether the improvement in diastolic function and the systolic left ventricular remodeling are directly related.


RECENT STUDIES have shown that global remodeling of the left ventricle occurs immediately after infarction, involving structural changes in both infarcted and noninfarcted segments.1-6 The result of this process is a dilated left ventricle, with some degree of regional hypertrophy in noninfarcted segments and some degree of infarct expansion in the infarcted segment.3 In some instances, ventricular dilatation after myocardial infarction may continue for months,7 inducing further left ventricular dysfunction and heart failure.

According to the model proposed by McKay et al.,3 the trigger for these progressive changes in left ventricular geometry is increased diastolic wall stress. Thus, any intervention that lowers diastolic wall stress might be beneficial during the remodeling process. The intravenous administration of xamoterol (ICI 118,587, Corwin), a new β1-adrenoceptor partial agonist,8 has been shown to reduce mean diastolic wall stress in patients with a previous myocardial infarction,9 while producing only minimal changes in systolic function or myocardial oxygen uptake. Other studies confirmed that short-term dosing with xamoterol consistently reduced left ventricular filling pressure, not only at rest but also during exercise.10 Preliminary results indi-
cated that these beneficial effects on diastolic function were maintained during prolonged therapy.11

The purpose of this study was to examine whether the prolonged administration of xamoterol to patients with a previous myocardial infarction could significantly improve left ventricular diastolic function and affect the global remodeling process of the ventricle. Since other factors could influence the time course of change in left ventricular function in these patients, for example, infarct location, mitral regurgitation, and the presence of multiple-vessel disease, only patients with a recent transmural anterior myocardial infarction and single-vessel disease were enrolled in the study.

**Patients and methods**

In a double-blind study of xamoterol vs placebo, 36 patients with ischemic heart disease were recruited. Of those, 22 (20 men, two women) had a first transmural anterior myocardial infarction (confirmed by typical history and electrocardiographic and enzymatic changes) in the territory perfused by the left anterior descending coronary artery. In 20 patients, the circumflex coronary artery, its marginal branch, and the right coronary artery were normal. In the two remaining patients, minor lesions were found on other branches (30% stenosis on the circumflex and right coronary arteries in one patient of the placebo group and 40% stenosis on the right coronary artery in one patient of the xamoterol group). Five of eight patients in the placebo group and six of 14 in the xamoterol group had poor to fair collateral development, while no collateral circulation was observed in the remaining patients. It is also noteworthy that in two patients (one in each group), no significant coronary lesion was found at the baseline study, suggesting that the myocardial infarction had been caused by a thrombus with secondary spontaneous thrombolysis.

The patients complained mainly of fatigue and dyspnea on exertion and were considered to be in functional class II of the New York Heart Association. All patients were in sinus rhythm and gave their informed consent for the study, which had been approved by the Ethical Committee of our institution. No complications or side effects of xamoterol were observed and the frequency of ventricular or supraventricular arrhythmias was unchanged.

**Study protocol**

**Baseline study.** In all patients, cardiovascular drugs were stopped for at least 3 days before the control study, which was performed between 4 and 8 weeks after the acute myocardial infarction. Catheterization of the left side of the heart was performed by the femoral approach with the patient in the fasting state and without premedication. Aortic pressure was measured through a No. 8F pigtail catheter connected to a Statham P231D strain gauge. Left ventriculography was performed by single-plane 35 mm cinangiography at 50 frames/sec in the right anterior oblique projection (Philips Polydiagnost C, Philips Electronic Instruments), during which high-fidelity left ventricular pressure was recorded with a No. 5F micromanometer-tipped catheter (Millar Instruments). Opacification of the cavity was accomplished by the injection of 0.7 to 0.8 ml/kg of sodium meglumine diatrizoate at a rate of 18 ml/sec. The hemodynamic variables and a cinematographic frame marker were recorded on magnetic tape (Honeywell 101) and on paper (Honeywell 1858). Left ventricular pressure during ventriculography and the time of the peak of the R wave were also sampled synchronously with frame exposure and displayed in digital form on the corresponding cinematographic frame (Cine Data, Philips Electronic Instruments, Inc.).

In addition, a No. 7F Swan-Ganz thermodilution catheter (Webster Laboratories) was placed in the midcoronary sinus through an antecubital vein in seven of eight patients in the placebo group and 11 of the 14 patients of the xamoterol group. The position of this catheter was confirmed angiographically and by oxygen saturation. Coronary sinus blood flow was determined by the thermodilution method12 and arterial and coronary venous blood samples were obtained for determination of oxygen content and lactate concentrations. These metabolic measurements were obtained before diagnostic left ventriculography and coronary angiography.

**Second study (3 months later).** After the baseline study, patients were randomly assigned to placebo or xamoterol (one-third in the placebo group and two-thirds in treatment group). Placebos of xamoterol (200 mg) or matching placebo tablets were administered twice daily. Antithrombotic drugs (aspirin, dipyridamole) were allowed in all patients, but none received cardiac glycosides, diuretics, or vasodilators during the study period. The patients were seen at the outpatient clinic and compliance was checked by analysis of plasma for xamoterol. After 3 months of therapy, a second left heart catheterization and a metabolic study were performed with the same methods as in the baseline study. Average plasma level at the outpatient clinic 6 weeks after the start of the study was 74 ± 31 ng/ml and at the time of second catheterization, it ranged from 75 to 353 ng/ml (mean 170 ± 74 ng/ml). Since the effective plasma concentrations to obtain 50%, 75%, and 95% of the maximal response to xamoterol were from 8 to 16, 24 to 50, and 150 to 314 ng/ml, respectively, all patients had effective plasma concentrations of the drug throughout the study.

**Data analysis.** All data were analyzed in a blinded fashion. Analog hemodynamic data filtered at 100 Hz were digitized every 2 msec and processed off-line by means of a Hewlett-Packard A900 computer as described previously.15 For the analysis of the angiographic data, both premature and postpremature beats were excluded. Ventricular silhouettes were outlined frame by frame with a light pen on a video screen. The digitized contours were preprocessed by a computer system (LVV Philips 100) that derived the correction factor for radiographic magnification and calculated volumes applying Simpson's rule. Using the long axis of the left ventricular silhouette as the reference system,14 the left ventricle was divided into eight segments, four anterior and four inferior, and the areas of all segments were determined. The preprocessed data were then directed to an HP 21 MX computer for smoothing by a cubic spline method15 and for the computation of the various indexes of left ventricular function.

Midwall circumferential stress was calculated by the formula of Mirsky16: Stress = [Pb/H]1/[1 − b2(2a/H)2] − H/2b, where P = left ventricular pressure, H = wall thickness; a = midwall semimajor axis; b = midwall semiminor axis. Wall thickness was determined at end-diastole in the anterobasal area and computed for other diastolic frames assuming a constant left ventricular mass. The mean diastolic wall stress was determined by averaging the data from the start of the ventricular filling to the peak of the R wave.

An index of the left ventricular elastic properties, the elastic myocardial stiffness (E) was computed according to Kurnik et al.17 This method assumed the model of a thick-walled prolate sphere and an exponential stress-strain relationship: stress = C1 + C4b/C3, where C1, C4, C3 = constants calculated by a nonlinear best-fit method. These data were fitted from the minimum left ventricular pressure to the end of diastasis and E was then calculated at a constant physiologic level of stress (30 kdynes/cm²) from the equation E = C3 ∗ stress − C1 ∗ C3.
Regional systolic function was considered normal when the end-systolic area of a given segment fell within the range of values observed in normal ventricles and abnormal when the end-systolic area was greater than the higher normal value for that segment. By this approach, three classes of segments were defined (normal segments, abnormal anterior segments, abnormal inferior segments) and the effects of therapy on each class was examined. Moreover, to evaluate the left ventricular shape change in the anterior and inferior segments, the areas of the four anterior and four inferior segments were summed at end-diastole (taken at the peak of the R wave) and at end-systole (taken at the maximum left ventricular pressure-volume ratio).

Blood oxygen content was determined with a Lex-O₂-CON Analyzer and lactate plasma concentrations were determined by an enzymatic method. Angiographic cardiac output was calculated as the product of the stroke volume in the 30 degree right anterior oblique projection multiplied by the heart rate during angiography; these values were corrected by use of the regression equation obtained in our laboratory using phantoms. Systemic vascular resistance was calculated as: (mean aortic pressure/cardiac output) × 80 (dyne-sec-cm⁻²).

**Statistical analysis.** All normally distributed data are presented as mean ± SD and were compared with use of a paired t test. For the ratio (total anterior area/total inferior area), both the absolute values at end-systole and the changes observed during follow-up were skewed. Accordingly, the median values and the range are presented for this variable and the statistical comparisons before and after treatment were made by a rank test (Mann-Whitney U test). Comparisons of the changes induced between groups by placebo or xamoterol were also made with a nonparametric rank test (Mann-Whitney U test) or a Fisher’s (2 × 2) exact test, when frequencies were compared. For reference purposes, the normal values for each variable in our laboratory are also provided at the bottom of table 1.

**Results**

**Comparison of the placebo group and xamoterol group at baseline.** At baseline, the two groups were comparable in terms of age, sex, coronary lesions, and degree of collateral development. The baseline ejection fraction (table 1), the diastolic left ventricular pressure-volume relationships (figure 1, top), and the index of myocardial elastic stiffness (580 ± 297 and 526 ± 260 in placebo and xamoterol groups, respectively; NS) were also well matched.

**Changes in global left ventricular function and metabolism.** No consistent changes in heart rate, left ventricular systolic pressure, or in mean aortic pressure (95 ± 11 to 98 ± 15 mm Hg with placebo, 101 ± 14 to 104 ± 14 mm Hg with xamoterol; both NS) were observed after 3 months (table 1). Left ventricular end-diastolic and end-systolic volume index tended to decrease in both groups and ejection fraction increased slightly in the placebo group, but none of these changes were statistically significant when placebo and xamoterol groups were compared. However, angiographic cardiac output increased in patients on placebo (5.0 ± 0.5 to 5.7 ± 0.9 liters/min; p < .025), while it decreased slightly in patients on xamoterol (5.6 ± 1.6 to 4.9 ± 1.5 liters/min; p < .05). Calculated systemic vascular resistance declined in the placebo group from 1552 ± 304 to 1400 ± 248 dyne·sec·cm⁻² (p < .05), while it tended to rise with xamoterol (1560 ± 408 to 1880 ± 680 dyne·sec·cm⁻²; p < .1 vs baseline), the differences between placebo and xamoterol being significant (-10% vs +20%; p < .05). Several other significant differences were also observed between placebo and xamoterol groups.

An important difference concerned the changes in left ventricular end-diastolic pressure and in mean diastolic wall stress. Both variables were higher than normal in both groups at baseline and remained unchanged.

### TABLE 1

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Serial hemodynamic and angiographic data for patients with anterior myocardial infarction and single-vessel disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
</tr>
<tr>
<td>Xamoterol group</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>&lt;.0001</td>
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<tr>
<td>Normal values</td>
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<tr>
<td>Mean</td>
<td>74</td>
</tr>
<tr>
<td>SD</td>
<td>9</td>
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</tbody>
</table>

HR = heart rate; LVEDP, LVSP = left ventricular end-diastolic and systolic pressure; EDVI, ESVI = end-diastolic and end-systolic volume index; EF = ejection fraction; HR*, LVEDP* = heart rate and end-diastolic pressure during the cardiac cycle analyzed to derive angiographic measurements; Diast = diastolic; B = baseline data; T = data obtained during therapy.
in the placebo group but decreased significantly in the xamoterol group (table 1), the difference between the groups being statistically significant (figure 2). The average diastolic pressure-volume relationship was shifted downward after treatment with xamoterol (figure 1, bottom), suggesting improved chamber compliance. Furthermore, the index of myocardial elastic stiffness decreased in 13 of the 14 patients after xamoterol therapy (from 526 ± 260 to 371 ± 194 kdynes/cm²; p < .02), but it increased in four of the eight patients in the placebo group, the average change from 580 ± 297 to 488 ± 334 being nonsignificant.

Another difference between groups was in the isovolumetric index of inotropic state (dP/dt)/Dp40, i.e., dP/dt measured and normalized at a developed pressure of 40 mm Hg.20 In the placebo group, this index decreased in all but one patient from 25.4 ± 6.5 to 24.2 ± 5.5 sec⁻¹, while in the xamoterol group it increased in 10 of 14 patients from 23.7 ± 6.6 to 25.7 ± 5.4 (p < .05 placebo vs xamoterol).

A final difference was observed when examining myocardial metabolism. Coronary sinus blood flow was unchanged in the placebo group (104 ± 17 to 99 ± 22 ml/min; NS) and in the xamoterol group (104 ± 14 to 105 ± 9 ml/min; NS). Myocardial oxygen uptake was also unchanged (12.9 ± 3.5 to 12.0 ± 3.8 ml/min with placebo and 14.4 ± 5.6 to 13.8 ± 4.1 ml/min after xamoterol; both NS), but myocardial lactate extraction fraction decreased in all patients treated with placebo and tended to improve in the xamoterol group (figure 3).

Changes in regional left ventricular function. Table 2 summarizes the changes in regional left ventricular function in the different classes of left ventricular segments.

Normal segments. The mean end-diastolic area of the normal segments was unchanged after placebo (531 to
538 mm²; n = 19 segments; NS), but decreased after xamoterol (660 to 626 mm²; n = 37 segments; p < .03). This difference between group was almost significant (p < .07). Moreover, despite unchanged systolic and end-diastolic pressures (tables 1 and 2), the mean end-systolic area decreased significantly in normal segments after placebo (289 ± 140 to 248 ± 126 mm²; p < .004), while it was unchanged after xamoterol (340 ± 110 to 343 ± 121 mm²; NS), the difference between groups being highly significant (−41 ± 54 vs 3 ± 53 mm²; p < .006).

Abnormal segments. The mean end-diastolic area decreased similarly in the anterior abnormal segments after placebo (752 to 712 mm²; p < .01) and after xamoterol (754 to 721 mm²; p < .01). The mean end-systolic area of these abnormal anterior segments tended to decrease after placebo (table 2) and was consistently decreased after xamoterol (577 ± 192 to 534 ± 198 mm²; p < .00001). For the inferior segments with abnormal wall motion, the directional changes in mean end-systolic area paralleled those in the normal segments (table 2).

Left ventricular geometry. The total end-diastolic and end-systolic anterior and inferior areas were significantly increased at baseline when compared with those in normal ventricles. In the placebo group, the end-

**FIGURE 2.** Individual values of the changes induced by placebo (P) and xamoterol (Xamo) therapy in left ventricular end-diastolic pressure (Δ LVEDP), in mean diastolic wall stress (Δ Mean Diast. W. Stress), and in the ratio between end-systolic area of the anterior and inferior segments (Δ ES Area (Ant/Inf)). For the first two variables the mean values are given, but in the last panel, median values are presented because the distribution was skewed.

systolic area of both anterior and inferior segments tended to decrease after 3 months and no significant difference in improvement between anterior or inferior regions was present when the absolute changes in areas of the anterior and inferior segments were compared (figure 4). In the xamoterol group, however, systolic shortening improved predominantly in the anterior area, with a 7% (p < .016) reduction in end-systolic area of the anterior segments, while end-systolic area remained normally unchanged in the inferior segments. The difference in response to therapy between ante-

**FIGURE 3.** Individual values for transcardiac lactate extraction fraction before and after 3 months of therapy with placebo or xamoterol.
TABLE 2  
Regional left ventricular function in patients with anterior myocardial infarction and single-vessel disease

<table>
<thead>
<tr>
<th></th>
<th>Normal segments (mm²)</th>
<th>Abn ant segments (mm²)</th>
<th>Abn inf segments (mm²)</th>
<th>ESP (mm Hg)</th>
<th>Ratio ant/inf area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED B T</td>
<td>ED B T</td>
<td>ED B T</td>
<td>ED B T</td>
<td>B T</td>
</tr>
<tr>
<td>Placebo group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>531 538 289 248</td>
<td>752 712 519 489</td>
<td>845 820 596 555</td>
<td>126 127</td>
<td>Median 0.90</td>
</tr>
<tr>
<td>SD</td>
<td>251 224 140 126</td>
<td>180 168 147 141</td>
<td>308 319 194 205</td>
<td>19 26</td>
<td>Median 0.85</td>
</tr>
<tr>
<td>p value</td>
<td>NS .004</td>
<td>NS .01</td>
<td>NS .1</td>
<td>NS .015</td>
<td>NS</td>
</tr>
<tr>
<td>n</td>
<td>19 19</td>
<td>29 29</td>
<td>16 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xamoterol group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>660 626 340 343</td>
<td>754 721 577 534</td>
<td>776 727 520 513</td>
<td>137 140</td>
<td>Median 0.96</td>
</tr>
<tr>
<td>SD</td>
<td>195 192 110 121</td>
<td>199 196 192 198</td>
<td>259 281 162 175</td>
<td>15 17</td>
<td>Median 0.96</td>
</tr>
<tr>
<td>p value</td>
<td>.03 NS</td>
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</tr>
<tr>
<td>n</td>
<td>37 37</td>
<td>52 52</td>
<td>23 23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abn = abnormal; ant = anterior; inf = inferior; ESP = end-systolic pressure; ED = end-diastole; ES = end-systole; B = baseline; T = treatment; n = number of segments.

To further determine whether the geometry of the left ventricular silhouette was altered, the ratio of the anterior/inferior areas was calculated (table 2). At end-diastole, this ratio was comparable to the values observed in normal ventricles (median 0.99, range 0.70 to 1.29), indicating that ventricular dilatation was uniformly distributed. At end-systole (normal median value 0.66, range 0.51 to 0.99), the ratio at baseline was significantly greater than normal (p < .01) in both groups, and was skewed toward high values, reflecting the distortion of the end-systolic shape caused by the anterior infarct. After treatment with placebo, this index of distortion of the ventricle slightly deteriorated, its median value increasing by 5%, while it improved by 11% in the xamoterol group (table 2), the difference between groups again being significant (figure 2).

Discussion

To correctly interpret the pathophysiologic meaning of our observations, the characteristics of the patients must be emphasized. The baseline study was obtained more than 4 weeks after acute myocardial infarction and all patients had single-vessel disease. Thus, most of the early remodeling process of the ventricle
table 1 had probably already taken place under relatively optimal conditions. Significant increases in end-diastolic and end-systolic volumes were present at baseline. Compensatory hypertrophy and/or dilation of the remaining normal segments had already occurred, as indicated by the increase in end-diastolic inferior areas, and systolic pump function was satisfactory in most cases.

Several indexes, however, indicated that these patients had important alterations in left ventricular diastolic function. Besides the increase in left ventricular end-diastolic pressure, mean diastolic wall stress was also significantly increased. In the presence of a myocardial infarction, wall stress computations performed with the Mirsky formula or the formula of Sandler and Dodge may be of limited value during systole because of regional wall motion abnormalities, but their use seems justified in diastole, when the shape of the cavity is close to normal (table 2).

Our data indicate that, in this clinical setting, prolonged administration of xamoterol may produce substantial decreases in left ventricular filling pressure and in mean diastolic wall stress, accompanied by a downward shift of the diastolic pressure/volume relationship.

FIGURE 4. Individual changes in the end-systolic area (Δ Area) for the anterior (ANT) segments and the inferior (INF) segments of the same left ventricle observed after 3 months of therapy with placebo or xamoterol (XAMO). After xamoterol, the decrease in end-systolic area was consistently more important in the anterior than in the inferior segments.
and by a decrease in the index of myocardial elastic stiffness. The decrease in left ventricular end-diastolic pressure was accompanied by a moderate reduction in left ventricular end-diastolic size that was relatively uniformly distributed in normal and abnormal areas of the ventricle.

This therapeutic effect of xamoterol may elucidate some of the mechanisms responsible for the impaired left ventricular distensibility observed in these patients. Indeed, the decrease in distensibility caused by the replacement of necrotic tissue by fibrosis is unlikely to be affected by a \( \beta_1 \)-adrenoceptor partial agonist or any other drug. On the other hand, as suggested by McKay et al., there may be upward shifts in the diastolic pressure-volume relationship in the presence of chronic ischemia in the border zone of the infarct. Despite the presence of normal coronary vessels, subendocardial ischemia could also occur in other areas of the ventricle because of the increased wall stress and the hypertrophy process. In the presence of transmural necrosis, myocardial denervation occurs, which may also affect myocardial relaxation in these areas.

Xamoterol, being a \( \beta_1 \)-adrenoceptor partial agonist with a sympathomimetic activity of 43%, might improve these abnormalities by several mechanisms. Under basal conditions, when the sympathetic tone is low, \( \beta_1 \)-adrenoceptors are stimulated in normal as well as in any denervated area, thereby improving contractility and relaxation rate. Because of its dual pharmacologic action, xamoterol also acts as an antagonist when the sympathetic tone is high and exhibits a significant anti-ischemic action during exercise. During prolonged administration, this might result in a reduction of the repeated ischemic stunning of underperfused areas and in an improvement of their diastolic properties. Thus, xamoterol may improve diastolic function by its positive inotropic and lusitropic support (improved contractility and relaxation) and by its protection against the deleterious effects of excessive sympathetic stimulation. Xamoterol lacks any direct stimulant effects on \( \beta_2 \)-adrenoceptors. Instead, at the plasma levels observed in this study, it acts as a \( \beta_2 \)-blocker. This \( \beta_2 \)-antagonist action may play a role in explaining the different evolution of systemic vascular resistance and cardiac output in the two groups, but its effects on the myocardium is undefined.

Reductions in left ventricular filling pressures and downward shifts of the diastolic pressure-volume relationship may also be caused by factors external to the ventricle, such as a change in pericardial or right-sided pressure. Simonsen has shown that, after intravenous administration of xamoterol in patients with dilated cardiomyopathy, the decrease in left ventricular filling pressure is not accompanied by a reduction in right atrial pressure. After intravenous xamoterol, however, cardiac output increases, which was not the case in our patients. The lack of increase in cardiac output in the present study is unlikely to be related to a depression in left ventricular function during long-term therapy with xamoterol. A worsening of ischemia is, indeed, unlikely when coronary sinus flow and myocardial oxygen uptake are unchanged. A negative inotropic effect can also be ruled out, as indicated by the increase in the isovolumetric index of inotropic state and by the lack of change in end-systolic dimensions. It is likely, therefore, that some of the effects on diastolic function might have been related to effects of xamoterol on the right side of the heart, on the left atrium, or on the venous return.

Nevertheless, our data suggest that xamoterol therapy had additional effects on the left ventricular myocardium. Indeed, elastic stiffness, an index that allows comparison of patients at a common stress level, decreased significantly in the xamoterol group. This index was developed by Kurnik et al., who showed that it should be affected little by extracardiac factors. The decrease in this index of myocardial stiffness, therefore, supports the hypothesis that the distensibility of the myocardium itself has improved during therapy. The composite nature of this index gives no clue, however, to the mechanisms underlying this increased distensibility of the myocardium.

Finally, it is also noteworthy that after placebo, the end-diastolic area decreased significantly in the abnormal anterior areas despite unchanged left ventricular end-diastolic pressure. This suggests a further reduction in diastolic distensibility of these areas in the placebo group during the follow-up. In summary, our data are compatible with the hypothesis that the reduced left ventricular compliance observed after myocardial infarction is partially an active process that can be influenced by therapy. This aspect of left ventricular function should therefore be carefully examined when the clinical results of interventions such as thrombolysis are assessed.

Since it is possible to reduce the mean diastolic wall stress in these patients over the long term, one may speculate whether this could have an influence on the late remodeling of the ventricle and affect systolic function and the long-term prognosis. In this respect, Pfeffer et al. have shown recently in rats that prolonged reduction of preload and afterload with an angiotensin-converting enzyme inhibitor blunted the changes in left
ventricular geometry after an experimental infarct and improved survival. In their study, however, intervention started early after infarction. Since most of the remodeling occurs in the first week, we may have underestimated the impact of therapy on this process. Moreover, because we selected a group with one-vessel disease in whom cardioactive drugs could be withdrawn, residual systolic function was well preserved. The present results may, therefore, also underestimate the spontaneous changes in left ventricular function that occur at between 1 and 3 months in the presence of larger myocardial infarctions. Nevertheless, although the global changes in left ventricular volume were comparable in the two groups, there is a possibility that late ventricular remodeling could have been different, particularly in normal segments.

In the placebo group, the diastolic size of the normal segments was unchanged, but their end-systolic area decreased significantly. Since peak systolic and end-systolic pressures were unchanged, it is likely that the improved systolic function in the normal areas was related to a change in myocardial function, most likely hypertrophic changes rather than to a reduction in afterload. In contrast, in the xamoterol group, the use of the Starling mechanism was reduced in all classes of segments and systolic shortening improved in the anterior abnormal region but not in normal regions (table 2). This relatively selective improvement in the anterior segments partially corrected the distortion of the ventricle at end-systole. The mechanisms for this relatively selective improvement in abnormal anterior segments after xamoterol therapy are unclear. A similar finding was made after the short-term intravenous administration of xamoterol to patients with a previous myocardial infarction. A denervation supersensitivity to β-stimulation was recently reported in noninfarcted areas apical to transmural infarction and could explain the greater response in the denervated area surrounding the scar tissue. An alternative hypothesis is that of a regional redistribution of blood flow related to the reduction in diastolic wall stress.

Thus, the difference in remodeling between groups mainly affected the normal segments and could not be explained by alterations in systolic or end-systolic pressure. Moreover, the shape of the end-systolic silhouette became more normal with xamoterol therapy but deteriorated slightly with placebo. This suggests that compensatory mechanisms, probably hypertrophy triggered by the elevated wall stress, were still active in normal zones with placebo but not with xamoterol. The difference in diastolic and systolic behavior in patients on xamoterol and placebo also resulted in different values of cardiac output. It appeared that some preload reserve was restored at the expense of resting cardiac output in patients on xamoterol while a “volume overload” type of increase in cardiac output, consistent with the model of McKay et al., was taking place in patients on placebo.

Finally, one may speculate on whether real remodeling occurred during long-term xamoterol therapy or whether the changes observed simply reflect the short-term action of the drug. Since the short-term effects of xamoterol were not measured in our patients, the short- and long-term responses cannot be compared. It is also difficult to compare the present data with those from other studies in which xamoterol was administered to patients with more severe left ventricular dysfunction and two- or three-vessel disease in whom sustained increases in cardiac output together with lower filling pressure were observed. The changes in regional wall motion and diastolic function reported herewith are, however, comparable to those observed after intravenous xamoterol or during long-term treatment in patients with more severe coronary artery disease. The various differences observed in the placebo group nevertheless suggest that xamoterol is at least able to prevent some remodeling of the ventricle, if not to modify the remodeling process itself. The unfavorable changes in myocardial lactate extraction fraction seen in the placebo group, with lactate production in some patients, and the depression in an isovolumetric index of inotropic state relatively independent of preload and afterload in seven of these patients, further suggest that adaptive changes in left ventricular function and metabolism were less beneficial in the placebo group than in the xamoterol group.

Additional studies are needed to confirm these hypotheses. Precise measurements of anterior and inferior wall thickness are particularly important in this respect. Although it is evident that xamoterol improves diastolic function, it is also necessary to determine whether these effects of xamoterol on diastolic function are responsible for the improvements in exercise tolerance in patients with heart failure that have been reported in other studies. Furthermore, to understand the functional consequences of the balance between the agonist action of the drug in patients at rest and during moderate exercise and its antagonist action during maximal exercise, we need more detailed study that includes pressure-volume measurements in the left ventricle and right-sided pressure measurements not only at rest but also during exercise.
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Long-term effects of xamoterol on left ventricular diastolic function and late remodeling: a study in patients with anterior myocardial infarction and single-vessel disease.

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