EFFECT OF XAMOTEROL ON MYOCARDIAL ENERGETICS IN MAN

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We analyzed the effect of xamoterol (β₁-partial agonist) on myocardial energetics in 8 patients with normal left ventricular function. We measured resting systemic and coronary hemodynamics before and after a single intravenous injection of xamoterol (0.1 mg/kg). This agent increased heart rate from 70 ± 7 to 80 ± 11 beats/min (p < 0.05) and cardiac index from 2.9 ± 0.5 to 3.2 ± 0.5 L/min·m² (p < 0.01), respectively. Left ventricular peak positive dp/dt (1870 ± 350 vs 2620 ± 580 mmHg/sec (p < 0.01)) and left ventricular ejection fraction (62 ± 7 vs 70 ± 7% (p < 0.01)) also increased, while left ventricular end-diastolic pressure (9 ± 3 vs 5 ± 3 mmHg (p < 0.01)) and volume index (70 ± 14 vs 58 ± 16 ml/m² (p < 0.01)) decreased. Coronary blood flow and total myocardial oxygen consumption did not change significantly after intervention. As a result, xamoterol enhanced left ventricular external mechanical work versus myocardial oxygen consumption ratio (mechanical efficiency) from 20 ± 4 to 24 ± 5% (p < 0.01). Myocardial oxygen extraction ratio decreased significantly (p < 0.01) from 66 ± 5 to 62 ± 5% after xamoterol. We conclude that xamoterol augments left ventricular mechanical efficiency accompanied by a decrease in coronary vascular tone in patients with normal cardiac function.

The clinical actions of a newly-developed cardioselective β₁ partial agonist (xamoterol) have been investigated in detail. In the previous study its maximal agonist activity is approximately 43% of that of isoprenaline. This drug apparently exhibits positive inotropic activity in patients with mild to moderate heart failure. However, the information on the effects of this agent on myocardial energetics and coronary circulation have not been clarified. The present study was designed to determine whether or not xamoterol affects myocardial energetics, and to clarify xamoterol’s effects on vasodilation of large and small coronary arteries. To separate this from vascular effects secondary to changes in myocardial metabolism, coronary sinus O₂ content and A-V O₂ content difference were evaluated.

METHODS

Patients: The study comprised 8 men ranging in age from 43 to 66 years (mean 52). All were in sinus regular rhythm and New York Heart Association Functional class I or II. Six patients had previous myocardial infarctions associated with normal left ventricular global function. Two had atypical chest pain with normal coronary arteriograms.

Study protocol: All 8 patients underwent

Key words:
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TABLE 1  HEMODYNAMIC AND LEFT VENTRICULAR (LV) FUNCTIONAL DATA

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Control</th>
<th>Xamoterol</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>70 ± 7</td>
<td>80 ± 11</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>LV peak systolic pressure (mmHg)</td>
<td>147 ± 25</td>
<td>150 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mmHg)</td>
<td>9 ± 3</td>
<td>5 ± 3</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>LV peak (+) dp/dt (mmHg/sec)</td>
<td>1870 ± 350</td>
<td>2620 ± 580</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>110 ± 17</td>
<td>114 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg)</td>
<td>16 ± 3</td>
<td>14 ± 4</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Mean right atrial pressure (mmHg)</td>
<td>4 ± 2</td>
<td>3 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Total systemic resistance (dyne.sec.cm⁻⁵)</td>
<td>2000 ± 430</td>
<td>1870 ± 340</td>
<td>NS</td>
</tr>
<tr>
<td>Total pulmonary resistance (dyne.sec.cm⁻⁵)</td>
<td>290 ± 80</td>
<td>230 ± 80</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Cardiac index (l/min.m²)</td>
<td>2.9 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Stroke volume index (ml/m²)</td>
<td>40 ± 6</td>
<td>40 ± 7</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LV function</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume index (ml/m²)</td>
<td>70 ± 14</td>
<td>58 ± 16</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>LV end-systolic volume index (ml/m²)</td>
<td>27 ± 9</td>
<td>18 ± 9</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62 ± 7</td>
<td>70 ± 7</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

Cardiac catheterization study in the postabsorptive state. All drugs were discontinued at least 12 hours before the study, and no patient received any sedative premedication. After the completion of diagnostic coronary arteriography performed by the Sones technique, a high fidelity micromanometer-tipped catheter (Millar Instruments) was inserted into the left ventricular cavity through the left brachial artery, which allowed simultaneous pressure measurements during angiography. A thermodilution catheter (Wilton-Webster Laboratory) was inserted into the coronary sinus through the brachial vein, its position was checked by a small bolus injection of contrast medium. Coronary sinus flow was determined by the continuous infusion of isotonic saline solution at the rate of 46 ml/min using thermodilution computer-Thermodflow RF (Goodman Laboratory). A thin wall canule was then inserted into the femoral artery for continuous systemic arterial pressure monitoring. A Swan-Ganz thermodilution catheter was placed in the pulmonary artery to measure cardiac output and right atrial and pulmonary arterial pressures. Cardiac output was determined using thermodilution computer-9520A (Edward Laboratory). After a rest period following the positioning of the catheters, pressures, cardiac output and coronary sinus flow were measured. Thereafter, coronary sinus blood and arterial blood were drawn simultaneously for measurements of oxygen saturation and lactate concentration. Then, control left ventricular cineangiography was performed in the 30° right anterior oblique projection using Tohshiba 9 inch image intensification system. Left ventricular opacification was achieved by injecting 30 to 40 ml of radiopaque contrast medium (80% meglumine diatrizoate) through the Millar angiographic catheter at a rate of 12 ml/sec. Films were exposed at rates of 60 frames/sec using Ari 35 mm cine camera. Ten minutes after control left ventriculography when the effect of contrast medium was negligible, 0.1 mg/kg of xamoterol was injected intravenously over a 5 min period. Fifteen minutes after the end of administration, the measurements were repeated and a second left ventriculography was performed. The dose of xamoterol and time schedule were determined by referring previous studies.²,⁴,⁶

Data analysis: The boundary of the ventricular silhouette was delineated manually using an OSCON cine analyser and the left ventricular volumes were calculated by the area-length method. Systemic and coronary hemodynamics were calculated as follows. Total systemic resistance (dyne.sec.cm⁻⁵) = Mean arterial pressure x 80 / Cardiac output. Total pulmonary resistance (dyne.sec.cm⁻⁵) = Mean pulmonary pressure.
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Fig. 1. Coronary sinus flow before and after an administration of xamoterol. C = control; X = xamoterol.

Fig. 2. Coronary sinus oxygen content before and after xamoterol. CS = coronary sinus; C = control; X = xamoterol.

arterial pressure x 80 / Cardiac output, Coronary vascular resistance (mmHg·min/ml) = Mean arterial pressure / Coronary sinus flow. Oxygen saturation was determined by OSM2 Hemoximeter (Radiometer Laboratory) and Lactate concentration was measured by the enzymatic fluorometric method. Oxygen content and coronary metabolism were obtained as follows. Oxygen content (ml/dl) = Hemoglobin concentration x Oxygen saturation x 0.0135, Myocardial oxygen extraction ratio (%) = (Arterial oxygen content - Coronary sinus oxygen content) x 100 / Arterial oxygen content, Myocardial oxygen consumption (ml/min) = (Arterial oxygen content - Coronary sinus oxygen content) x Coronary sinus flow x 10^-2, Lactate extraction ratio (%) = (Arterial lactate concentration - coronary sinus lactate concentration) x 100 / Arterial lactate concentration. Total cardiac work was derived from myocardial oxygen consumption. Mechanical efficiency was calculated by determining the ratio of left ventricular external work (Stroke Work) to total cardiac work per beat. Calculation was as follows. Stroke work (J) = Mean systolic arterial pressure x Stroke volume x 1.33 x 10^-4, Total cardiac work (J) = Myocardial oxygen consumption x 20.2, Mechanical efficiency ratio (%) = Stroke work x 100 / (Total cardiac work / Heart rate).

Statistics: All data are presented as the mean ± SD. Differences were analyzed for significance by the paired Student’s t test. A P value less than 0.05 was considered statistically significant.

RESULTS

There were no unexpected complications due to an administration of xamoterol, and the drug appears to have little arhythmogenic potential.

Systemic hemodynamics: The systemic hemodynamic responses to an administration of xamoterol are shown in Table I. Cardiac index measured by thermodilution method increased from 2.9 ± 0.5 to 3.2 ± 0.5 l/min·m² (p < 0.01) after xamoterol. This increase was accompanied by a significant (p < 0.05) increase in heart rate (70 ± 7 to 80 ± 11 beats/min) as well as in left ventricular peak positive dp/dt (1870 ± 350 to 2620 ± 580 mmHg/sec, p < 0.01). This was associated with decreases in left ventricular end-diastolic (9 ± 3 to 5 ± 3 mmHg, p < 0.01) and mean pulmonary arterial (16 ± 3 to 14 ± 4 mmHg, p < 0.05) pressures. The calculated total systemic resistance and total pulmonary resistance also decreased from 2000 ± 430 and 290 ± 80 dyne·sec·cm⁻² under the baseline.

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conditions to $1870 \pm 340$ and $230 \pm 80$ dynesec-cm$^{-5}$ after xamoterol, respectively. Whereas left ventricular peak systolic, mean arterial and mean right atrial pressures remained unchanged as well as stroke volume index.

**Left ventricular function:** After the administration of xamoterol, both left ventricular end-diastolic and end-systolic volume indices decreased from $70 \pm 14$ and $27 \pm 9$ to $58 \pm 16$ and $18 \pm 9$ ml/m$^2$ ($p < 0.01$), respectively. Ejection fraction increased significantly ($p < 0.01$) from $62 \pm 7$ to $70 \pm 7\%$ probably due to a positive inotropic effect of this compound (Table 1).

**Coronary Circulation:** Coronary blood flow showed slight increase from $131 \pm 28$ in the basal state to $136 \pm 22$ ml/min after xamoterol (Fig. 1). Since coronary driving pressure (mean arterial pressure) remained unchanged after xamoterol, coronary vascular resistance tended to decrease from $0.86 \pm 0.16$ in the control state to $0.83 \pm 0.15$ mmHg-min/ml after xamoterol but these changes were not statistically significant.

**Myocardial oxygen utilization and mechanical efficiency:** The baseline arterial oxygen content was $17.8 \pm 2.6$ ml/dl and revealed an equivalent value of $17.8 \pm 2.7$ ml/dl after xamoterol. The baseline coronary sinus oxygen content was $6.1 \pm 1.2$ ml/dl and increased to $6.8 \pm 1.4$ ml/dl ($p < 0.01$) by an injection of this drug (Fig. 2). The slight increase in coronary blood flow was counterbalanced by a reduction in A-V $O_2$ content difference ($11.7 \pm 2.2$ vs $11.1 \pm 2.1$ ml/dl, $p < 0.01$) (Fig. 3), leading to an almost equivalent myocardial oxygen consumption ($15.3 \pm 4.2$ vs $14.9 \pm 3.2$ ml/min, N.S.) (Fig. 4). The oxygen extraction ratio decreased from $66 \pm 5\%$ in the basal state to $62 \pm 5\%$ ($p < 0.01$) after the administration of the drug (Fig. 5). Following xamoterol, the stroke work tended to increase from $0.86 \pm 0.15$ to $0.90 \pm 0.13$ J/beats (N.S.). The calculated myocardial efficiency (cardiac external work relative to oxygen utilization) increased from $20 \pm 4$ to $24 \pm 5\%$ ($p < 0.01$), presumably due to a decrease in wall stress through an augmented inotrope (Fig. 6).

**Lactate metabolism:** The arterial lactate concentration was not changed by the administration of xamoterol ($9.8 \pm 5.8$ vs $9.5 \pm 5.6$ mg/dl). The coronary sinus lactate concentration also remained unchanged from $7.4 \pm 6.3$ to $7.5 \pm 5.7$ mg/dl. The lactate extraction ratio tended to decrease from $24 \pm 18\%$ in the basal state to $20 \pm 12\%$ after xamoterol.

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DISCUSSION

This study confirms that xamoterol acts as an inotrope and improves left ventricular contractility in patients with normal resting cardiac function. The salient findings are 1) xamoterol augments mechanical efficiency of the heart and 2) the arterial venous oxygen content difference becomes smaller by this agent in the presence of comparable myocardial oxygen consumption.

Despite the obvious positive inotropic action of this agent, myocardial oxygen consumption did not increase. This may be explained, in part, by the evidence that wall stress decreases as a result of reduced left ventricular volume throughout a cardiac cycle. Myocardial oxygen uptake did not change significantly after an administration of 0.1 mg/kg of xamoterol as shown by Rousseau et al.². Thus, stroke work is augmented without an expense of oxygen supply.

In the present study, oxygen content in coronary sinus blood was increased significantly by this agent, indicating that coronary blood flow was augmented improporionally to an increase in myocardial metabolic activity. This luxurious coronary flow may be attributed to the following mechanisms. Martin et al.⁷ observed that coronary sinus oxygen content increased after an administration of MDL 17043 together with an increment in coronary blood flow, and explained this by the intracoronary shunt of arterial blood. There is a possibility that xamoterol has the same action. An alternative explanation is the unexpected reduction in coronary vascular tone, which may be ascribed to the direct influence of this compound on coronary vessels. It is generally accepted that xamoterol acts as the β₁-agonist under the conditions of normal cardiac performance.¹,⁸ Indeed, in all patients in this study, both heart rate and myocardial contractility were increased by this β₁ adrenergic action. Therefore, it is probable that xamoterol also acts as a β₁-agonist on coronary vessels.

Vatner et al.⁺ proposed the possibility of vasodilatory effect on large and small coronary arteries. In their study of a conscious dog preparation, the effects of prenalterol (β₁ agonist) on large and small coronary arteries were evaluated separately. Changes in coronary arterial diameter of the proximal part of coronary arterial trees were measured by the dimension gauge technique, and those in total coronary arterial resistance were calculated as a ratio of mean arterial pressure and coronary blood flow. Prenalterol increased the diameter of a large coronary artery, but decreased total coronary resistance. If
xamoterol dilates both large and small coronary vessels irrespective of an alteration in myocardial metabolism, coronary sinus oxygen content would be enhanced. It has been demonstrated that oxygen supply to the myocardium is affected by not only coronary inflow, but also oxygen extraction ratio. In a variety of physiological and experimental conditions, the myocardial oxygen extraction ratio changes considerably. Feigl et al. showed that the arterial venous oxygen content difference is reduced by an administration of norepinephrine in the presence of α-blocker. Thus, it is assumed that the vasodilation mediated by β1-agonist induces the increase in venous oxygen content without intracoronary shunting. Findings reported here indicate that xamoterol can be administered safely without an increase in myocardial oxygen consumption.

Acknowledgment
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