BLOCKADE OF CARDIAC CALORIGENIC EFFECT OF EPINEPHRINE BY SOTALOL (MJ-1999)

Young W. CHO*, Mia Myungja HUR CHO** and Shoji SAITO

Department of Pharmacology, Nihon University School of Medicine,
Itabashi-ku 173, Tokyo, Japan

Accepted June 5, 1973

Abstract - While the increase in cardiac work, force and rate are known to be a function of beta-adrenergic receptor stimulation, the mechanism of metabolic actions is uncertain. This study was undertaken to clarify the "calorigenic" action of epinephrine and its relation to hemodynamic changes. In a group of canine heart-lung preparations, the intra-atrial infusion of 0.01, 0.03 and 0.1 μg/kg of epinephrine did not change the cardiac work, force and rate, or the myocardial oxygen consumption, as compared to the control. However, intra-atrial infusion of 0.5 μg/kg of epinephrine caused an increase in cardiac work, cardiac isometric contraction, coronary flow and a marked elevation in the myocardial oxygen consumption above and beyond the rate of its effect on the cardiac hemodynamic parameters. Addition of 0.5 mg/kg of Sotalol did not cause depression of these parameters of left ventricular functions, including the coronary flow. However, 0.5 mg/kg of Sotalol effectively blocked the "calorigenic" action of 0.5 μg/kg of epinephrine. Apparently, more oxygen is being extracted by the myocardium after 0.5 μg/kg of epinephrine. Sotalol blocks this calorigenic action of epinephrine. Since the metabolic effects of epinephrine have not been shown to be beta-adrenergic receptor-mediated changes, it is concluded that Sotalol has the unique property of blocking the metabolic action of epinephrine.

According to investigators, the increased metabolic activity which is produced in the myocardium by epinephrine was thought to be secondary to the increased cardiac contractile activity (1, 2, 3, 4, 5). Epinephrine apparently increases oxygen consumption rate and augments the reduction of ATP concentration only in working heart muscle and not in resting muscular preparations (1, 2, 3). Recent evidence, however, suggests that epinephrine may possess certain calorigenic effects (6), especially at relatively low doses, which are not accompanied by a concomitant rise in the cardiac contraction or work. Catecholamines may cause "oxygen wasting" in the heart and other organs in vivo (7, 8).

The effects of epinephrine on cardiac hemodynamic actions, including the work, force developed and the rate, are known to be a function of beta-adrenergic receptor stimulation (5). The mechanism of metabolic actions of epinephrine is however uncertain (9).

The present study was undertaken to clarify the metabolic actions of epinephrine and the relationship to hemodynamic changes. This was carried out by applying a beta-

* Present address: Associate Professor of Pharmacology & Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana 70112, U.S.A.;
** Present address: Research Associate in Clinical Pharmacology, Louisiana State University School of Medicine, New Orleans, Louisiana 70112, U.S.A.
adrenergic receptor blocking agent, Sotalol, dl-4-(20 isopropylamino-1-hydroxyethyl) methanesulfonanilide. Sotalol, also known as MJ-1999, has been reported to exert a selective blockade on beta-adrenergic receptors without undue depression of the heart (10, 11).

MATERIALS AND METHODS

Twenty mongrel dogs of both sexes weighing 17-22 kg were anesthetized with 30 mg/kg of I.V. sodium pentobarbital. A heart lung preparation was made in the classical manner with the following modifications. A cannula was sutured into the orifice of the coronary sinus and a Shipley-Wilson rotometer was used to measure coronary sinus flow. Aortic flow was measured by a second rotometer connected to a Starling resistance unit. Cardiac output was obtained by adding coronary sinus flow to aortic flow. The aortic pressure was kept at a constant level of 80 mm Hg throughout the study by adjusting the Starling resistance unit. A catheter was inserted into the appendage of the left atrium and attached to a Statham transducer for pressure measurements. Blood samples collected from the aorta and coronary sinus were analyzed for oxygen content by the Van Slyke manometric method. The left ventricular function curve was constructed by changing the level of the venous reservoir from 5 to 10 to 15 cm heights. The left atrial pressure, heart rate, cardiac output, cardiac work, coronary sinus flow (ml/min/100 g heart) and myocardial oxygen consumption (ml O₂/min/g heart) were measured. The first derivative of rise in left ventricular pressure (dP/dT) was measured throughout the study using left ventricular and aortic blood pressure tracings recorded at a paper speed of 100 mm/sec.

A ventricular function curve was constructed in the first group of dogs by elevating the venous reservoir. After obtaining the control values of left ventricular function, the process was repeated after right atrial infusion of epinephrine (0.01 μg/kg) for one, three and ten min durations.

A ventricular function curve was constructed in the second group of dogs and the control variables mentioned previously were recorded. Each variable was evaluated after right atrial infusion of epinephrine (0.1 μg/kg/min) for five min. With the return of control levels, Sotalol (0.5 mg/kg) was added to the venous reservoir, ventricular function curve was again reconstructed and values recorded for each cardiac variable. After a control state had been re-established, right atrial infusion of epinephrine (0.1 μg/kg) was given for five min. Sotalol (0.5 mg/kg) was added to the venous reservoir and cardiac values were re-evaluated.

RESULTS

Elevation of the venous reservoir caused an increase in left atrial pressure. The left ventricular function curve (Fig.) showed a linear correlation between cardiac output (Y) and left atrial pressure (X), which follows the regression formula of

\[ Y = 0.0944X + 0.1235; \quad r = 0.927; \quad t = 13.433 \text{ and } p < 0.001. \]

The curve remained at control levels when 0.01, 0.03 and 0.1 μg/kg of epinephrine, 0.5
<table>
<thead>
<tr>
<th>Reservoir height (cm)</th>
<th>Procedures</th>
<th>Heart rate (beats/min)</th>
<th>Left atrial P. (mmHg)</th>
<th>Cardiac output (L/min)</th>
<th>Coronary flow (ml/100 G/min)</th>
<th>qO₂ (ml O₂/G/min)</th>
<th>Work</th>
<th>dP/dT (mmHg/Sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Control</td>
<td>115 ± 12.9</td>
<td>3 ± 1.2</td>
<td>0.322 ± 0.0900</td>
<td>98 ± 21.3</td>
<td>0.103 ± 0.0324</td>
<td>32 ± 2.5</td>
<td>782 ± 18.5</td>
</tr>
<tr>
<td></td>
<td>Epi (0.01)</td>
<td>113 ± 7.5</td>
<td>3 ± 8.8</td>
<td>0.292 ± 0.0910</td>
<td>100 ± 18.0</td>
<td>0.113 ± 0.0232</td>
<td>26 ± 3.0</td>
<td>982 ± 88.2</td>
</tr>
<tr>
<td></td>
<td>Epi (0.03)</td>
<td>116 ± 11.1</td>
<td>2 ± 1.1</td>
<td>0.289 ± 0.0911</td>
<td>98 ± 19.8</td>
<td>0.110 ± 0.0409</td>
<td>32 ± 3.0</td>
<td>1230 ± 229.6</td>
</tr>
<tr>
<td></td>
<td>Epi (0.1)</td>
<td>124 ± 18.9</td>
<td>2 ± 0.8</td>
<td>0.272 ± 0.0820</td>
<td>92 ± 11.9</td>
<td>0.104 ± 0.0119</td>
<td>24 ± 3.6</td>
<td>1384 ± 167.3</td>
</tr>
<tr>
<td></td>
<td>Epi (0.5)</td>
<td>130 ± 6.6</td>
<td>3 ± 0.6</td>
<td>0.480 ± 0.0395</td>
<td>100 ± 8.0</td>
<td>0.194 ± 0.0591</td>
<td>38 ± 2.7</td>
<td>1093 ± 95.4</td>
</tr>
<tr>
<td></td>
<td>Sotalol (5)†</td>
<td>104 ± 8.0</td>
<td>4 ± 0.6</td>
<td>0.385 ± 0.0546</td>
<td>78 ± 4.7</td>
<td>0.073 ± 0.0342</td>
<td>28 ± 3.9</td>
<td>797 ± 98.7</td>
</tr>
<tr>
<td></td>
<td>Sotalol plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epi (0.5)</td>
<td>97 ± 4.1</td>
<td>3 ± 0.5</td>
<td>0.475 ± 0.0515</td>
<td>96 ± 9.1</td>
<td>0.105 ± 0.0570</td>
<td>37 ± 3.5</td>
<td>826 ± 92.2</td>
</tr>
<tr>
<td>10</td>
<td>Control</td>
<td>116 ± 6.9</td>
<td>5 ± 0.9</td>
<td>0.527 ± 0.0748</td>
<td>125 ± 23.2</td>
<td>0.138 ± 0.0290</td>
<td>65 ± 6.1</td>
<td>1240 ± 197.3</td>
</tr>
<tr>
<td></td>
<td>Epi (0.01)</td>
<td>115 ± 6.5</td>
<td>4 ± 0.5</td>
<td>0.508 ± 0.0749</td>
<td>125 ± 21.8</td>
<td>0.141 ± 0.0396</td>
<td>52 ± 3.6</td>
<td>1458 ± 124.9</td>
</tr>
<tr>
<td></td>
<td>Epi (0.03)</td>
<td>116 ± 6.9</td>
<td>4 ± 0.6</td>
<td>0.492 ± 0.0830</td>
<td>131 ± 20.1</td>
<td>0.140 ± 0.0171</td>
<td>64 ± 7.7</td>
<td>1500 ± 170.2</td>
</tr>
<tr>
<td></td>
<td>Epi (0.1)</td>
<td>123 ± 8.5</td>
<td>3 ± 0.5</td>
<td>0.489 ± 0.0730</td>
<td>148 ± 19.6</td>
<td>0.175 ± 0.0868</td>
<td>60 ± 6.6</td>
<td>1772 ± 60.6</td>
</tr>
<tr>
<td></td>
<td>Epi (0.5)</td>
<td>141 ± 9.6</td>
<td>4 ± 0.8</td>
<td>0.736 ± 0.0549</td>
<td>110 ± 13.3</td>
<td>0.241 ± 0.0724</td>
<td>60 ± 3.9</td>
<td>1500 ± 30.3</td>
</tr>
<tr>
<td></td>
<td>Sotalol (5)</td>
<td>109 ± 7.0</td>
<td>6 ± 1.1</td>
<td>0.678 ± 0.0502</td>
<td>87 ± 8.7</td>
<td>0.107 ± 0.0499</td>
<td>53 ± 5.8</td>
<td>971 ± 9.0</td>
</tr>
<tr>
<td></td>
<td>Sotalol plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epi (0.5)</td>
<td>97 ± 4.1</td>
<td>5 ± 0.7</td>
<td>0.666 ± 0.0427</td>
<td>106 ± 15.3</td>
<td>0.144 ± 0.0631</td>
<td>54 ± 3.6</td>
<td>1065 ± 78.4</td>
</tr>
<tr>
<td>15</td>
<td>Control</td>
<td>-</td>
<td>8 ± 1.3</td>
<td>0.801 ± 0.0832</td>
<td>98 ± 9.6</td>
<td>-</td>
<td>67 ± 7.2</td>
<td>1170 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>Epi (0.5)</td>
<td>-</td>
<td>6 ± 0.9</td>
<td>1.022 ± 0.0620</td>
<td>106 ± 12.7</td>
<td>-</td>
<td>91 ± 9.8</td>
<td>1752 ± 95.0</td>
</tr>
<tr>
<td></td>
<td>Sotalol (5)</td>
<td>-</td>
<td>8 ± 1.9</td>
<td>0.858 ± 0.1109</td>
<td>94 ± 6.7</td>
<td>-</td>
<td>71 ± 9.8</td>
<td>1003 ± 17.5</td>
</tr>
<tr>
<td></td>
<td>Sotalol plus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epi (0.5)</td>
<td>-</td>
<td>7 ± 1.1</td>
<td>0.902 ± 0.0517</td>
<td>114 ± 17.2</td>
<td>-</td>
<td>78 ± 5.2</td>
<td>1090 ± 83.9</td>
</tr>
</tbody>
</table>

*Epi = Epinephrine (in μg/kg); †Sotalol in mg/kg.
FIG. 1. Ventricular function curve during the control, after infusion of epinephrine (0.01, 0.03, 0.1 and 0.5 μg/kg), after addition of Sotalol (0.5 mg/kg) into the venous reservoir, and after epinephrine (0.5 μg/kg) infusion in the presence of Sotalol (5 mg/kg) in 20 heart-lung preparations.

FIG. 2. Comparative changes in coronary blood flow after epinephrine (0.5 μg/kg; open triangle), and after Sotalol (0.5 mg/kg; closed circle) in 10 heart-lung preparations.

FIG. 3. Comparative changes in coronary blood flow after epinephrine (0.5 μg/kg) with and without Sotalol (0.5 mg/kg) in 10 heart-lung preparations.
mg/kg Sotalol plus 0.5 µg/kg of epinephrine were given. However, 0.5 µg/kg of epinephrine caused a shift to the left which had a linear regression formula of

\[ Y = 0.1535X - 0.1070; \quad r = 0.9981; \quad t = 22.177 \quad \text{and} \quad p < 0.001 \] (Fig. 1).

The coronary sinus flow was increased with 0.5 µg/kg of epinephrine but was not altered from control values with Sotalol (0.5 mg/kg) (Figs. 2 and 3). The sinus flow, after Sotalol (0.5 mg/kg) and epinephrine (0.5 µg/kg) had been administered simultaneously was similar to the flow recorded after epinephrine (0.5 µg/kg) alone.

Elevation of the venous reservoir also caused an increase in myocardial oxygen consumption (qO2). Fig. 4 shows a linear correlation between qO2 (Y) and cardiac work load.

![Fig. 4](image1.png)

**Fig. 4.** Changes of myocardial oxygen consumption, during control, during infusion of epinephrine, after Sotalol, and Sotalol plus epinephrine infusion, are compared to the corresponding changes in cardiac work load.

![Fig. 5](image2.png)

**Fig. 5.** Effects of raising the reservoirs during control, during infusion of epinephrine, after Sotalol, and Sotalol plus epinephrine, on the myocardial oxygen consumption rates, as plotted against the corresponding changes of dP/dT of the left ventricle.
(X) which follows the regression formula of

\[ Y = 0.0012X^{0.0617}; r = 0.7134; t = 4.602 \text{ and } p < 0.005. \]

The curve remained at control levels when 0.01, 0.03 and 0.1 \( \mu \)g/kg of epinephrine, 0.5 mg/kg Sotalol and 0.5 mg/kg Sotalol plus 0.5 \( \mu \)g/kg of epinephrine were given. However, 0.5 \( \mu \)g/kg of epinephrine caused a shift to the left (Fig. 4).

Fig. 5 shows a linear correlation between the isometric contractility \( \frac{dP}{dT} \) (Y) and \( qO_2 \) (X) which follows the regression formula of

\[ Y = 3653.8X - 620; r = 0.7801; t = 5.809 \text{ and } p < 0.001. \]

The curve remained at control levels when 0.01, 0.03 and 0.1 \( \mu \)g/kg of epinephrine, 0.5 mg/kg Sotalol and 0.5 mg/kg of Sotalol plus 0.5 \( \mu \)g/kg of epinephrine were given. However, 0.5 \( \mu \)g/kg of epinephrine caused a shift to the right (Fig. 5), which indicates that more oxygen is being consumed after 0.5 \( \mu \)g/kg of epinephrine while performing the same degree of isometric contraction or cardiac work.

Fig. 6 shows a linear correlation between coronary flow (Y) and \( qO_2 \) (X) which follows the regression formula of

\[ Y = 369.8X - 57.1; r = 0.956; t = 12.000 \text{ and } p < 0.001. \]

The curve remained at control levels when 0.01, 0.03 and 0.1 \( \mu \)g/kg of epinephrine, 0.5 mg/kg Sotalol and 0.5 mg/kg of Sotalol plus 0.5 \( \mu \)g/kg of epinephrine were given. However, 0.5 \( \mu \)g/kg of epinephrine caused a shift to the right (Fig. 6), which indicates that more oxygen is being consumed after 0.5 \( \mu \)g/kg of epinephrine while performing the same degree of isometric contraction or cardiac work.

Fig. 7 shows a linear correlation between coronary flow (Y) and \( qO_2 \) (X) which follows the regression formula of

\[ Y = 369.8X - 57.1; r = 0.956; t = 12.000 \text{ and } p < 0.001. \]

The curve remained at control levels when 0.01, 0.03 and 0.1 \( \mu \)g/kg of epinephrine, 0.5 mg/kg Sotalol and 0.5 mg/kg of Sotalol plus 0.5 \( \mu \)g/kg of epinephrine were given. However, 0.5 \( \mu \)g/kg of epinephrine caused a shift to the right (Fig. 5), which indicates that more oxygen is being consumed after 0.5 \( \mu \)g/kg of epinephrine while performing the same degree of isometric contraction or cardiac work.
0.01, 0.03 and 0.1 \( \mu g/kg \) of epinephrine, 0.5 mg/kg of Sotalol and 0.5 \( \mu g/kg \) of Sotalol plus 0.5 \( \mu g/kg \) of epinephrine were given. However, 0.5 \( \mu g/kg \) of epinephrine caused a shift to the right suggesting that more oxygen is being extracted by the myocardium.

Fig. 7 does not show a linear correlation between \( qO_2 \) (X) and heart rate (Y) for 0.01, 0.03 and 0.1 \( \mu g/kg \) of epinephrine, 0.5 mg/kg of Sotalol and 0.5 mg/kg Sotalol plus 0.5 \( \mu g/kg \) of epinephrine. The \( qO_2 \) was markedly increased by these drugs with a very minimal change in heart rate. Epinephrine, 0.5 \( \mu g/kg \), caused an increase in \( qO_2 \), from an average of 0.194 (control) to 0.241 (post-infusion) with an increase in heart rate from an average of 130 (control) to 142 (post-infusion).

**DISCUSSION**

Small doses of epinephrine (0.01, 0.03 and 0.1 \( \mu g/kg \)) did not affect the left ventricular function curve, coronary flow or myocardial oxygen consumption, however, an epinephrine infusion of 0.5 \( \mu g/kg \) did increase cardiac output, left atrial pressure, heart rate, cardiac work, coronary sinus flow, isometric contraction (dP/dT) and myocardial oxygen consumption.

Other investigators have reported that the increased myocardial metabolic rate, after epinephrine infusion, is directed towards producing positive inotropic and chronotropic changes. However, data recorded in this experiment showed that the myocardium utilized more oxygen than was needed to increase the cardiac work and isometric contraction (dP/dT) after 0.5 \( \mu g/kg \) of epinephrine. This excess oxygen was apparently “wasted”. Epinephrine has been reported to possess an “oxygen wasting” effect or “calorigenic” effect in the heart and other organs *in vivo* (7, 8) and our data concurs with these findings. The increased oxygen utilized by the heart exceeds the increase in coronary flow, therefore, the heart must be extracting more oxygen from coronary blood.

Sotalol (0.5 mg/kg) blocked all of the cardiac effects of epinephrine (0.5 \( \mu g/kg \)) except the increase in coronary blood flow. Other beta-receptor blockers such as propranolol will block the effects of epinephrine, however, these, unlike Sotalol, cause cardiac depression (11). Since the metabolic effects of epinephrine have not been shown to be beta-receptor mediated changes (9) it is concluded that Sotalol may possess this unique property of blocking the calorigenic action of epinephrine.

It could be argued that the blockade of chronotropic changes induced by epinephrine (0.5 \( \mu g/kg \)) was the mechanism by which the increased oxygen consumption was blocked by Sotalol. It was found however, that tachycardia was not essential for increased oxygen consumption after epinephrine in heart lung preparations (12). Data compiled in Fig. 7 concurs with these findings. Other investigators have suggested that factors other than contractile, rate or tension are responsible for increased oxygen consumption following epinephrine (13, 14). Whatever the mechanism of oxygen consumption, it was blocked by Sotalol. It is tempting to conclude that this blockade of epinephrine’s oxygen consumption is responsible for its clinical anti-anginal properties.
REFERENCES