Beneficial Effect of OPC-8212 (3,4-Dihydro-6-[4-(3,4-Dimethoxybenzoyl)-1-Piperazinyl]-2(1H)-Quinolinone) on Myocardial Oxygen Consumption in Dogs with Ischemic Heart Failure

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The effect of a new inotropic agent, OPC-8212 (2(1H)-quinolinone derivative), on myocardial oxygen consumption (MVO₂) following intravenous administration (1 and 3 mg/kg/min) was studied in normal and ischemic failing hearts in open chest dogs. Ischemic failing heart was obtained by intracoronary injection of 15-μm microspheres and volume loading. OPC-8212 significantly increased LV max dP/dt and decreased mean aortic pressure, whereas heart rate was not altered in both normal and failing hearts. Despite the remarkable positive inotropic effect, this agent did not increase MVO₂ in the normal hearts and even decreased MVO₂ in the ischemic failing hearts associated with a decrease in LV end-diastolic pressure and hence, LV chamber size.

These results indicate that OPC-8212 does not increase myocardial oxygen demand, probably because the increase in MVO₂ by positive inotropic effect is offset by a decrease in MVO₂ due to a decrease in chamber size. Thus, OPC-8212 may be promising for the treatment of congestive heart failure with reduced coronary flow reserve.

OPC-8212 (3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone) is a new inotropic agent which is noncatechol and non-glycoside but orally effective. Previous studies demonstrated that this compound has a potent inotropic action which is not achieved through α- or β-adrenergic stimulation, although its underlying mechanism is still unknown. A significant increase in cardiac output and a decrease in pulmonary arterial pressure were observed in the clinical trial in which absence of changes in heart rate and mean aortic pressure was also demonstrated. However, absence of an increase in myocardial oxygen demand is another clinically important characteristic in the treatment of congestive heart failure, since patients with heart failure may have a decreased coronary reserve due to coronary atherosclerosis and/or elevation of resting myocardial oxygen demand because of cardiac hypertrophy. In such patients any further increase in myocardial oxygen demand may precipitate myocardial ischemia and deteriorate myocardial function.

In our previous study we demonstrated that OPC-8212 increases myocardial oxygen demand in proportion to increased contractility in the canine heart when given into the coronary arteries. In the clinical setting, however, aug-

Key Words:
OPC-8212
Positive inotropic agent
Ischemic failing heart
Myocardial oxygen demand

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Japanese Circulation Journal Vol. 50, July 1986 659
### TABLE I  CONTROL VALUES IN EACH PROTOCOL

<table>
<thead>
<tr>
<th>Protocol</th>
<th>mAoP (mmHg)</th>
<th>LVEDP (mmHg)</th>
<th>max dp/dt (mmHg/sec)</th>
<th>CBF (ml/min/100g)</th>
<th>CO (L/min)</th>
<th>HR (b/min)</th>
<th>CVR ($10^5$ dynes/sec/cm$^2$·100g)</th>
<th>SVR ($10^5$ dynes/sec/cm$^2$)</th>
<th>AVO$_2$D (ml/dl)</th>
<th>MVO$_2$ (ml/min·g)</th>
<th>LER (%)</th>
</tr>
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<tbody>
<tr>
<td>OPC-8212</td>
<td>92 ± 8.2</td>
<td>2.7 ± 0.9</td>
<td>2600 ± 250</td>
<td>106 ± 8.8</td>
<td>1.7 ± 0.5</td>
<td>150 ± 24</td>
<td>0.81 ± 0.24</td>
<td>4.5 ± 0.84</td>
<td>6.3 ± 2.1</td>
<td>6.9 ± 1.9</td>
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<tr>
<td>Sulfolane</td>
<td>88 ± 6.9</td>
<td>3.0 ± 1.3</td>
<td>3000 ± 680</td>
<td>110 ± 24</td>
<td>1.7 ± 0.6</td>
<td>150 ± 30</td>
<td>0.66 ± 0.12</td>
<td>4.8 ± 0.38</td>
<td>5.5 ± 2.0</td>
<td>6.7 ± 1.5</td>
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#### Protocol II

**Before embolization**

<table>
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<th>Protocol</th>
<th>mAoP (mmHg)</th>
<th>LVEDP (mmHg)</th>
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<th>CBF (ml/min/100g)</th>
<th>CO (L/min)</th>
<th>HR (b/min)</th>
<th>CVR ($10^5$ dynes/sec/cm$^2$·100g)</th>
<th>SVR ($10^5$ dynes/sec/cm$^2$)</th>
<th>AVO$_2$D (ml/dl)</th>
<th>MVO$_2$ (ml/min·g)</th>
<th>LER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPC-8212</td>
<td>115 ± 14</td>
<td>3.7 ± 0.5</td>
<td>2500 ± 410</td>
<td>93 ± 27</td>
<td>1.9 ± 0.7</td>
<td>150 ± 17</td>
<td>1.07 ± 0.35</td>
<td>5.6 ± 0.24</td>
<td>6.3 ± 2.9</td>
<td>5.9 ± 3.1</td>
<td>19 ± 20</td>
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<tr>
<td>Sulfolane</td>
<td>95 ± 20</td>
<td>8.5 ± 0.8**</td>
<td>2200 ± 600</td>
<td>110 ± 21</td>
<td>1.8 ± 0.5</td>
<td>140 ± 17</td>
<td>0.68 ± 0.12</td>
<td>4.5 ± 0.13</td>
<td>4.9 ± 1.1</td>
<td>5.4 ± 1.4</td>
<td>-17 ± 21*</td>
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**After embolization**

<table>
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<th>Protocol</th>
<th>mAoP (mmHg)</th>
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<th>CBF (ml/min/100g)</th>
<th>CO (L/min)</th>
<th>HR (b/min)</th>
<th>CVR ($10^5$ dynes/sec/cm$^2$·100g)</th>
<th>SVR ($10^5$ dynes/sec/cm$^2$)</th>
<th>AVO$_2$D (ml/dl)</th>
<th>MVO$_2$ (ml/min·g)</th>
<th>LER (%)</th>
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<tbody>
<tr>
<td>OPC-8212</td>
<td>100 ± 14*</td>
<td>8.8 ± 0.7**</td>
<td>2100 ± 210*</td>
<td>108 ± 17</td>
<td>1.5 ± 0.3</td>
<td>140 ± 13</td>
<td>0.78 ± 0.20</td>
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<td>-44 ± 34**</td>
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<td>Sulfolane</td>
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<td>110 ± 21</td>
<td>1.8 ± 0.5</td>
<td>140 ± 17</td>
<td>0.68 ± 0.12</td>
<td>4.5 ± 0.13</td>
<td>4.9 ± 1.1</td>
<td>5.4 ± 1.4</td>
<td>-17 ± 21*</td>
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Values are mean ± SD. Abbreviations: mAoP = mean aortic pressure; LVEDP = LV end-diastolic pressure; max dp/dt = maximum value of the first derivative of LV pressure; CBF = coronary blood flow; CO = cardiac output; HR = heart rate; CVR = coronary vascular resistance; SVR = systemic vascular resistance; AVO$_2$D = arteriovenous oxygen difference; MVO$_2$ = myocardial oxygen consumption; LER = lactate extraction ratio. * = p < 0.05; ** = p < 0.01 vs before embolization.

### TABLE II  HEMODYNAMIC AND MYOCARDIAL METABOLIC CHANGES FOLLOWING THE ADMINISTRATION OF OPC-8212 (NET CHANGE) AND SULFOLANE IN PROTOCOL I

<table>
<thead>
<tr>
<th>Protocol</th>
<th>mAoP (%)</th>
<th>LVEDP (%)</th>
<th>max dp/dt (%)</th>
<th>CBF (%)</th>
<th>CO (%)</th>
<th>HR (%)</th>
<th>CVR (%)</th>
<th>SVR (%)</th>
<th>AVO$_2$D (%)</th>
<th>MVO$_2$ (%)</th>
<th>LER (%)</th>
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<tbody>
<tr>
<td>OPC-8212</td>
<td>1 mg/kg/min</td>
<td>-7.1 ± 6.5</td>
<td>-0.2 ± 0.7</td>
<td>31 ± 25*</td>
<td>16 ± 19</td>
<td>16 ± 9.5*</td>
<td>0.2 ± 5.0</td>
<td>-14 ± 15</td>
<td>-20 ± 6.0*</td>
<td>-25 ± 28</td>
<td>-5.5 ± 26</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/min</td>
<td>-8.2 ± 5.8*</td>
<td>-0.3 ± 0.5</td>
<td>65 ± 34**</td>
<td>31 ± 33</td>
<td>21 ± 21</td>
<td>5.3 ± 14</td>
<td>-24 ± 17*</td>
<td>-21 ± 18*</td>
<td>-22 ± 30</td>
<td>-2.3 ± 25</td>
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</table>

<table>
<thead>
<tr>
<th>Protocol</th>
<th>mAoP (%)</th>
<th>LVEDP (%)</th>
<th>max dp/dt (%)</th>
<th>CBF (%)</th>
<th>CO (%)</th>
<th>HR (%)</th>
<th>CVR (%)</th>
<th>SVR (%)</th>
<th>AVO$_2$D (%)</th>
<th>MVO$_2$ (%)</th>
<th>LER (%)</th>
</tr>
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<tbody>
<tr>
<td>Sulfolane</td>
<td>0.05 ml/kg/min</td>
<td>1.0 ± 4.4</td>
<td>0.3 ± 0.5</td>
<td>1.7 ± 3.3</td>
<td>-1.2 ± 8.3</td>
<td>1.8 ± 9.2</td>
<td>0.5 ± 11</td>
<td>-1.5 ± 6.2</td>
<td>2.7 ± 6.4</td>
<td>4.7 ± 13</td>
<td>-4 ± 23</td>
</tr>
<tr>
<td></td>
<td>0.15 ml/kg/min</td>
<td>-6.2 ± 5.8</td>
<td>0.7 ± 0.7</td>
<td>4.7 ± 5.2</td>
<td>4.8 ± 9.7</td>
<td>4.6 ± 12</td>
<td>3.2 ± 6.8</td>
<td>-5.8 ± 10</td>
<td>-11 ± 14</td>
<td>7.0 ± 13</td>
<td>-3.5 ± 21</td>
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</table>

Values are mean ± SD. Abbreviations are the same as in Table I. * = p < 0.05; ** = p < 0.01 vs control; † = Changes in LVEDP are expressed by changes in absolute value.
Fig.1. Representative records of hemodynamic parameters before and during the infusion of OPC-8212 in a normal canine heart (Fig. 1-a) and in an ischemic failing heart (Fig. 1-b). Panels (a) and (b) show the effects of OPC-8212 of 1 and 3 mg/kg/min, respectively. Arrows indicate the onset of intravenous administration.

Abbreviations: AoP = aortic pressure; LVP = augmented left ventricular pressure; dP/dt = first derivative of LVP; CO = cardiac output; CBF = regional coronary blood flow.
mented contractility and vasodilation elicited by OPC-8212 may decrease the ventricular volume and hence offset the increase in myocardial oxygen demand associated with an augmentation of contractile state. To test this hypothesis we studied myocardial oxygen consumption following intravenous administration of OPC-8212 in the normal and the ischemic failing hearts.

**METHODS**

*Preparation*

Twelve mongrel dogs weighing 10–24 kg were anesthetized with pentobarbital sodium (30 mg/kg i.v.). Trachea was intubated for mechanical ventilation with constant-volume respirator (Aika ventilator R-60). The heart was exposed by mid-sternal thracotomy and transection of the fourth left intercostal space. Electromagnetic flow transducers (Nihon Koden) were placed around the ascending aorta and the left anterior descending coronary artery (LAD). High fidelity LV pressure and the first derivative of LV pressure (dP/dt) were obtained from a miniature pressure transducer (Konigsberg P-7) inserted into the left ventricle through a stab wound in the apex. Aortic pressure was also monitored by Statham P23D pressure transducer with a short fluid-filled catheter inserted into the aortic arch through the left carotid artery. Blood samples were taken from the ascending aorta and the coronary vein. Blood oxygen saturation was measured with ABL-2 blood gas analyzer (Radiometer Copenhagen). Lactate concentration was measured by enzymatic assay.\(^{14}\) Myocardial oxygen consumption (MVO\(_2\)) was expressed as the product of LAD flow and arteriovenous oxygen difference (AVO\(_2\)D) in ml/min/g of myocardium.

*Protocols*

Protocol I (normal heart): Effects of OPC-8212 were examined in six open chest dogs with no specific treatment. OPC-8212, dissolved in 60% sulfonamide (20 mg/ml), was administered intravenously 1 mg/kg/min or 3 mg/kg/min for three minutes in each run. All hemodynamic parameters were continuously monitored until they returned to the control values. Blood was sampled from the aorta and coronary vein in the control period and three minutes after the onset of infusion. The effects of the vehicle alone (sulfonamide: 0.05 ml/kg/min and 0.15 ml/kg/min) were also examined. The order of administration

<table>
<thead>
<tr>
<th>TABLE III</th>
<th>HEMODYNAMIC AND MYOCARDIAL METABOLIC CHANGES FOLLOWING THE ADMINISTRATION OF OPC-8212</th>
<th>Panel Discussion of Opinions of Cardiotonic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mAoP (%)</td>
<td>LVESP (mmHg)</td>
</tr>
<tr>
<td>OPC-8212</td>
<td>1 mg/kg/min</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg/min</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>0.05 ml/kg/min</td>
<td>2.8 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>0.15 ml/kg/min</td>
<td>2.8 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Abbreviations are the same as in Table I. *p < 0.05 vs control; †p = 0.05 vs control.

*Japanese Circulation Journal Vol. 50, July 1986*
Fig. 2. A representative record of myocardial segment length (SL) and other hemodynamic parameters following the intravenous administration of OPC-8212 (1 mg/kg/min) in a dog with LV failure. Abbreviations: SL = segment length, others are as in Fig. 1.

of OPC-8212 and the vehicle was randomized.

Protocol II (failing heart): The same protocol as protocol I was performed in canine hearts with ischemic left ventricular failure. Ischemic failing heart was obtained by intracoronary injection of 15-μm microspheres (3M Co.) into the left main coronary artery through Downey's cannula\textsuperscript{15} Furthermore, volume loading was imposed to increase LV end-diastolic pressure (LVEDP) to 8–10 mmHg.

In one dog, a pair of miniature ultrasonic dimension gauges (Schuessler, 5MHz) was placed in the subendocardium of the anterior wall to measure myocardial segment length. The net effect of OPC-8212 was assessed by subtracting the effect of the vehicle, sulfolane, from the gross effect of OPC-8212 (dissolved in sulfolane).

Statistical analysis

For statistical comparison of the data, appropriate t-tests were employed. Values were expressed as mean ± SD and \( p < 0.05 \) was considered significant.

RESULTS

Protocol I (normal heart): Table I shows the systemic and coronary hemodynamic parameters before administration of OPC-8212 and sulfolane. The mean net effect of OPC-8212 (1 and 3 mg/kg/min) and sulfolane (0.05 and 0.15 ml/kg/min) three minutes after administration are shown in Table II. Representative hemodynamic changes are also depicted in Fig. 1-a. At the low dose (1 mg/kg/min) OPC-8212 increased max \( dP/dt \) and cardiac output (CO) and decreased systemic vascular resistance (SVR). At the high dose (3 mg/kg/min) these hemodynamic changes were associated with significant reductions of mean aortic pressure (mAoP) and coronary vascular resistance (CVR) (Table II). In contrast to these changes, LVEDP, heart rate (HR), LAD flow and MVO\textsubscript{2} showed no significant changes following administration of OPC-8212. Administration of sulfolane alone elicited no significant alterations in systemic and coronary hemodynamics.

Protocol II (failing heart): Table I shows the systemic and coronary hemodynamics before and after microsphere embolization. After intracoronary injection of microspheres (3.8 ± 0.8 \( \times 10^{5} \) g myocardium) and volume loading, LVEDP increased up to 8.8 ± 0.7 mmHg (before OPC-8212) and 8.5 ± 0.8 mmHg (before sulfolane) and lactate extraction ratio turned to negative value. No significant difference was recognized in any parameter between the control states before administration of OPC-8212 and
sulfonamide. Figure 1-b shows the representative hemodynamic changes following administration of OPC-8212 (1 and 3 mg/kg/min) in a dog with ischemic failing heart. Table III shows the mean net effects of OPC-8212 and sulfonamide. OPC-8212 elicited similar hemodynamic alterations as in protocol I except for a significant decrease in LVEDP. Figure 2 depicts a marked decrease in segment length associated with a decrease in LVEDP and an increase in max dP/dt in a dog. In contrast to protocol I, however, MVO₂ showed significant reduction with administration of OPC-8212 (at 1 mg/kg/min). In the high dose administration AVO₂D was significantly decreased.

Sulfonamide alone also showed a slight but significant reduction of LVEDP, whereas other parameters were insignificantly altered. In neither protocol arrhythmogenic effect was observed during infusion of OPC-8212.

**DISCUSSION**

The present study demonstrated that a new inotropic agent, OPC-8212, could augment the inotropic state without an increase in myocardial oxygen demand in both normal and ischemic failing canine hearts. In failing hearts, myocardial oxygen demand (MVO₂) was even decreased following administration of this agent despite a marked increase in max dP/dt.

OPC-8212 elicited a positive inotropic effect with modest vasodilatory action in normal hearts (protocol I), and did not increase heart rate as observed in our previous study.¹² A significant decrease in coronary vascular resistance was also observed during infusion of OPC-8212, indicating that this agent may dilate the coronary arteries not only through an increase in oxygen demand but also through its direct action. The direct vasodilatory effect of coronary artery may also be supported by a significant decrease in coronary arteriovenous oxygen difference (AVO₂D) in high dose administration to the failing heart.

MVO₂ is dependent on systolic wall stress as well as ventricular contractility. Therefore, MVO₂ during administration of inotropic agent is determined by the balance between increase in contractility and reduction of cardiac chamber size.

In our previous study we demonstrated that OPC-8212 increased MVO₂ in proportion to an increase in myocardial oxygen demand when selectively administered into the coronary artery. It should be noted, however, that in the previous study, regional administration did not alter the systemic hemodynamics and hence, volume of the heart was not decreased during administration as evidenced by the absence of a change in LVEDP. In contrast, when the agent is given intravenously, its vasodilatory action and positive inotropic action may decrease the heart size and have an unloading effect on the heart. Indeed, in protocol II (failing heart) LVEDP was decreased following administration of OPC-8212 in a dose-dependent manner. Figure 2 clearly shows a marked decrease in myocardial segment length associated with a decrease in LVEDP during infusion of OPC-8212. A decrease in muscle length implies a decrease in ventricular volume and hence, a decrease in wall stress based on Laplace's law. Therefore, the present results are not incompatible with our previous results but rather indicate that OPC-8212 does not increase MVO₂ when administered intravenously: the "oxygen wasting effect" is offset by a reduction of wall stress due to decrease in the chamber size.

It was reported that in normal subjects digitalis glycosides increased MVO₂, whereas in patients with congestive heart failure the effects of increases in contractility on stimulation of MVO₂ were offset by reduction in ventricular chamber and thus, wall stress.¹⁶ Milrinone has a similar effect on myocardial energetics although mechanism of positive inotropic action is different from that of the digitalis glycosides; it increases MVO₂ in the normal heart but does not increase MVO₂ in the failing heart despite a marked increase in cardiac output.¹⁷ In our study, the ratio of the increase in cardiac output (ΔCO) versus the increase in MVO₂ (ΔMVO₂), i.e., the left ventricular external efficiency, was much higher in the failing heart, particularly in the high dose protocol (3 mg/kg/min). These results indicate that the volume-reducing effect of inotropic agents is markedly manifested when the ventricle is extremely dilated. Thus, left ventricular external efficiency may be improved in severe congestive heart failure.

In the present study ischemic failing heart was obtained by the intracoronary embolization of 15-µm microspheres. This model of failing heart has advantages over the previous ischemic model obtained by occlusion of the coronary arteries: 1) the myocardium is diffusely depressed and thus, asynergic movement is not
induced, 2) myocardial ischemia is relatively stable for a few hours; and 3) extent of myocardial ischemia can be controlled by varying the dose of microspheres. Histochemical examination (succinic dehydrogenase staining) of myocardium embolized with 15-μm microspheres demonstrated the distribution of disseminated patchy ischemias with diameters of 100–150 μm throughout the ventricular wall. 

Although this model is somewhat different from a model with common coronary artery disease, the present results strongly suggest that OPC-8212 may not increase MVO₂ in ischemic heart failure, but may improve left ventricular external efficiency. Recently, Opie proposed several criteria for a desirable inotropic agent in his review. He emphasized that the absence of chronotropic effect and minimal increase in MVO₂ are very important characteristics for the inotropic agent since an increase in MVO₂ has the potential to exacerbate underlying myocardial dysfunction and arrhythmia in congestive heart failure.

The present study clearly demonstrated that OPC-8212 fulfills these criteria. A modest vaso-dilatory effect is also salutary for heart failure commonly associated with overcompensation of peripheral vasoconstriction. Therefore, these results strongly suggest that OPC-8212 is promising for the treatment of congestive heart failure although further clinical studies are necessary to support this conclusion.

Acknowledgement

The authors thank Otsuka Pharmaceutical Co., Ltd. for supplying OPC-8212.

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