REGULATION OF CORONARY BLOOD FLOW BY COUNTERACTION OF CORONARY VASCULAR α AND β ADRENERGIC ACTIVATION DURING EXPERIMENTAL PLIAIBLE CORONARY STENOSIS

Susumu Sakamoto, M.D., Mitsuhiro Yokoyama, M.D. and Hisashi Fukuzaki, M.D.

In order to evaluate the role of adrenergic receptor-mediated vasomotions of large epicardial coronary arteries in changing coronary blood flow (CBF), the effects of intracoronary norepinephrine (NE), 1.0 µg/min, were examined in dogs with coronary stenosis which preserved stenosis vasomobility. In untreated dogs, NE caused no significant changes in CBF and stenosis resistance (SR). In dogs treated with propranolol, NE decreased CBF by 65 ± 7.0% (mean ± SE) and produced 12-fold intensification of SR followed by LV dP/dt reduction. Similar detrimental responses to NE were observed in dogs treated with atenolol. In dogs treated with phenolamine, NE increased CBF by 33 ± 5.6% and decreased SR by 65 ± 7.1%. When NE was administered directly distal to the stenosis to exclude responses of the stenosed coronary segment, NE failed to affect CBF and SR. These results indicated that α receptor stimulation intensified stenosis severity, profoundly decreased CBF and evoked myocardial ischemia, whereas β stimulation dilated coronary stenosis and increased CBF. The net effects of NE were due to balanced α and β stimulation. Thus, disproportionate activation of α and β (probably β1) adrenergic receptors in large coronary arteries with pliable stenosis could modulate their tone and plays an important role in the regulation of CBF.

It is well established that primary reduction in coronary blood flow due to total or subtotal reversible epicardial coronary arterial narrowing is responsible for variant angina pectoris.1-2 Although the pathogenesis of coronary spasm is unknown, several studies have demonstrated that pharmacological3 and reflex stimulation4 of coronary α adrenergic receptors can mediate episodes of coronary spasm. They have suggested that sympathetic control of large coronary arterial tone may play an important role in the regulation of myocardial blood flow. Both in vitro and in vivo experiments have provided evidences of α receptor-mediated vasoconstriction5-8 and β vasodilation5,9 However, no investigation has characterized the influence of adrenergic receptor-mediated vasomotion in large coronary arteries on the regulation of coronary blood flow and stenosis severity.

Recently, we have developed a canine model with a pliable coronary stenosis which preserved active vasomotion in a stenosed segment10 resembling human coronary stenosis in patients.

Key Words:
Norepinephrine
Coronary blood flow
Coronary stenosis
Adrenergic receptors

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The First Department of Medicine, Kobe University School of Medicine, Kobe, Japan
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Mailing address: Susumu Sakamoto, M.D., First Department of Medicine, Kobe University School of Medicine, Kusunoki-cho 7-chome Chuoku, Kobe 650, Japan

Fig. 1. Experimental preparation. LAD = left anterior descending coronary artery; Cx = left circumflex coronary artery

with vasospastic angina pectoris. Our previous reports demonstrated dynamic changes in coronary blood flow and stenosis severity as a result of alterations of large coronary arterial tone following administration of ergonovine, nitroglycerin and nifedipine.10–13

The present study was designed to evaluate whether adrenergic stimulation in large epicardial arteries with pliable coronary stenoses altered coronary blood flow and to corroborate sympathetic control of large coronary vessels of the beating heart. We examined the effects of intracoronary infusion of norepinephrine (NE), in a dose low enough to avoid systemic hemodynamic changes, on coronary vasculature in the presence and absence of α and β adrenergic blockades using this experimental model.

METHODS

Mongrel dogs of either sex, weighing 11–15 kg, were premedicated with morphine sulfate, 1 mg/kg, and anesthetized with α chloralose, 100 mg/kg, iv. Dogs were intubated and ventilated with a mechanical respirator with positive pressure, using room air supplemented with oxygen. Blood gases and acid/base balance were maintained within normal limits. A catheter was passed through the right femoral artery and advanced into the aortic arch for aortic pressure monitoring. Another catheter was also placed in the right femoral vein for intravenous infusion. The left thoracotomy was then performed through the fifth intercostal space, and the heart was supported in a pericardial cradle. A stiff catheter (10 cm long) was inserted into the left ventricle through the apex to record left ventricular (LV) pressure and its first derivative (LV dP/dt). The left common carotid artery was exposed and the proximal portion of the left circumflex coronary artery was dissected free. Following administration of 5,000 units heparin, the circumflex artery was ligated, promptly cannulated at just its distal portion with a thin metal cannula (2.4 mm i.d.) and continuously perfused from the left carotid artery through the perfusion tubing with a minimal internal diameter of 2.4 mm (Fig. 1). Heparin, 2,000 units, was supplemented every 30 minutes. Coronary perfusion pressure at the tip of the cannula was measured and it was confirmed that mean coronary perfusion pressure and mean aortic pressure were identical in each experiment. In addition, the adequacy of this perfusion system was demonstrated by a preserved autoregulatory reserve greater than 300% peak reactive hyperemic response after a 15 second total coronary occlusion in each dog. Circumflex coronary blood flow (CBF) was measured with a precalibrated extracorporeal electromagnetic flow probe (Nihonkoden MF-26, 3 mm i.d.). A polyethylene catheter was placed to a small branch of the circumflex artery distal to the occlusion site for measurement of distal coronary pressure (DCP). Pressures were measured with Statham transducers (P23Db). Measurements of heart rate, aortic pressure, LV pressure, LV dP/dt, LV end-diastolic pressure (LVEDP), DCP and CBF were continuously recorded. The preparation was allowed to stabilize for at least 30 minutes after coronary cannulation.

Coronary stenosis was produced with the specially made microballoon occluder, consisting of a minute rubber balloon attached to the tip of polyethylene tubing (0.6 mm o.d.). The construction of the microballoon occluder and the characteristics of the experimental model were reported previously.10 This occluder was inserted through the side arm of the perfusion tubing and advanced into the intact proximal portion of the left circumflex coronary artery. It was ascertained that the insertion of the microballoon occluder into the coronary artery affected neither resting CBF and its phasic pattern nor the peak reactive hyperemic response before inflation of the balloon occluder. The size of the balloon was finely adjusted by expansion with saline to obtain the pressure gradient across the stenosis by approximately
TABLE 1  EFFECTS OF NOREPINEPHRINE WITHOUT ADRENERGIC BLOCKADES

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Mean aortic pressure (mmHg)</th>
<th>LV pressure systolic (mmHg)</th>
<th>LV pressure end-diastolic (mmHg)</th>
<th>LV dP/dt (mmHg/sec)</th>
</tr>
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<tbody>
<tr>
<td><strong>Without stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection</td>
<td>134 ± 5.8</td>
<td>101 ± 3.6</td>
<td>123 ± 4.1</td>
<td>5.8 ± 0.7</td>
<td>2344 ± 158</td>
</tr>
<tr>
<td>During NE</td>
<td>137 ± 6.1</td>
<td>102 ± 3.8</td>
<td>125 ± 4.4</td>
<td>5.6 ± 0.7</td>
<td>2881 ± 170**</td>
</tr>
<tr>
<td><strong>With stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preocclusion</td>
<td>134 ± 5.7</td>
<td>103 ± 3.9</td>
<td>127 ± 4.5</td>
<td>6.4 ± 0.8</td>
<td>2338 ± 144</td>
</tr>
<tr>
<td>Preinjection</td>
<td>132 ± 5.8</td>
<td>102 ± 3.8</td>
<td>126 ± 4.1</td>
<td>6.4 ± 0.8</td>
<td>2294 ± 142</td>
</tr>
<tr>
<td>During NE</td>
<td>132 ± 5.9</td>
<td>103 ± 3.9</td>
<td>127 ± 4.3</td>
<td>6.0 ± 0.7</td>
<td>2800 ± 156**</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

LV = left ventricular; NE = norepinephrine

**Compared to above p < 0.01.

Fig. 2. Effects of norepinephrine (NE) without adrenergic blockades on coronary blood flow (CBF), mean distal coronary pressure (mDCP) and stenosis resistance (SR). P = preinjection

25–30 mmHg, and the expansion volume was kept constant. Stenosis resistance (SR) was calculated by dividing the mean pressure gradient across the stenosis by mean CBF. The mean pressure gradient was calculated as mean aortic pressure minus mean DCP.

Effects of NE without adrenergic blockades

In eight dogs without any treatment, the effects of intracoronary infusion of NE, 1.0 μg/min, were examined in the presence and absence of partial coronary obstruction. During both conditions, a 10-minute stabilization period was allowed before NE administration, and then an intracoronary infusion of NE was performed via coronary perfusion line for 2 minutes at a rate of 0.2 ml/min. It was confirmed that this perfusion rate of physiologic saline, a vehicle of NE, did not affect coronary hemodynamic parameters, and that the transit time between injection site and cannula tip was less than one second in the presence and absence of coronary stenosis in the preliminary examinations. Measurements of hemodynamic parameters were continuously made during the preinfusion control period and drug infusion. The sequence of the conditions with and without coronary stenosis to be examined was selected randomly. There was a 20–30 minute interval between respective NE infusion.

Effects of NE with adrenergic blockades

Nonselective β adrenergic blockade was accomplished with propranolol, 0.5–1.0 mg/kg, iv, in 8 dogs and selective β1 blockade was accomplished with atenolol, 0.5–0.8 mg/kg, iv, in another 6 dogs, and verified by the failure of heart rate to change following an intravenous injection of isoproterenol, 3.0 μg/kg. In 8 dogs, α blockade was accomplished with phentolamine,
TABLE II  EFFECTS OF NOREPINEPHRINE WITH β ADRENERGIC BLOCKADE

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Mean aortic pressure (mmHg)</th>
<th>LV pressure</th>
<th>LV dP/dt (mmHg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>systolic</td>
<td>end-diastolic</td>
</tr>
<tr>
<td>Without stenosis</td>
<td></td>
<td></td>
<td>(mmHg)</td>
<td>(mmHg)</td>
</tr>
<tr>
<td>Preinjection</td>
<td>98 ± 3.4</td>
<td>104 ± 4.5</td>
<td>123 ± 5.0</td>
<td>9.0 ± 0.6</td>
</tr>
<tr>
<td>During NE</td>
<td>98 ± 3.4</td>
<td>105 ± 4.1</td>
<td>123 ± 4.8</td>
<td>9.0 ± 0.6</td>
</tr>
<tr>
<td>With stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preocclusion</td>
<td>103 ± 4.0</td>
<td>104 ± 4.1</td>
<td>124 ± 4.2</td>
<td>8.9 ± 0.7</td>
</tr>
<tr>
<td>Preinjection</td>
<td>104 ± 3.8</td>
<td>103 ± 4.3</td>
<td>123 ± 4.3</td>
<td>8.9 ± 0.7</td>
</tr>
<tr>
<td>During NE</td>
<td>102 ± 3.6</td>
<td>100 ± 4.1</td>
<td>100 ± 4.2</td>
<td>9.2 ± 0.6</td>
</tr>
<tr>
<td>Distal NE with stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preocclusion</td>
<td>105 ± 3.8</td>
<td>105 ± 4.3</td>
<td>126 ± 4.4</td>
<td>8.6 ± 0.7</td>
</tr>
<tr>
<td>Preinjection</td>
<td>105 ± 4.0</td>
<td>105 ± 4.2</td>
<td>125 ± 4.1</td>
<td>8.7 ± 0.7</td>
</tr>
<tr>
<td>During NE</td>
<td>103 ± 4.1</td>
<td>104 ± 4.1</td>
<td>123 ± 4.1</td>
<td>8.7 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
LV = left ventricular; NE = norepinephrine
**Compared to above p < 0.01.

Fig. 3. Effects of norepinephrine (NE) with propranolol on coronary blood flow (CBF), mean distal coronary pressure (mDCP) and stenosis resistance (SR).
*p < 0.05, **p < 0.01 compared to preinjection (P).

0.5–1.0 mg/kg, iv, and verified by 4-fold increase in the intravenous norepinephrine dose that elevated mean aortic pressure by 15 mmHg. Twenty minutes later, the effects of intracoronary NE, 1.0 μg/min, were examined in the presence and absence of coronary stenosis utilizing the methods outlined above. In addition, the effects of NE directly infused into coronary arteries distal to the stenosis were examined in order to evaluate whether the coronary responses to NE were due to its direct action to the stenosed portion of the coronary artery or due to the other indirect mechanisms. A polyethylene tubing (0.6 mm o.d.) was advanced retrogradely until its tip was just distal to the stenosis through a small branch of the circumflex coronary artery. A distal coronary infusion of NE, 1.0 μg/min, was performed via this tubing at the same infusion rate for 2 minutes in the presence of partial coronary obstruction in dogs treated with propranolol or phentolamine. At the conclusion of each experiment, it was confirmed that similar magnitude of coronary flow responses to intracoronary infusion of adenosine, 3 μM/min, was observed between via the coronary perfusion line and the distal coronary infusion tubing in the absence of coronary stenosis.

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Statistical Analysis

The mean and standard error of the mean (SEM) were calculated for all variables. Data for single response in the same animal were analyzed by t test for paired comparison. Data were analyzed between groups with and without adrenergic blockades using analysis of variance and Tukey's test.

RESULTS

There were no significant differences in resting values of all hemodynamic parameters in the absence of partial coronary obstruction between groups with and without adrenergic blockades. Preinjection values of coronary hemodynamic parameters after application of coronary stenosis were not different between groups. The data during NE infusion were expressed as the values at the end of each NE infusion.

Effects of NE without adrenergic blockades

Table I and Fig. 2 summarize the effects of intracoronary NE in untreated animals. In the absence of partial coronary obstruction, NE did not affect mean aortic and LV systolic pressures, LVEDP and heart rate but did increase LV dP/dt and CBF by 538 ± 53 mmHg/sec and 21 ± 1.5%, respectively. Application of coronary stenosis reduced CBF and mean DCP by 19 ± 2.0% and 25 ± 2.0 mmHg, respectively. In the presence of coronary stenosis, NE did not cause significant changes in CBF, mean DCP, SR and other systemic hemodynamics with exception of LV dP/dt elevation.

Effects of NE with β blockades

Table II and Fig. 3 summarize the effects of NE in dogs treated with propranolol. Intravenous injection of propranolol, 0.5–1 mg/kg, decreased heart rate, LV dP/dt and CBF by 36 ± 2.6 beats/min (p < 0.01), 860 ± 81 mmHg/sec (p < 0.01) and 34 ± 2.8% (p < 0.01), respective-

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TABLE III  EFFECTS OF NOREPINEPHRINE WITH α ADRENERGIC BLOCKADE

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Mean aortic pressure (mmHg)</th>
<th>LV pressure systolic (mmHg)</th>
<th>LV pressure end-diastolic (mmHg)</th>
<th>LV dP/dt (mmHg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection</td>
<td>139 ± 4.5</td>
<td>98 ± 4.8</td>
<td>123 ± 5.3</td>
<td>5.4 ± 0.6</td>
<td>2420 ± 178</td>
</tr>
<tr>
<td>During NE</td>
<td>142 ± 4.2</td>
<td>98 ± 4.7</td>
<td>124 ± 5.0</td>
<td>5.2 ± 0.6</td>
<td>2894 ± 188**</td>
</tr>
<tr>
<td><strong>With stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoclusion</td>
<td>139 ± 4.2</td>
<td>100 ± 4.5</td>
<td>125 ± 4.8</td>
<td>5.7 ± 0.6</td>
<td>2481 ± 194</td>
</tr>
<tr>
<td>Preinjection</td>
<td>137 ± 4.4</td>
<td>99 ± 3.9</td>
<td>123 ± 4.4</td>
<td>5.8 ± 0.7</td>
<td>2454 ± 190</td>
</tr>
<tr>
<td>During NE</td>
<td>140 ± 4.0</td>
<td>100 ± 4.0</td>
<td>123 ± 4.5</td>
<td>5.7 ± 0.7</td>
<td>2981 ± 202**</td>
</tr>
<tr>
<td><strong>Distal NE with stenosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoclusion</td>
<td>140 ± 5.2</td>
<td>99 ± 4.1</td>
<td>122 ± 4.4</td>
<td>5.7 ± 0.7</td>
<td>2460 ± 188</td>
</tr>
<tr>
<td>Preinjection</td>
<td>141 ± 5.0</td>
<td>98 ± 4.2</td>
<td>122 ± 4.5</td>
<td>5.9 ± 0.7</td>
<td>2423 ± 190</td>
</tr>
<tr>
<td>During NE</td>
<td>140 ± 5.0</td>
<td>98 ± 4.0</td>
<td>122 ± 4.4</td>
<td>6.0 ± 0.7</td>
<td>2876 ± 184**</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.  
LV = left ventricular; NE = norepinephrine  
**Compared to above p < 0.01.

Fig.5. Effects of norepinephrine (NE) with phentolamine on coronary blood flow (CBF), mean distal coronary pressure (mDCP) and stenosis resistance (SR). **p < 0.01 compared to preinjection (P).

ly, and elevated LVEDP by 2.8 ± 0.4 mmHg (p < 0.05). In the absence of coronary stenosis, CBF was slightly decreased during NE infusion, but this reduction was not statistically significant. CBF and mean DCP were reduced by partial coronary obstruction by 15 ± 2.6% and 23 ± 3.0 mmHg, respectively. In the presence of coronary stenosis, NE drastically decreased CBF and mean DCP by 65 ± 7.0% and 41 ± 5.0 mmHg, respectively, and caused 12-fold intensification of SR associated with LV dP/dt reduction by 324 ± 83 mmHg/sec. Figure 4 shows typical response to NE in a dog treated with propranolol. Distal coronary administration of NE had little effects on systemic and coronary hemo-
dynamic parameters.

Pretreatment with atenolol, 0.5–0.8 mg/kg, iv, decreased heart rate, LV dP/dt and CBF by 41 ± 3.2 beats/min (p < 0.01), 763 ± 80 mmHg/sec (p < 0.01) and 38 ± 4.0% (p < 0.01), respectively. In the absence of coronary stenosis, NE had no significant effects on all hemodynamic parameters. Application of coronary stenosis decreased CBF and mean DCP by 14 ± 3.1% and 21 ± 3.2 mmHg, respectively. During coronary stenosis, NE produced marked decreases in CBF and mean DCP by 73 ± 9.1% (p < 0.01) and 44 ± 3.8 mmHg (p < 0.01), respectively, and 15-fold intensification of SR (p < 0.05) associated with LV dP/dt reduction

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by 288 ± 42 mmHg/sec (p < 0.05). There were no significant changes in heart rate, mean aortic and LV systolic pressures and LVEDP. These responses of CBF, mean DCP and SR to NE were not significantly different from those in dogs treated with propranolol.

Effects of NE with α blockades

Table III and Fig. 5 summarize the effects of NE in dogs treated with phentolamine. Intravenous injection of phentolamine, 0.5–1 mg/kg, reduced mean aortic and LV systolic pressures by 10 ± 2.6 mmHg (p < 0.01) and 9 ± 2.8 mmHg (p < 0.01), respectively, and increased heart rate by 8 ± 2.2 beats/min (p < 0.05). In the absence of coronary stenosis, LV dP/dt and CBF increased during NE infusion by 474 ± 53 mmHg/sec and 26 ± 2.4%, respectively. These increments in LV dP/dt and CBF were not different from those in untreated dogs. Partial coronary obstruction decreased CBF and mean DCP by 21 ± 1.5% and 28 ± 3.2 mmHg, respectively. In the presence of coronary stenosis, NE produced significant increases in CBF and mean DCP by 33 ± 5.6% and 15 ± 2.3 mmHg, respectively, and decreased SR by 65 ± 7.1%. Figure 6 shows typical response to NE in a dog treated with phentolamine. Distal coronary infusion of NE did not change systemic and coronary hemodynamic parameters, with exceptions of a similar increase in LV dP/dt as that induced by NE via coronary perfusion line.

DISCUSSION

The results of this study showed that during pliable coronary stenosis, intracoronary NE intensified SR and profoundly decreased CBF followed by a decline in LV dP/dt in dogs with β blockades, whereas this agent reduced SR and increased CBF in dogs treated with α blockade. In untreated dogs, NE did not cause significant changes in SR and CBF.

Many previous reports have demonstrated sympathetic control of coronary vasculature in changing coronary flow.5,14 However, this effect...
was attributed exclusively to alterations in distal resistance vessel tone. Since the contribution of large coronary arteries to total coronary vascular resistance in the normal heart is small (about 5% \textsuperscript{15}) large coronary vasomotion have little importance in the regulation of coronary flow in intact animals. The change in coronary flow is practically determined by vasomotion of resistance vessels\textsuperscript{6} It is assumed that when coronary arterial inflow is restricted by partial coronary obstruction, that normal vasomotion of large epicardial coronary arteries can play an important role in the regulation of coronary flow? The purpose of the present investigation was to prove this hypothesis using newly developed experimental model of coronary stenosis.

The present experiment employed a canine model of coronary stenosis produced by an intraluminal placement of a microballoon occluder\textsuperscript{10–13} This preserved active vasomotion in a stenosed segment and was capable of changing its severity as a result of alterations of large coronary arterial tone. Using this model, adrenergic stimulation was achieved by an intracoronary administration of NE, 1.0 \textmu g/min. This NE dose was chosen because its dose was low enough to avoid systemic hemodynamic alterations and gave cardiac and coronary effects of a magnitude similar to that observed during carotid baroreceptor reflex sympathetic activation\textsuperscript{16} NE was infused into circumflex coronary arteries proximal to the stenosis via coronary perfusion system or into the arteries distal to the stenosis. Direct actions of NE to the stenosed coronary segment were assessed by comparing the effects of NE through these two infusion routes which produced similar effects on distal coronary bed and cardiac muscles.

\( \alpha \) Receptor mediated coronary vasoconstriction is well recognized in animal and human studies\textsuperscript{6,16–20} These reports have demonstrated that, under normal resting conditions, coronary arterial \( \alpha \) tone has a modest restricting effect on myocardial blood flow. In the presence of coronary stenosis, sympathetic vasoconstrictor influence competes with local metabolic control of the coronary circulation and increases coronary vascular resistance. In our experiments, a constant infusion of NE, 1.0 \textmu g/min, did not reduce CBF in dogs treated with \( \beta \) blockade in the absence of coronary stenosis, because \( \alpha \) adrenergic vasoconstriction of coronary arteries could be compensated for by the autoregulatory vasodilation of intramyocardial arterioles. On the contrary, NE infusion decreased CBF and LV dP/dt during partial coronary obstruction in \( \beta \) blockade dogs. The NE that was infused directly into coronary arteries distal to the stenosis had no coronary hemodynamic effects, so activation of \( \alpha \) receptors in large coronary arteries was thought to be responsible for this detrimental response. Therefore, an increase in large coronary arterial tone in response to \( \alpha \) adrenergic stimulation could intensify the severity of stenosis and reduce CBF and LV dP/dt, indi-
cating a manifestation of myocardial ischemia. Our experimental results are relevant to clinical observation that an intensification of stenosis severity due to sympathetic large coronary vasconstriction is a most likely mechanism for the decline in myocardial blood flow during cold pressor stress\(^{19}\) and isometric handgrip exercise\(^{20}\) in some humans with coronary artery disease.

After \(\alpha\) adrenergic blockade, NE increased CBF, in the absence of coronary stenosis, as a result of resistance vessel dilatation mainly due to an increase in myocardial metabolism. Similar responses to NE were observed in untreated animals without coronary stenosis. During partial coronary obstruction, NE increased CBF and decreased SR in the presence of \(\alpha\) blockade, whereas there appeared no responses to NE when this agent was infused into coronary arteries distal to the stenosis. These results indicated that direct \(\beta\) receptor stimulation in large epicardial coronary artery caused its dilating actions and reduced stenosis severity. The presence of adrenergic vasodilator \(\beta\) receptors in large coronary arteries has been demonstrated using isolated coronary vessel strips\(^{5}\). Recently, Vatner et al.\(^{9}\) reported that \(\beta\) receptor stimulation could dilate large epicardial coronary arteries by means of measurement of the coronary arterial diameter in intact conscious dogs. However, they suggested that this dilating response was possibly due to an increase in myocardial metabolic demands and not due to direct activation of \(\beta\) adrenergic receptors within large coronary arteries. In our experiment, NE administration through two different infusion routes induced similar elevations of LV \(dP/dt\), indicating that the increases in myocardial metabolic demands were similar. Therefore, our results showed that direct \(\beta\) receptor mediated vasodilation exists in large epicardial coronary arteries independent of changes in myocardial metabolism. In contrast to the studies using a normal heart without coronary stenosis, flow-dependent vasodilation was almost excluded by the presence of flow-limiting coronary stenosis in our experimental model\(^{21,22}\).

In untreated dogs, NE produced no significant changes in CBF and SR during coronary stenosis in contrast to those in dogs treated with adrenergic blockades (Fig. 7). These findings suggested that the net effects of NE were due to balanced \(\alpha\) and \(\beta\) receptor activation and that disproportionate activation of \(\alpha\) and \(\beta\) receptor activation could modulate large vessel tone.

There is still controversy about the subclassification of \(\beta\) receptors in coronary arteries. In this study, atenolol was equipotent to manifest \(\alpha\) adrenergic vasoconstriction by NE infusion as that of propranolol, suggesting that the \(\beta\) adrenergic receptor subtype that counteracts \(\alpha\) vasoconstriction is not \(\beta_2\) but \(\beta_1\). Therefore, the relaxant response of large coronary arteries might be mediated by \(\beta_1\) receptors.

In conclusion, the results of present investigations indicated that \(\alpha\) receptor stimulation constricted large coronary arteries and profoundly decreased CBF associated with a manifestation of myocardial ischemia, whereas \(\beta\) receptor stimulation caused large vessel dilatation and increased CBF. Thus, the balance between \(\alpha\) and \(\beta\) adrenergic receptor activation in large coronary arteries could modulate their tone and play a significant role in the regulation of CBF within coronary stenotic lesions that preserved its vasomobility. These finding may be of importance in understanding of the pathophysiology of ischemic heart disease.

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