Mechanism of Ergonovine-Induced Hyperconstriction of the Large Epicardial Coronary Artery in Conscious Dogs a Month After Arterial Injury

Kensuke Egashira, Hitonobu Tomoike, Yasuo Hayashi, Akira Yamada, Motoomi Nakamura, and Akira Takeshita

This study investigated the mechanism of ergonovine-induced hyperconstriction of coronary artery in conscious dogs that had undergone endothelial denudation one month earlier. The diameter of the large epicardial coronary artery was continuously measured by a sonomicrometer in 12 dogs in which two pairs of 10-MHz piezoelectric crystals had been surgically implanted at the denuded and nondenuded sites of coronary arteries. A month after the endothelial denudation, intravenous ergonovine (0.01, 0.1, 0.3, and 1.0 mg) produced transient dilation followed by dose-dependent constriction. The degrees of dilation were comparable between the denuded and nondenuded sites. The magnitudes of constriction induced by ergonovine were significantly larger in the denuded site than in the nondenuded site: the percent reductions in diameter evoked by 0.3 mg ergonovine were 14.4±2.3% and 3.8±0.8% (p<0.01) at the denuded and nondenuded sites, respectively. The magnitudes of constriction induced by intravenous phenylephrine (0.02, 0.06, and 0.2 mg) were comparable in the denuded and nondenuded sites. Methysergide (a nonselective serotonergic blocker) in a dose of 0.5 mg/kg significantly inhibited vasoconstriction induced by ergonovine (0.3 mg) from 13.1±1.1% to 2.7±1.0% (p<0.01) at the denuded site and from 4.2±0.6% to 0.8±0.3% (p<0.05) at the nondenuded site. Diltiazem (1.0 mg/kg) selectively inhibited the ergonovine-induced hyperconstriction. Ketanserin (0.5 mg/kg), prazosin (1.0 mg/kg), or indomethacin (5.0 mg/kg) did not prevent the ergonovine-induced hyperconstriction. Histological study revealed intimal thickening and regenerated endothelium in the denuded site. These results suggest that the ergonovine-induced coronary hyperconstriction in our conscious canine model may be mediated by activation of serotonergic receptors with a subsequent increase in calcium influx into vascular smooth muscle cells. (Circulation Research 1992;71:435–442)

Key Words • coronary vasospasm • ergonovine • serotonin • endothelium • coronary circulation

Enhanced vasoconstriction to vasoactive stimuli has been noted in coronary arteries a few months after arterial injury in pigs and dogs.1–4 Augmented vasoconstriction in response to these agonists is also demonstrated in atherosclerotic blood vessels of rabbits,5–7 monkeys,8,9 and humans.10,11 These abnormal constricting responses may result mostly from local hyperreactivity in the arterial wall, which relates to dysfunction of the endothelium, hypersensitivity of vascular smooth muscle, or both.12 This local vascular hyperreactivity may contribute not only to the pathogenesis of vasospasm13 but also to restenosis after angioplasty.13

Ergonovine maleate is one of the agents that has been used to induce coronary vasospasm in humans.14–16 The loci of angiographically documented coronary vasospasms by ergonovine are reported to be identical to those where spasms occur spontaneously.17 An intracoronary infusion of ergonovine induces focal vasospasm in patients with variant angina, suggesting the importance of local hyperreactivity.18 Coronary vasospasm usually occurs at atherosclerotic lesions,12,19,20 implying a possible contribution of atherosclerosis to coronary vasospasm. Previous experimental studies have reported that ergonovine causes vasoconstriction of intact arterial tissues by serotoninergic or α-adrenergic receptors and/or by vasoconstrictor prostanoids.21–24 However, the mechanism by which ergonovine induces hypercon-
striction or vasospasm of the coronary artery in vivo has not been determined.

We previously created a canine model in which an intravenous administration of ergonovine caused angiographically documentable focal hyperconstriction of coronary arteries at a site where endothelial denudation had been performed a few months before. In this animal model, in vitro contractile responses evoked with ergonovine and serotonin were markedly augmented in the denuded coronary artery. The purpose of this study was 1) to reproduce this ergonovine-induced coronary hyperconstriction in our conscious dog model and 2) to investigate the mechanism of ergonovine-induced hyperconstriction by using various pharmacological antagonists.

Materials and Methods

Drugs

Ergonovine maleate (Takeda Pharmaceuticals, Osaka, Japan), methysergide (Sandoz Chemicals, Basel, Switzerland), ketanserin (Kyowa Hakko Chemicals, Tokyo), prazosin (Taito-Pfizer, Tokyo), indomethacin (Sigma Chemical Co., St. Louis, Mo.), and diltiazem (Tanabe Chemicals, Tokyo) were used. All drugs were diluted in 5 ml physiological salt solution except for prazosin and indomethacin. Prazosin was diluted in warmed distilled water. Indomethacin was diluted with 0.8% sodium bicarbonate solution.

Animal Model

Adult mongrel dogs (20–28 kg) were housed individually under conditions of controlled room temperature and were fed a commercial regular diet. Under general anesthesia with sodium pentobarbital (20 mg/kg), a preshaped Kifa catheter was inserted from the carotid artery into the orifice of the left coronary artery. After an intravenous injection of heparin (5,000 units), the endothelial surface of the proximal portion of the left circumflex coronary artery was denuded using a balloon catheter as previously described.1–4 Coronary arteriography was performed, and the arteriograms were recorded during the balloon-denudation procedure. Animals were treated in accordance with the guidelines of the American Physiological Society.

A month after the endothelial denudation, dogs were anesthetized with sodium pentobarbital (25 mg/kg), intubated, and ventilated with room air via a positive pressure respirator. A left thoracotomy was performed under sterile surgical conditions. Pairs of 10–MHz miniature piezoelectric crystals (Murata Inc., Kyoto, Japan) were attached with a quick-drying glue (Sumitomo 3M, Tokyo) to the adventitia of opposing surfaces of the denuded left circumflex coronary artery site and the nondenuded site as described.25 The denuded site of the coronary artery was identified by carefully reviewing angiograms taken during the balloon-denudation procedure. After completion of the surgery, coronary arteriography was again performed, and the appropriate placement of the crystals in the denuded site was confirmed as we described.26 The nondenuded site was a segment of the left circumflex coronary artery either proximal or distal to the denuded site. A catheter was inserted into the aortic arch from the right internal thoracic artery. All wires and a catheter were tunneled subcutaneously to the back of the neck. The chest cavity was closed, and the dogs were allowed to recover from the surgery. Aminobenzylpenicillin (2 g per day) and gentamycin (40 mg per day) were administered for 6 days after the surgical procedure.

Measurements and Data Analysis

Arterial pressure was measured by a Statham pressure transducer connected to the previously implanted catheter. The external coronary diameter was measured by using a sonomicrometer as described.24,25 Arterial pressure, heart rate, and the coronary artery diameter were continuously monitored and recorded on a multichannel pen recorder (NEC San-Ei Polygraph System, Tokyo). The percent changes in coronary diameter were calculated as follows: [% (the diameter after drug—the baseline diameter)/the baseline diameter] ×100%.

Experimental Protocol

Seven to 10 days after the surgery, the following studies were performed on conscious dogs in a dimly lit quiet room. Protocol 1. Ergonovine (0.01, 0.1, 0.3, and 1.0 mg) and phenylephrine (0.02, 0.06, and 0.2 mg) were administered intravenously to six dogs. We waited for at least 6 hours before the next dose of ergonovine was infused, because preliminary experiments had indicated that ergonovine-induced vasoconstriction would last for a few hours. We waited for 2 hours before the next dose of phenylephrine was administered. Ergonovine and phenylephrine at the graded doses were administered at random.

Protocol 2. Ergonovine in a dose of 0.3 mg was administered before and after pretreatment with the following antagonists: saline (n=8); 0.5 mg/kg methysergide (n=7), a nonselective serotonin receptor antagonist;27 0.5 mg/kg ketanserin (n=6), a selective 5-hydroxytryptamine type 2 serotonin receptor antagonist;28 1.0 mg/kg prazosin (n=5), an α1-adrenoceptor antagonist; 5.0 mg/kg indomethacin (n=4), a cyclooxygenase inhibitor; and 1.0 mg/kg diltiazem (n=6), a calcium channel blocker. After baseline response to 0.3 mg ergonovine was recorded, the same dose of ergonovine was administered 10 minutes after methysergide, ketanserin, and diltiazem and 30 minutes after prazosin and indomethacin. We waited for at least 24 hours before beginning treatment with the other antagonist. Blockade of the α1-adrenoceptor with prazosin was confirmed by our observation that 1.0 mg/kg prazosin attenuated the pressor response to 0.2 mg i.v. phenylephrine from 18±6 to 5±2 mm Hg (n=4, p<0.05).

Histological Study

At the end of the study, the dogs were killed by a lethal dose of sodium pentobarbital. For analysis by light microscopy, 5-mm coronary artery segments were isolated from both the denuded and nondenuded sites and fixed with 20% formaldehyde solution (n=6). Tissues were imbedded in paraffin, sectioned at 5-μm thickness, and mounted on glass slides. The preparations were stained with hematoxylin and eosin and with van Gieson’s elastic stain. Intimal and medial thickness was measured using a light microscope as previously described.1–3
For analysis by scanning electron microscopy, the coronary artery segments were fixed with 2% buffered glutaraldehyde solution for a few days. The artery segments \((n=4)\) were dried, longitudinally bisected, sputter-coated with gold and palladium, and examined through a scanning electron microscope (Hitachi, Tokyo).

**Statistical Analysis**

Data are presented as mean±SEM. Analysis of variance (ANOVA) followed by Bonferroni’s multiple comparison test was used for comparisons of three or more data points (arterial pressure, heart rate, and the diameters of coronary arteries). ANOVA of repeated measures was used for comparisons of vasomotor responses evoked with several doses of ergonovine or phenylephrine.\(^29\) A value of \(p<0.05\) was considered significant.

**Results**

Baseline values of the external coronary diameter, arterial pressure, and heart rate did not significantly differ among experiments (Tables 1, 2, and 3). The baseline diameter at the denuded site did not differ from that at the nondenuded site.

Figure 1 shows experimental recordings demonstrating that the intravenous administration of ergonovine decreased the diameter of the denuded and nondenuded site in a dose-dependent manner. The magnitudes of ergonovine-induced vasoconstriction were greater at the denuded site than at the nondenuded site. Arterial pressure increased after intravenous ergonovine in doses above 0.1 mg, and heart rate increased after ergonovine in doses above 0.3 mg (Table 1). The intravenous administration of ergonovine resulted in biphasic changes in the diameter: a transient dilation and sustained constriction (Figures 1 and 2). The initial dilation caused by ergonovine was comparable in the denuded and nondenuded sites. The dose-dependent decreases in the diameter evoked with ergonovine were greater \((p<0.01\) by ANOVA) in the denuded site than in the nondenuded site (Figure 3). The intravenous administration of phenylephrine at graded doses caused dose-dependent and comparable decreases in the diameter at the denuded and nondenuded sites (Figure 3 and Table 2).

Figure 2 shows experimental recordings in which ergonovine (0.3 mg) was administered before and after the pretreatment with methysergide (0.5 mg/kg), demonstrating that although the initial coronary dilation induced by ergonovine was not affected by methysergide, the ergonovine-induced coronary constriction at the denuded and nondenuded sites was markedly attenuated by methysergide. Effects of various antagonists are summarized in Table 3. Methysergide significantly \((p<0.01)\) inhibited the decrease in the diameter of the denuded and nondenuded sites evoked with ergonovine (0.3 mg). Methysergide did not significantly change the baseline arterial pressure and heart rate, but it signifi-
cantly attenuated the increases in these hemodynamic variables in response to ergonovine.

In contrast, ketanserin (0.5 mg/kg) decreased arterial pressure and increased heart rate. Despite the fact that ketanserin attenuated the changes in these hemodynamic variables induced by ergonovine, ketanserin did not inhibit the decrease in the diameters of the denuded and nondenuded sites. Neither pretreatment with prazosin (1.0 mg/kg) nor indomethacin (5 mg/kg) inhibited ergonovine-induced coronary constriction.

Diltiazem (1.0 mg/kg) significantly (p<0.01) inhibited the ergonovine-induced hyperconstriction at the denuded site but did not affect the ergonovine-induced constriction at the nondenuded site (Table 3). Diltiazem decreased resting arterial pressure and attenuated the changes in hemodynamic variables induced by ergonovine.

The magnitudes of initial dilation induced by ergonovine did not change after the administration of any of the antagonists tested.

Histological study revealed that the fibromuscular thickening of the intima and regenerated endothelium was noted in the denuded site but not in the nondenuded site (Figure 4). Morphometric analysis revealed that the intimal and medial thicknesses were 61±12 and 160±23 μm, respectively, at the denuded site, and 10±1 and 139±30 μm, respectively, at the nondenuded site. There was no significant difference in medial thickness at the denuded and nondenuded sites.

Scanning electron microscopy of the nondenuded site revealed an intact lining of endothelial cells with a fusiform shape. In contrast, in the denuded site, the endothelial cells exhibited an apparent morphological abnormality with multishaped cells of varying sizes (i.e., a cobblestone appearance).

### Discussion

The major findings of this study are that ergonovine caused a significant hyperconstriction at the coronary artery site where the endothelial injury had been performed a month before; phenylephrine caused comparable constriction at the denuded and nondenuded sites. Methysergide inhibited ergonovine-induced constriction at the denuded and nondenuded sites. Ketanserin, prazosin, or indomethacin did not affect the magnitudes of the ergonovine-induced constriction. These findings suggest that hyperconstriction of the denuded coronary artery evoked by ergonovine may be caused by activation of serotonergic receptors of vascular smooth muscle cells.

In conscious dogs, we continuously measured the external coronary artery diameter at the denuded and nondenuded sites using a sonomicrometer technique. The advantages of studying coronary artery constriction evoked with ergonovine in our canine model are as follows: 1) The adverse effects of contrast material, anesthetic agents, and acute surgery can be excluded. 2) The geometric effects of vascular contraction on the luminal diameter can be ruled out by measuring the external diameter of the blood vessel.

Holtz et al demonstrated that an intravenous infusion of ergonovine (5 μg/kg per minute for 12 minutes) caused biphasic changes in the coronary diameter in intact conscious dogs. Our findings are in agreement with the results of Holtz et al and further indicate that the denuded site of the coronary artery also showed biphasic responses to ergonovine. The magnitudes of initial dilation induced by ergonovine were comparable between the two sites, whereas those of constriction induced by ergonovine were greater in the denuded site than in the nondenuded site.
As we showed previously, intimal thickening with regenerated endothelium was noted at the denuded site. The thickness of the tunica media at the denuded site did not differ from that at the non-denedded site. In addition, the hyperconstriction of the denuded site was provoked selectively by ergonovine but not by phenylephrine. These findings suggest that the ergonovine-induced coronary hyperconstriction may have resulted mainly from an augmented contractile response of vascular smooth muscle cells evoked with ergonovine but not from a nonspecific increase in smooth muscle cells caused by vascular hypertrophy or hyperplasia. The cause of the initial dilation induced by ergonovine is not clear in the present study. It is unlikely that the ergonovine-induced dilation resulted from the changes in arterial pressure (i.e., perfusion pressure) caused by ergonovine, because dilation occurred at low doses that did not alter arterial pressure and heart rate. It has been demonstrated that ergonovine at low concentrations relaxes the precontracted arterial tissues through the release of endothelium-dependent relaxing factors. Thus, we speculate that ergonovine-induced dilation might have resulted from endothelium-dependent mechanisms.

It has been demonstrated that endothelium-dependent relaxations of the isolated canine coronary artery were impaired several weeks after endothelial denudation. These findings may imply that the coronary hyperconstriction evoked with ergonovine might have resulted from dysfunction of the regenerated endothelium at the denuded site. However, Kawachi et al showed that ergonovine-induced hyperconstriction of the canine coronary artery occurred a few months, but not immediately, after the endothelial denudation. In the study by Kawachi et al, contractile responses of vascular smooth muscle per se evoked with ergonovine.

**Figure 2.** Representative recordings in which ergonovine in a dose of 0.3 mg was administered before (top panel) and after (bottom panel) pretreatment with 0.5 mg/kg methysergide in a dog.
were significantly augmented in the coronary artery tissues isolated from the denuded site. Hayashi et al. examined the effects of ergonovine and acetylcholine on the large coronary artery vasomotion before and after the endothelial removal in conscious dogs and showed that the constrictive response to ergonovine did not change at all from 1 to 10 days after endothelial denudation, whereas endothelium-dependent dilation evoked with acetylcholine was markedly impaired. Thus, these findings suggest that ergonovine-induced hyperconstriction of the coronary artery in our canine model results primarily from hyperreactivity of vascular smooth muscle cells to ergonovine but not from endothelial dysfunction.

Our results indicated that prazosin and indomethacin failed to prevent constriction evoked with ergonovine. These results suggest that neither \( \alpha_1 \)-adrenoceptors nor the activation of cyclooxygenase cascade was involved in the genesis of ergonovine-induced hyperconstriction.

**Table 2. Effects of Phenylephrine on Coronary Artery Diameter and Hemodynamic Variables**

<table>
<thead>
<tr>
<th>Doses of Phe</th>
<th>0.02 mg</th>
<th>0.06 mg</th>
<th>0.2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter of coronary artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denuded site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (μm)</td>
<td>3,415±249</td>
<td>3,415±254</td>
<td>3,406±251</td>
</tr>
<tr>
<td>After Phe (% change)</td>
<td>-1.7±0.5</td>
<td>-2.7±0.4*</td>
<td>-4.6±1.9*</td>
</tr>
<tr>
<td>Nondenuded site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (μm)</td>
<td>3,461±404</td>
<td>3,406±386</td>
<td>3,343±387</td>
</tr>
<tr>
<td>After Phe (% change)</td>
<td>-0.7±0.2</td>
<td>-1.6±0.4*</td>
<td>-3.8±0.6*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>93±3</td>
<td>91±3</td>
<td>88±4</td>
</tr>
<tr>
<td>After Phe</td>
<td>95±3</td>
<td>104±5*</td>
<td>108±3*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>95±3</td>
<td>96±4</td>
<td>92±5</td>
</tr>
<tr>
<td>After Phe</td>
<td>93±4</td>
<td>94±4</td>
<td>93±5</td>
</tr>
</tbody>
</table>

Phe, phenylephrine; bpm, beats per minute. Values are mean±SEM.

\( *p<0.05 \) and \( **p<0.01 \) vs. corresponding value before Phe (control).

Although ketanserin in a dose of 0.5 mg/kg inhibited the pressor response to ergonovine, ketanserin did not prevent ergonovine-induced vasconstriction at the denuded and nondenuded sites. In contrast, methysergide in a dose of 0.5 mg/kg significantly attenuated ergonovine-induced coronary constriction. These findings suggest that serotoninergic receptors other than \( \alpha_1 \)-receptor may play a role in ergonovine-induced hyperconstriction. The present findings are compatible in part with previous studies. Holtz et al. have indicated that constricting responses of large coronary arteries to ergonovine were markedly attenuated after pretreatment with methysergide (0.5 mg/kg) in intact conscious dogs. Henry and Yokoyama\(^5\) and Yokoyama et al.\(^6\) have demonstrated that the ergonovine-induced augmented constriction of atherosclerotic blood vessels in rabbits was inhibited by methysergide and other nonselective serotoninergic receptor antagonists. Heistad et al.\(^8\) have also shown that serotonin-evoked enhanced constriction of the hind limb vascular bed in atherosclerotic monkeys was also inhibited by methysergide.

The present study revealed that diltiazem in a dose of 1.0 mg/kg inhibited the ergonovine-induced constriction at the denuded site but did not affect constriction at the nondenuded site. We selected this dose of diltiazem because it attenuated the augmented constrictive response of the denuded site to histamine in our swine model of coronary spasm\(^7\); however, this dose of diltiazem attenuated the constricting responses of the nondenuded site to histamine as well. Thus, a plausible explanation for a mechanism by which diltiazem at this dose selectively inhibited ergonovine-induced hyperconstriction at the denuded site of canine coronary artery is not available, but we speculate that the mechanism might have been related to blockade of either calcium influx into smooth muscle cells, serotoninergic receptors, or both. Therefore, further studies investigating the new effects of diltiazem remain to be performed.

In summary, the results of this study suggest that the functional changes in serotoninergic receptors in vascular smooth muscle may be a primary mechanism of ergonovine-induced hyperconstriction in our canine model. The increase in \( \text{Ca}^{2+} \) influx into smooth muscle

**Figure 3. Graphs showing coronary vasoconstriction at the denuded and nondenuded sites induced by ergonovine and phenylephrine. Ergonovine caused a significant hyperconstriction at the denuded site, but phenylephrine induced a comparable constriction at the denuded and nondenuded sites. \( *p<0.05 \) and \( **p<0.01 \) versus the nondenuded site.**
cells might have been involved in the pathogenesis. Our findings are strengthened by clinical studies that showed that the pretreatment with clinical doses of ketanserin did not prevent coronary vasospasm that was induced by ergonovine or that occurred spontaneously in patients with variant angina and that intracoronary infusion of serotonin induced occlusive coronary vasospasm in patients with variant angina. Since significant coronary artery hyperconstriction evoked with ergonovine and other vasoactive drugs had been noted several months (References 1–4, 37, and 41 and this study) but not immediately after the endothelial injury, the mechanism of ergonovine-induced hyperconstriction may be related to a pathological process (i.e., the healing process) that may occur after arterial injury. In this regard, Bertrand et al demonstrated that the presence of coronary vasospasm induced by ergonovine 6 months after successful percutaneous transluminal...
angioplasty was frequently accompanied by restenosis. Therefore, the analysis of pathological events that are linked to the intimal thickening or proliferation of smooth muscle cells that occurs after arterial injury may provide an important clue that will pave the way for identifying the cellular and molecular mechanisms of coronary vasospasm or restenosis after coronary angioplasty.

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