ALPHA ADRENERGIC RECEPTOR ACTIVITY OF EPICARDIAL CORONARY ARTERY IN THE ANESTHETIZED DOG

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The epicardial coronary artery plays an important role not only as a conduit artery but also as a locus of coronary spasm. Accordingly, diameter change of the large epicardial coronary artery of the in situ canine heart was continuously measured by ultrasonic dimension gauge technique and the effects of alpha adrenergic stimulation on the caliber were studied.

After the intravenous administration of phenylephrine the aortic pressure increased by 28 mmHg, however, the left circumflex coronary artery diameter decreased by 3.4% (p < 0.01). Norepinephrine and sciatic nerve stimulation after propranolol (1 mg/kg) induced coronary vasoconstriction by 1.3 (p < 0.025) and 2.5% (p < 0.05) against the obvious increases of aortic pressure by 16 and 19 mmHg, respectively.

Thus alpha adrenergic stimulation, in situ in dogs, was shown to directly constrict the large epicardial coronary artery.

SYMPATHETIC alpha adrenergic activity is considered to participate in the elicitation of coronary artery spasm not only in patients not only with variant angina but also in those with effort angina and myocardial infarction.1–5 Zuberbuhler and Bohr6 found in vitro studies that vasoconstriction by alpha adrenergic stimulation was more intense in strips from the large (1.5–2.4 mm in diameter) than the small (0.25–0.50 mm in diameter) coronary arteries. Toda7 evaluated a regional difference in the responsiveness of isolated monkey coronary arteries to norepinephrine, epinephrine and field electrical stimulation, and found that the quantity or the susceptibility of alpha-adrenoceptors is in the order of large, medium and small size arteries. Similarly in the in situ heart, increase in coronary vascular resistance occurs during the sympathetic alpha receptor stimulation both in anesthetized8–10 and conscious dogs.11–13 Kelley and Fiigl14 when measuring the segmental resistance of the large epicardial coronary artery, found no significant effect of sympathetic stimulation on the resistance. They explained these findings as being due to the competition between sympathetic alpha receptor mediated coronary vasoconstriction and the local metabolic control of the coronary circulation. It should also be noted that the role of conduit artery in controlling the total coronary resistance was less than 10%,15 thus it would be difficult to detect changes of the resistance along the large coronary artery, even should an 80% reduction of the conduit artery diameter be induced. Accordingly, the role of alpha adrenergic stimu-

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lation on the conduit artery may be directly evaluated by measuring the diameter change of the epicardial coronary artery. Recent evidence tends to suggest that not only the adrenergic stimulation by methoxamine\textsuperscript{16} but also the metabolic state can influence these vessels\textsuperscript{17}.

In the present work, we attempted to determine whether various kinds of alpha adrenergic stimulation directly control the vascular tone of the large coronary artery, and to do so we measured the external diameter of the left circumflex coronary artery in anesthetized open chest dogs.

**METHODS**

Nine mongrel dogs weighing 20–25 kg were anesthetized with an intravenous administration of 25 mg/kg sodium pentobarbital. Thoracotomy was performed through the fourth intercostal space under the positive pressure breathing by a Harvard respirator (Model 607). A Millar catheter tip manometer (Millar Instrument Co., Houston, Tx) was inserted from the carotid artery into the ascending aorta. The coronary artery diameter was measured by sonomicrometry as described previously\textsuperscript{18}. Briefly, the proximal left circumflex coronary artery was...
TABLE 1 THE HEMODYNAMIC EFFECTS OF PROPRANOLOL 1.0 mg/kg i.v.

<table>
<thead>
<tr>
<th></th>
<th>before</th>
<th>after prop.</th>
<th>probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic aortic blood pressure (mmHg)</td>
<td>102 ± 12</td>
<td>94 ± 12</td>
<td>N.S.</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>166 ± 11</td>
<td>138 ± 8</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Diastolic Coronary Diameter (mm)</td>
<td>2.71 ± 0.15</td>
<td>2.63 ± 0.16</td>
<td>p &lt; 0.05</td>
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All values are mean ± S.E.; prop. = propranolol

Fig.3. Time course of the effects of norepinephrine on heart rate, diastolic aortic pressure and % changes of the coronary diameter before (dotted line) and after (real line) propranolol. Values are expressed as mean ± S.E. *= p < 0.05; ** = p < 0.01 between before and after propranolol.

minimumly dissected and a pair of 10 MHz lead zirconate titanate crystals (diameter = 1.5 mm, weight = 7.5 mg) attached to 0.3 cm² nylon patches were sutured face to face to the adventitia of the coronary artery with 6–0 silk using an atraumatic needle. The underestimation in distance measurement due to crystal rotation was corrected by adding a convex lens to the crystals. A 5 French polyvinyl catheter was inserted into the antecubital or femoral vein for administration of drugs.

The left sciatic nerve was exposed near the hip joint, ligated with silk and the distal site of the nerve was cut off. A bipolar platinum electrode was placed beneath the sciatic nerve proximal to the ligature and warmed paraffin oil was used to protect nerve and surrounding tissues from drying and cooling.

Hydraulic cuff occluders (Model OC-16, IVM, U.S.A.) were placed around the thoracic aorta and the inferior vena cava to increase and decrease the pressure. In this manner, the pressure dependency of the left circumflex coronary diameter was determined.

Pharmacological and electrical stimulations were conducted as follows; 1) intravenous bolus

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administration of phenylephrine (10 μg/kg) in six dogs, 2) intravenous administration of norepinephrine (1 μg/kg) before and after propranolol (1 mg/kg) in the same six dogs and 3) direct somatic nerve stimulation before (n = 4) and after propranolol (n = 5). In three dogs, phenotolamine (10 mg/dog) was administered intravenously 2 minutes after phenylephrine in order to attenuate the sympathetic alpha adrenergic tone. The left sciatic nerve was stimulated at a supramaximal voltage (15 V) with 30 seconds train of rectangular pulses of a frequency of 20 Hz and a duration of 1 msec, delivered by an electrical stimulator (SEN3201, Nihonkoden, Tokyo, Japan). The interval of these interventions was at least 10 minutes. To avoid possible depletion of the endogenous catecholamines, sciatic nerve stimulation was performed only once.

During the experiment, coronary diameter, aortic pressure and electrocardiogram were recorded continuously by a multichannel oscillograph. The recorded variables were collected from 10 to 12 beats at the end-diastole during the end-expiration.

All results were expressed as the mean ± standard error (S.E.). A paired t-test was used for statistical analysis between the control and interventions.

RESULTS

A representative tracing of aortic pressure and coronary diameter during alpha adrenergic stimulation by phenylephrine and subsequent alpha adrenergic blockade by phenotolamine is shown in Fig. 1. The coronary diameter which decreased after an intravenous bolus administration of phenylephrine reverted to baseline levels after phenotolamine, despite a marked increase and decrease in the aortic pressure, respectively.

Changes in heart rate, diastolic aortic pressure and LCX diameter (% of control) before and after an intravenous administration of phenylephrine were summarized in Fig. 2. The LCX diameter was decreased from 2.79 ± 0.19 mm during control to 2.69 ± 0.16 mm (p < 0.01) 1 minute after the drug administration. The maximum reduction in coronary diameter was 3.4 ± 0.7% decrease from the control period (p < 0.01), despite an unequivocal increase in the aortic pressure at distole from 104 ± 8 to 132 ± 8 mmHg (p < 0.05). The coronary vasoconstriction induced by phenylephrine continued for about 10 minutes.

After the bolus administration of propranolol 1 mg/kg, with nonsignificant change in diastolic aortic pressure (Table 1), the coronary diameter was decreased from 2.71 ± 0.15 to 2.63 ± 0.16 mm (3.1 ± 1.3% decrease from the control level; p < 0.05). Heart rate decreased significantly from 166 ± 11 to 138 ± 8 (p < 0.01).

Figure 3 shows the effects of norepinephrine before and after propranolol on heart rate, aortic pressure and coronary diameter in five dogs. The LCX diameter increased maximally 30 seconds after the intravenous bolus administration of norepinephrine from 2.71 ± 0.15 mm during control to 2.76 ± 0.16 mm (1.8 ± 0.7% increase from the control period; p < 0.05), along with the increase in diastolic aortic pressure by about 30 mmHg. Thus, the LCX diameter increased according to the rise in aortic pressure after norepinephrine. Under the influence of propranolol, a bolus administration of norepinephrine increased the diastolic aortic pressure by about 16 mmHg, and decreased coronary diameter.
from 2.63 ± 0.16 to 2.59 ± 0.16 mm (1.3 ± 0.6% decrease from the control period; p < 0.025).

During sciatic nerve stimulation, the LCX diameter increased maximally around 20 seconds in all four dogs by 1.9 ± 0.6% along with the increase in diastolic aortic pressure by about 10 mmHg.

Effects of sciatic nerve stimulation on heart rate, diastolic aortic pressure and coronary diameter in five dogs after propranolol were presented in Fig. 4. The coronary diameter decreased from 2.65 ± 0.11 to 2.58 ± 0.12 mm (2.5 ± 1.2% decrease from the control level; p < 0.05), while the diastolic aortic pressure was increased by about 19 mmHg. Hemodynamic and coronary diameter changes observed during sciatic nerve stimulation disappeared after the cessation of electrical stimulation.

DISCUSSION

Behavior of the large epicardial coronary artery and coronary circulation during variant angina have been documented using coronary angiographic technique and hemodynamic recordings. In such patients, total segmental coronary occlusion of the major coronary arteries has been demonstrated during a bout of sympathetic stimulation such as a cold pressor test and after the administration of alpha-receptor agonist.

These clinical experiences are in accord with the previous in vitro studies in which there was noted a more intense distribution of the sympathetic alpha receptors along the large epicardial coronary artery, as compared to findings in the small ones.

In the present study using intact canine coronary arteries, propranolol unmasked the sympathetic α-adrenergic tone by which the external coronary arterial diameter decreased by 3.1%. These results may coincide with the exacerbation of vasotonic angina by propranolol as well as exercise after pretreatment with propranolol in patients with coronary artery spasm.

Our study demonstrates that sympathetic alpha adrenergic stimulation with pharmacologic agents and electrical stimulation of the somatic nerve after pretreatment with beta blockade directly induces a constriction of the large epicardial coronary artery. The maximum vasoconstriction in the present study was 3.4 ± 0.7% of the measured external diameter. This value was well in accord with the finding of others on the fibrillating heart and a little smaller than the data in conscious dogs.

Vatner et al. observed in conscious instrumented dog that methoxamine (50 μg/kg per min) reduced mean external left circumflex coronary diameter by 9 ± 2% below control. This discrepancy in degree of coronary constriction by alpha receptor agonist between our results and those of Vatner et al. may be attributed to the effects of anesthetics and recent surgical manipulation on coronary vasoactivity.

One of the major findings in the present study was the vasoconstrictive effect of somatic nerve stimulation after pretreatment with propranolol, which coincides with the increase in coronary vascular tone noted during static exercise through spinal cord ventral nerve stimulation. This finding provides support that the vasoconstriction induced by a cold pressor test and arm exercise is mediated through the stimulation of sympathetic alpha receptors.

The competition between sympathetic alpha mediated coronary vasoconstriction and local metabolic control of the coronary circulation has been a matter of dispute when attempting to elucidate the role of sympathetic stimulation. Macho et al. and Gould and Kelley suggested that peripheral coronary factors and metabolism can influence these vessels, however the mechanism is still unknown. We could not exclude the influence of metabolic factor on the caliber of this vessel in the present study. Accordingly, we tried to measure the epicardial coronary artery diameter which area is structurally independent from the myocardium by epicardial fat. In addition in the present study, norepinephrine as well as sciatic nerve stimulation constricted the epicardial coronary artery after propranolol despite the substantial increases in aortic pressure which invariably increases the myocardial oxygen demands. Thus, alpha adrenergic stimulation by α-agonist as well as sympathetic stimulation after pretreatment with β-blockade constricts directly the large epicardial coronary artery.

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