Effects of Anti-Anginal Agents on Cyclical Reductions of Coronary Blood Flow

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SUMMARY

The effects of coronary vasodilating agents and alpha- and beta-adrenergic blocking agents on cyclical reductions of blood flow in the partially constricted coronary artery of anesthetized dogs were examined. Intravenous injections of nitroglycerin (50 $\mu\text{g}/\text{Kg}$), SG 75 (150 $\mu\text{g}/\text{Kg}$), papaverine (1 mg/Kg), and nicotinic acid (10 mg/Kg) eliminated both cyclical reductions of flow and ST elevation (group 1). Nifedipine (10 $\mu\text{g}/\text{Kg}$), verapamil (500 $\mu\text{g}/\text{Kg}$), diltiazem (500 $\mu\text{g}/\text{Kg}$), and propranolol (500 $\mu\text{g}/\text{Kg}$) suppressed ST elevation, but they could not eliminate cyclical reductions of flow (group 2). Dipyridamole (1 mg/Kg) and phentolamine (500 $\mu\text{g}/\text{Kg}$) augmented both ST elevation and cyclical reductions of flow (group 3). The results indicate that ST elevation due to cyclical reductions of coronary blood flow was eliminated by spasmolytic actions of group 1 on coronary artery, was suppressed by negative chronotropic and/or inotropic actions of group 2, and was augmented by peripheral actions of group 3.

Additional Indexing Words :

Coronary blood flow Surface electrogram Systolic bulge Coronary spasm Prostaglandins

IN 1973, Uchida et al observed cyclical reductions of blood flow in the partially constricted coronary artery of anesthetized dogs, and they suggested participation of coronary spasm induced by prostaglandin E_2 in this phenomenon.¹⁾⁻⁶⁾ This phenomenon was frequently associated with cyclical elevation of ST segment of surface electrogram and also with ventricular premature contractions,^{2),7)} and therefore closely resembles Prinzmetal's variant angina pectoris.⁸⁾⁻¹⁰⁾ This similarity led us to examine whether the agents which could alleviate attacks in patients with Prinzmetal's variant angina, could also eliminate cyclical reductions of coronary flow and ST elevation of anesthetized dogs.

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This work was partly reported at the 50th session of American Heart Association, Miami Beach, 1977; supported in part by Grant in Aid for Scientific Research, the Ministry of Education, Japanese Government.

Received for publication April 27, 1978.

METHODS

1. *Surgical preparations:*

Thirty-five beagle dogs were anesthetized with intravenous sodium pentobarbital (40–45 mg/Kg). The trachea was intubated for artificial positive pressure respiration with air. The upper 7 ribs on the left side were removed. After pericardiotomy, the proximal segment of either the anterior descending or circumflex artery was dissected free of surrounding tissues and a magnetic flowmeter was placed on it for measurement of coronary blood flow. A segment of the artery 0.5 to 1 cm distal to the flowmeter was also dissected free and a cylindrical constrictor was placed on it for partial constriction. A small catheter was introduced in retrograde fashion into a small peripheral branch of the artery to measure coronary blood pressure. A unipolar electrode was fixed to a portion of the left ventricular wall irrigated by the artery for recording surface electrogram. A force-displacement strain gauge arch was sewn to the ventricular wall to measure contractile force of the myocardium. Another catheter was introduced into the right femoral artery to measure systemic blood pressure. Heart rate was obtained by a pulse-integrator triggered by femoral arterial pressure pulse.

2. *Administrations of chemical agents:*

Cyclical reductions of coronary pressure and flow developed in 30 preparations. In general, coronary pressure and flow decreased gradually and increased rapidly, and the changes were repeated. After recording successive 3 cycles of reduction of coronary pressure and flow, the following agents were injected intravenously 30 sec to 1 min after the fourth abrupt increase in coronary pressure and flow: nitroglycerin, SG 75(2-nicotinamidoethyl nitrate),¹¹⁾ papaverine, nicotinic acid, nifedipine, verapamil, diltiazem, dipyridamole, propranolol, phentolamine, and atropine. The doses injected were shown in Figs. 6–8. The time from the injection to reappearance of reduction of coronary pressure was compared with the average length of the preceding 3 cycles. It was considered that the agent eliminated the cyclical reductions when the former was significantly longer than the latter. Also, the time from the injection to reappearance of ST elevation of the same magnitude as that before the injection was compared with the average length of the preceding 3 cycles of ST elevation.

RESULTS

The intravenous injection of 150 μ g/Kg of SG 75 caused a slight fall in systemic pressure but no obvious change in heart rate. Following the injection of this dose, cyclical reductions in coronary pressure and flow and ST elevation disappeared. Passive stretching of the myocardium, i.e. the systolic bulge, which was observed in 3 of 5 preparations, also disappeared (Figs. 1 and 6). Twenty-eight to 42 min after the injection, however, a reduction in coronary pressure reappeared. This reduction was usually small and was not reflected on coronary flow and electrogram (Fig. 1). After 2 to 3 cycles, re-

Fig. 1. The effect of intravenous injection of SG 75 on cyclical reductions of coronary flow and ST elevation. From top: coronary pressure (CBP), coronary flow (CBF), systemic pressure (SBP), heart rate (HR), surface electrogram (ECG), and left ventricular contractile force (CF). A: before coronary constriction. B: during coronary constriction. e: ST elevation.

Fig. 2. The effect of nicotinic acid on cyclical reductions of coronary flow and ST elevation. SB: systolic bulge.

Fig. 3. The effect of nifedipine on cyclical reductions of coronary flow and ST elevation.

duction in pressure became larger and was now associated with ST elevation and reduced contractile force or systolic bulge (Fig. 1). Such a time course was the usual. Accordingly, the time required for reappearance of cyclical reduction in coronary pressure was shorter than that for reappearance of ST elevation (Fig. 6). With increasing dose to 300 $\mu\text{g/Kg}$, the time required for reappearance of cyclical reductions in coronary pressure and ST elevation became longer (Fig. 6).

The injections of 50 and 100 $\mu\text{g/Kg}$ of nitroglycerin caused a fall in

Fig. 4. The effect of propranolol on cyclical reductions of coronary flow and ST elevation.

Fig. 5. The effect of phentolamine on cyclical reductions of coronary flow and ST elevation.

systemic pressure and an increase in heart rate. Following the injection of this agent, cyclical reduction in coronary pressure and flow, ST elevation and systolic bulge disappeared as in the case of SG 75 injection (Fig. 6). Cyclical reduction in coronary pressure and flow, ST elevation and systolic bulge were also eliminated by 1 mg/Kg or over of papaverine and 10 mg/Kg or over of nicotinic acid (Figs. 2 and 7).

Dipyridamole caused a fall in systemic pressure and an increase in heart rate. However, this agent could not eliminate cyclical reductions in coronary pressure and flow. Although systolic bulge was reduced or eliminated, the magnitude of reduction in coronary flow was increased and ST elevation was augmented by the injection of 1 mg/Kg of this agent (Fig. 6).

The injections of nifedipine in doses of 5 and 10 µg/Kg, diltiazem in doses of 500 µg and 1 mg/Kg, and verapamil in a dose of 500 µg/Kg caused a fall in systemic pressure and a decrease in heart rate. Following the injections of these agents, ST elevation and systolic bulge were reduced in magnitude or eliminated. However, reductions in coronary pressure and

Fig. 8.

Figs. 6-8. Top one thirds: the control cycle length of reduction in coronary pressure, and the time required for reappearance of reduction in coronary pressure, expressed as mean $\pm$ SD. Middle one thirds: the control cycle length of ST elevation, and the time required for reappearance of ST elevation of the same magnitude as that before the injection. Bottom one thirds: the difference in cycle length between reduction of coronary pressure and ST elevation before the injection, and the difference in time required for reappearance between reduced coronary pressure and ST elevation. Solid circles indicate augmented ST elevation.

flow were not eliminated and the magnitude of reduction in coronary flow was unchanged or increased (Figs. 3 and 7).

Propranolol caused a slight fall in systemic pressure and a marked decrease in heart rate. Although ST elevation and systolic bulge were suppressed or eliminated, cyclical reductions in coronary pressure and flow were not eliminated as in the case of nifedipine (Figs. 4, 8). Phentolamine caused a fall in systemic pressure and an increase in heart rate as in the case of nitroglycerin and papaverine. Although systolic bulge was suppressed, cyclical reductions in coronary pressure and flow were not eliminated and ST elevation was augmented by 500 $\mu\text{g}/\text{Kg}$ of this agent. The changes caused by this agent was similar to those caused by dipyridamole (Figs. 5 and 8). Atropine in a dose of 500 $\mu\text{g}/\text{Kg}$ could not affect cyclical reductions in coronary pressure and flow, ST elevation and systolic bulge (Fig. 8).

DISCUSSION

The underlying mechanisms of the cyclical reductions of blood pressure and flow in the partially constricted coronary artery of anesthetized dogs have been extensively investigated by us. During reductions of coronary pressure and flow, segmental or diffuse narrowing was frequently observed arteriographically in the constricted arteries.³⁾ On the other hand, platelet aggregates were nonspecifically observed in the removed constricted segments of the arteries.³⁾ Therefore, the cyclical reductions in coronary blood pressure and flow were attributed to cyclical spasm of the constricted arteries. The cyclical reductions in coronary blood pressure and flow were eliminated by intravenous injections of aspirin which inhibited synthesis of endoperoxides,¹³⁾ benzydamine which inhibited synthesis of endoperoxides and thromboxane (TX) A_2 , phenylbutazone which inhibited synthesis of endoperoxides and prostaglandin (PG) $F_{2\alpha}$,¹²⁾ Cu-chlorophylline which inhibited synthesis of PG E_2 and accelerated synthesis of TXA_2 , and by PG I_2 (our unpublished observation), but were not eliminated by imidazole and 1-methyl-imidazole which selectively inhibited synthesis of TXA_2 .¹⁴⁾ The cyclical reductions were frequently induced by epinephrine which accelerated synthesis of PG E_2 , PG E_2 itself, and by reduced glutathione which accelerated synthesis of PG E_2 and inhibited synthesis of TXA_2 , but were not induced by PG $F_{2\alpha}$.⁵⁾ In addition, the action of TXA_2 itself was inconsistent.⁵⁾ The cyclical reductions were frequently augmented but were not induced by 15-hydroperoxy arachidonic acid which inhibited synthesis of PG I_2 .^{15), 16)} Therefore, we considered that PG E_2 but not TXA_2 played an important role in coronary spasm and accordingly in cyclical reductions of coronary blood pressure and flow.

Nitroglycerin, SG 75, papaverine, and nicotinic acid have coronary dilating actions. Among these agents, nitroglycerin and SG 75 eliminated coronary spasm in man.^{10),17)} In this study, all these 4 agents eliminated cyclical reductions in coronary pressure and flow, and ST elevation. It is likely that these agents eliminated coronary spasm, leading to elimination of reductions in coronary pressure and flow, and accordingly to elimination of ST elevation. Nitroglycerin has an action to accelerate synthesis of PG E₂.¹⁸⁾ However, we considered that this agent eliminated cyclical reductions not by its action on PG E₂ generating system but by its spasmolytic action on coronary smooth muscles. Although the actions on PG generating systems are not well known, SG 75, papaverine, and nicotinic acid may have eliminated cyclical reductions by their spasmolytic actions on coronary smooth muscles as in the case of nitroglycerin.

Nifedipine, verapamil, diltiazem, and dipyridamole also have coronary dilating actions. In this study, all these agents could not eliminate cyclical reductions in coronary pressure and flow. Sites of action on coronary artery differ among them. Diltiazem dilated large coronary arteries as in the case of nitroglycerin and SG 75 while the other agents could not.¹⁹⁾ It may be considered that nifedipine, verapamil, and dipyridamole could not eliminate spasm which usually occurred in large coronary arteries, and that the dilating action of diltiazem was not enough to eliminate spasm. Although cyclical reductions were not eliminated, ST elevation was suppressed or eliminated by nifedipine, verapamil, and diltiazem. These agents may have suppressed ST elevation by their negative chronotropic and inotropic actions. Similarly, propranolol suppressed ST elevation but it could not eliminate cyclical reductions. It is also likely that this agent suppressed ST elevation by its negative chronotropic and inotropic actions. Differing to these agents, a large dose of dipyridamole augmented ST elevation. A further decrease in coronary flow secondary to a fall in systemic blood pressure and an increase in heart rate may have augmented ST elevation. Also, phentolamine may have augmented ST elevation by the same mechanisms. Despite augmented ST elevation, systolic bulge was suppressed by dipyridamole and phentolamine. Reduced contractile force of the non-ischemic myocardium due to a decrease in after-load and accordingly a decrease in stretching of the ischemic myocardium by the non-ischemic myocardium may have contributed to suppression of systolic bulge.

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