EFFECT OF PROSTAGLANDIN I₂ ON CYCLICAL REDUCTIONS
OF CORONARY BLOOD FLOW

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The effects of prostaglandin (PG) I₂ and the agents which affect PG and
thromboxane (TX) generating systems on cyclical reductions of blood flow in
the partially constricted coronary artery of anesthetized dogs were examined.
Cyclical reductions were eliminated by PG I₂, but not by PG D₂, and were
augmented by 15-hydroperoxy arachidonic acid and tranlycypromine that
inhibited synthesis of PG I₂. The cyclical reductions were also eliminated by
Cu-chlorophylline that inhibited synthesis of PG E₂ and accelerated synthesis
of TX A₂, but were not by imidazole and 1-methyl imidazole that inhibited
synthesis of TX A₂. The results in this and in the previous studies indicate
that not TX A₂ but PG E₂ participates as an inducer while PG I₂ participates
as an inhibitor in cyclical reductions of coronary blood flow.

PATHOGENESIS of cyclical reductions of
blood pressure and blood flow in a partially
constricted coronary artery of anesthetized
dogs has been intensively studied by Uchida and
co-workers.1-10 In the previous studies,1-6 segmental or diffuse narrowing in the constricted artery
was frequently observed during reductions of pressure and flow. The cyclical reductions were
eliminated by the agents that inhibited synthesis of prostaglandin (PG) endoperoxides, and were
frequently induced by the agents that accelerated synthesis of PG E₂.11 In addition, the cyclical
reductions were induced by PG E₂, but were not
by PG F₂α and thromboxane (TX) A₂.7,8 Therefore, we suggested participation of spasm
induced by PG E₂ in cyclical reductions of coronary blood pressure and blood flow.

Besides PG E₂, PG F₂α and TX A₂ which
cause contraction of coronary smooth muscles,12
PG I₂ and PG D₂ are also generated from endoperoxides and cause relaxation of coronary
smooth muscles.13,14 However, it remained unclear whether PG I₂ and PG D₂ act as inhibitors
of the cyclical reductions. In this study, we
therefor examined the effects of PG I₂, PG D₂ and the inhibitors of PG I₂, 15-hydroperoxy
arachidonic acid and tranlycypromine,15,16 on the cyclical reductions. Also, we examined the
effects of several agents which affected PG and
TX generating systems, in order to confirm that
PG E₂ but not TX A₂ acts as an inducer of the
cyclical reductions of coronary blood pressure
and flow.

METHODS

1. Experimental Preparations
Thirty-nine beagle dogs were anesthetized
with intravenously administered sodium pento-
barbital (35-40 mg/kg). The trachea was intu-
bated for artificial positive pressure respiration

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with air. The upper 7 ribs on the left side were removed. After pericardiotomy, the proximal segment of either the left anterior descending or left circumflex coronary artery was dissected free of surrounding tissues and a magnetic flowmeter (Nihonkoden, MF-2) was placed on it for measurement of coronary blood flow. Zelo level of flow was determined by occluding a coronary segment distal to the flowmeter. A segment of the artery 1-1.5 cm distal to the flowmeter was also dissected free and a cylindrical constrictor of 3 mm in length and with one of several diameters was placed on it for partial constriction. A catheter of 1 mm in internal diameter was introduced in retrograde fashion into a small branch of the artery that nourished the apical area of the left ventricle to monitor peripheral coronary blood pressure. Another catheter was introduced into the right femoral artery to measure systemic blood pressure. Heart rate was obtained by a pulse-integrator triggered by the femoral arterial pulse. A monopolar electrode was fixed on the left ventricular wall to monitor surface electrogram. A force-displacement strain gauge arch was sewn to the left ventricular wall to measure contractile force.

By constriction, the mean peripheral coronary blood pressure was usually lowered to 40–70 percent of the control value. This was the degree that most frequently induced cyclical reductions of coronary blood pressure and flow in our preliminary studies. The 31 dogs in which cyclical reductions occurred within 30 min, were then given PG I₂, PG D₂ and the agents which affected PG and TX generating systems. The agents we administered were the following: PG I₂ and PG D₂ synthetized at the institute of Ono-yakuhin Co., Ltd.; 15-hydroperoxy arachidonic acid synthetized by the method of Hamburg and Samuelsson; tranylcypromine (SIGMA); Chlorophylline; I-126 and imidazole and 1-methyl imidazole. All these agents were dissolved in either ethanol or distilled water, and were injected through a catheter into the left jugular vein.

During the cyclical changes in peripheral blood pressure and blood flow in a partially constricted coronary artery, pressure and flow usually decreased gradually and then increased abruptly, and these changes were repeated. The length of cycle was fairly constant at least from the first to 13th cycle in our previous studies. Therefore, successive 3 cycles were timed, and the agents were injected 1–2 min after the fourth abrupt increase in pressure and flow, and the time required for reappearance of the cyclical reductions was compared to the average value of the preceding 3 cycles. When the time required for reappearance was significantly (Student t test, P < 0.05) longer than the average length of the preceding 3 cycles, the agent injected was considered to have eliminated the cyclical changes. Since the reduction of pressure reap- peared was usually small for 1–3 cycles and was frequently not reflected on flow, the time required for reappearance of pressure reduction was used for comparison.

RESULTS

1. PG I₂ and PG D₂

Fig. 1 shows the effect of intravenous injection of 0.15 μg/kg PG I₂ on cyclical reductions
Effect of PG I₂ on Cyclical Coronary Flow Reductions

**Fig. 2.** The effects of PG I₂ and PG D₂ on cyclical reductions of coronary blood pressure. The time in min required for reappearance of cyclical reductions in coronary blood pressure was compared to the control cycle length. n=number of trials. ΔMSBP(%)=percent changes in mean systemic blood pressure following the injections of the agents. ΔHR(%)=percent changes in heart rate following the injections of the agents.

**Fig. 3.** The effect of PG D₂ on cyclical reductions of coronary blood pressure and flow.

of coronary blood pressure and blood flow, and on the associated cyclical changes in surface electrogram and left ventricular contractile force. Following the injection of this agent, the cyclical reductions did not appear for about 42 min. Thereafter, small reductions in pressure and flow reappeared, and the length and magnitude of the reduction gradually returned to those of before

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the injection. Also, ST elevation disappeared and left ventricular contractile force was restored following the injection of the agent. Elimination of the cyclical reductions was observed with 0.15 µg/kg of the agent. With increasing dose to 0.3 µg/kg, the duration of elimination became longer (Fig. 2). On the other hand, PG D₂ in doses up to 20 µg/kg could not eliminate the cyclical reductions (Figs. 2 and 3).

2. 15-Hydroperoxy Arachidonic Acid and Transylcypromine

Following the injection of 1 mg/kg 15-hydroperoxy arachidonic acid, the magnitude of the increase in coronary blood pressure and flow was reduced and the duration of the reduction of pressure and flow became longer in 3 preparations (Fig. 4). In the remaining 2 preparations, both pressure and flow remained reduced for 14 and 20 min, and finally ventricular fibrillation occurred. The minimum dose required for augmentation of the cyclical reductions was not examined. In 4 preparations in which the cyclical reductions did not occur spontaneously, it was examined whether 15-hydroperoxy arachidonic acid could induce the cyclical reductions. However, 1 mg/kg of this agent failed to induce the cyclical reductions.

Following the injection of 2.5 mg/kg or over of transylcypromine, the cyclical reductions were augmented in 3 of 4 preparations. In addition, this agent induced the cyclical reductions in all 5 preparations in which the cyclical reductions did not occur spontaneously (Fig. 5).

3. Inhibitors of PG E₂ and TX A₂

The cyclical reductions were eliminated by 10 mg/kg Cu-chlorelphylline and by 400 µg/kg I-126 (Figs. 6, 7 and 8). On the other hand, both imidazole and 1-methyl-imidazole could not elimi-
Fig. 6. The effect of Cu-chlorophylline on cyclical reductions of coronary blood pressure and flow.

Fig. 7. The effect of I-126 on cyclical reductions of coronary blood pressure and flow.

Fig. 8. The effect of Cu-chlorophylline, I-126, imidazole and 1-methyl-imidazole on cyclical reductions of coronary blood pressure.

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nate the cyclical reductions (Fig. 8).

DISCUSSION

The results in this study indicate that synthesized PG I₂, but not PG D₂, can eliminate the cyclical reductions of blood flow in a partially constricted coronary artery. The minimum dose required for elimination was the smallest among the agents used in this and in the previous studies. In the previous studies, the effectiveness of the chemical agents on the cyclical reductions was not dependent on the directions and the magnitude of the changes in systemic blood pressure and heart rate. In this study, PG D₂ caused a fall in systemic blood pressure as in case of PG I₂ but it failed to eliminate the cyclical reductions. In addition, I-126 which did not alter systemic blood pressure and heart rate, eliminated the cyclical reductions. Therefore, it is unlikely that PG I₂ eliminated the cyclical reductions through its action on systemic blood pressure and heart rate.

It is well known that PG I₂ causes relaxation of vascular smooth muscles and inhibits platelet aggregation. Since segmental or diffuse narrowing simulating spasm was frequently observed in the constricted coronary artery during the cyclical reductions and since potent platelet aggregators such as PG E₁ and dipyridamole could not eliminate the cyclical reductions while nicotinic acid which did not affect platelet aggregation eliminated the cyclical reductions, it is likely that synthesized PG I₂ eliminated the cyclical reductions not through it inhibitory action on platelet aggregation but through its relaxing action on the coronary smooth muscles.

Existence of PG I₂ generating system in the coronary endothelial cells and smooth muscle cells in venous tissues in the lungs has been demonstrated by several workers. In this study, 15-hydroperoxy arachidonic acid and tranylcypromine that inhibited synthesis of PG I₂ augmented the cyclical reductions. Furthermore, the latter agent induced the cyclical
Effect of PG I₂ on Cylcical Coronary Flow Reductions

reductions. These agents may have induced or augmented the cyclical reductions by inhibiting synthesis of PG I₂ in the lungs or in the coronary artery.

Although the most potent constrictor of the coronary smooth muscles in vitro TX A₂ synthetized by adding thrombine to rabbit platelets could not induce the cyclical reductions. In addition, imidazole and 1-methyl-imidazole that selectively inhibited synthesis of TX A₂ failed to eliminate the cyclical reductions. Furthermore, Cu-chlorophylline that accelerated synthesis of TX A₂ eliminated the cyclical reductions. Thus, we could not obtain any definite evidence which supports that TX A₂ participates in the cyclical reductions (Fig. 9).

In the previous studies, the cyclical reductions were eliminated by aspirin, phenylbutazone and benzydamine that inhibited synthesis of PG endoperoxides; and were frequently induced by epinephrine that accelerated synthesis of PG E₂, and by PG E₂ itself, but not by PG F₂α. In this study, the cyclical reductions were eliminated by I-126 and Cu-chlorophylline that inhibited synthesis of PG E₂. The fact indicates that PG E₂ which caused contraction of the smooth muscles of the large coronary artery plays an important role in induction of the cyclical reductions. PG E₂ is generated in various tissues and regulate coronary circulation. In this study, we could not identify the site(s) of formation of PG E₂ which was considered to participate in the cyclical reductions. PG E₂ generated outside the heart and/or in the heart may have contributed to the cyclical reductions. Although definite evidence lacks, it is likely that the changes in production and/or wasting of PG E₂ and PG I₂, or the changes in PG E₂/PG I₂ ratio resulted in cyclical spasm of the large coronary artery, leading to the cyclical reductions of blood flow in the partially constricted coronary artery, and accordingly to cyclical changes of surface electrogram and left ventricular contractile force.

The cyclical phenomenon observed in this study closely resembles variant angina pectoris in that cyclical ST elevation occurs spontaneously and can be induced by PG E₂ in both.

REFERENCES


