EFFECTS OF PROSTAGLANDINS ON LATE CORONARY LIGATION ARRHYTHMIAS IN THE DOG

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Abstract—Effects of an intravenous injection of indomethacin, prostaglandins (PGs) E₁, E₂ and F₂α and prostacyclin were examined by the use of a model of two-stage coronary ligation arrhythmias in conscious dogs. Indomethacin had no effect on the arrhythmias occurring 48 hr after coronary ligation. PGs and prostacyclin were injected after the injection of indomethacin. PGs did not show any significant antiarrhythmic effects on the arrhythmias occurring 48 hr after coronary ligation, while prostacyclin showed a transient arrhythmogenic effect. From the foregoing results, both endogenous and exogenous PGs do not seem to play a significant role in the genesis of late coronary ligation arrhythmias in the dog.

There have been many studies on the effects of PGs on cardiac arrhythmias, and it seems that PGs are effective against chemically induced arrhythmias (1). However, different effects of PGs on animal coronary ligation arrhythmias have been reported depending on the animals used and the arrhythmia models used (2–6). Harvie et al. (2) and Au et al. (3) reported antiarrhythmic effects of PG E₂, PG F₁α and prostacyclin on the early arrhythmia soon after coronary ligation in the dog, but no such effects were observed on the 24 hr arrhythmia. Dix et al. (4) also reported the antiarrhythmic effect of prostacyclin on cat arrhythmia soon after ligation, and Coker and Parratt (5) reported antiarrhythmic effects of PG E₂, PG F₂α and prostacyclin on acute rat coronary ligation arrhythmia, while thromboxane was assumed to be arrhythmogenic. However, a recent report of Burke et al. (6) denied the arrhythmogenic effect of thromboxane A₂. It seems that PGs have effects on acute coronary ligation arrhythmia, while they have no effects on late coronary ligation arrhythmia. It may be worth trying to clarify whether PGs have no antiarrhythmic effect at all or even have an arrhythmogenic effect on late coronary ligation arrhythmia.

In our previous study, we demonstrated that canine 48 hr arrhythmia was less severe than 24 hr arrhythmia and that antiarrhythmic effects of drugs can be more easily detected (7). This canine 48 hr arrhythmia may also be suitable for examining the arrhythmogenic effect of drugs, so in the present study, we examined the effects of PGs on the canine 48 hr coronary ligation arrhythmias and compared them with the effects of antiarrhythmic drugs that we have reported (7, 8). One of our purposes of this study is to examine the cardiovascular effects of PGs on the sinoatrial node and vascular system of conscious dogs simultaneously with effects on the arrhythmia because previous studies only recorded ECG without examining other cardiovascular changes (2, 3, 6).
Materials and Methods

Twelve beagle dogs of either sex, weighing 9 to 11 kg, were used and operated on to produce the two-stage coronary ligation arrhythmia. The details of the surgical procedures were described in our previous papers (7, 8). In brief, the left anterior descending artery was ligated under halothane anesthesia by Harris’ method. Arterial and venous cannulae were inserted into the left carotid artery and jugular vein to record the arterial pressure and to inject drugs. Bipolar electrodes were sutured on the left atrial appendage to record the atrial electrogram. This was recorded in order to differentiate the conducted beats out of the ventricular ectopic beats and to examine drug effects on the sinoatrial node.

Experiments were performed 48 hr after the coronary ligation without anesthesia. The lead II ECG, the atrial electrogram and the blood pressure were recorded continuously using telemetry systems (Nihon Kohden and Nishimu).

Drugs used were indomethacin (Nippon Merck-Banyu Co., Ltd., Tokyo), PGs E₁, E₂ and F₂α and prostacyclin (these PGs were kindly provided by Ono Pharmaceutical Co., Ltd., Osaka). Indomethacin was dissolved in 0.1 M Na₂CO₃ and diluted with 0.9% saline (final concentration: 2 mg/ml). PGs were dissolved in 99.5% ethanol (1 mg/ml) and then PGs E₁, E₂ and F₂α were diluted in 0.9% saline. PG I₂ was diluted with Tris buffer (pH 8.5). Prostaglandins were injected after indomethacin injection. More than one prostaglandin was injected into one dog after an adequate time for recovery from the cardiovascular effects of previous drug injections.

All the data in the figures are expressed as the mean±standard deviation; the values after drug injection were compared to the 0 time values, and the P values less than 0.05 were considered as statistically significant using Student’s t-test for paired data.

Results

Forty-eight hours after coronary ligation, the dogs showed ventricular tachycardia which was continuous and so a convenient arrhythmia to examine antiarrhythmic effects of drugs. The arrhythmia 24 hr after ligation was characterized by multifocal ventricular tachycardia almost without any conducted beats, but the arrhythmia 48 hr after ligation was milder with decreased total heart rate and increased number of conducted beats.

Indomethacin at 10 mg/kg, i.v., which is a sufficient dose to inhibit prostaglandin biosynthesis (9), was injected into all dogs, and the results of this are shown in Fig. 1.
Smaller doses did not produce any significant changes. The number of conducted beats increased at 3 and 8 min after injection, but the ratio of the number of ventricular ectopic beats and the total heart rate, an arrhythmic ratio, did not change significantly. Thus we did not judge that indomethacin had an antiarrhythmic effect. The blood pressure was slightly elevated after indomethacin, but within 15 min after injection, all these effects disappeared and the arrhythmia persisted during the experiment, less than 3 hr after indomethacin injection. After observing the direct effect of indomethacin for 15 min, PGs and prostacyclin were injected.

Effects of PG E₁ (n=5), PG E₂ (n=5), PG F₂α (n=6) and prostacyclin (n=8) are shown in Figs. 2–5. We used 1 to 10 mcg/kg, but only the effects by 10 mcg/kg are shown because smaller doses did not show a qualitatively different effect on arrhythmia and showed only milder effects on other cardiovascular parameters. Prostacyclin increased the arrhythmic ratio, an arrhythmogenic effect, but for only a short period. Though the number of conducted beats decreased 1 and 5 min after injection, and the arrhythmic ratio increased at 1 min, we did not observe any
Fig. 5. Effects of prostacyclin at 10 mcg/kg, i.v., on the 48 hr arrhythmia. Arrhythmic ratio increased 1 min after injection. \*P<0.05, \**P<0.01.

fatal ventricular fibrillation. Other PGs did not show effects on the arrhythmic ratio. As for the total heart rate and atrial rate, only prostacyclin decreased them transiently as shown in Fig. 5. The blood pressure was decreased transiently by prostacyclin, PG E, and PG E2, while it was increased by PG F₂. Drugs used in the present study did not produce serious side effects related to the central nervous system such as excitement and convulsions or gastrointestinal effects such as vomiting and defecation.

Discussion

Indomethacin, a cyclooxygenase inhibitor, and PGs and prostacyclin had no antiarrhythmic effects on the 48 hr arrhythmia, and prostacyclin showed a transient worsening effect on the arrhythmia. These results seem to agree with previous studies that PGs and thromboxane A₂ are not effective on animal arrhythmias occurring late after myocardial ischemia (2, 3, 6). However, our results on prostacyclin are not consistent with the previous study (3) that prostacyclin had no effect on the canine late coronary ligation arrhythmia, but the difference in the two studies may not be too great because the arrhythmogenic effect of prostacyclin we observed was only transient and was not so serious as to induce fatal arrhythmias.

Compared with our study of the class 1 antiarrhythmic drugs of Vaughan Williams' classification (10) on the coronary ligation arrhythmias (7, 8, 11), all the drugs tested in the present study can be said to have no effect on the arrhythmia. Among the antiarrhythmic drugs we tested on the two-stage coronary ligation arrhythmia, β-blockers at β-blocking doses or concentrations, Ca-blockers and lidocaine were not effective on the 24 and 48 hr arrhythmias. Therefore, while it cannot be denied that PGs and prostacyclin may have antiarrhythmic effects on other arrhythmias relating to the sympathetic nerve and Ca channel (1, 12), they may not play an important role in the ischemic arrhythmias, even though there have been reports that ischemia releases various PGs (13).

In the present study, we also recorded changes in the atrial rate, which is a measure of the sinoatrial activity, and the blood pressure in conscious dogs. Only prostacyclin showed a transient negative chronotropic effect, but other drugs did not show effects on the atrial rate. However, on the blood pressure, PGs and prostacyclin showed their characteristic effects. The lack of significant effects of PGs on the late coronary ligation arrhythmia and on the sinoatrial node, but prominent effects of PGs on the blood pressure may indicate that PGs and prostacyclin play an important role on vascular smooth muscle, but not as much on cardiac muscle excitation. Therefore, attempts to decrease endogenous prostaglandins or in-
crease prostaglandin levels by exogenous administration may not have any therapeutic values in the treatment of already existing late ischemic arrhythmias.

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