# Protective Effects of Arbaprostil against Indomethacin-Induced Gastric Lesions in Rats: Significance of Maintained Gastric Blood Flow

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ABSTRACT — The purpose of the present study was to investigate the relationship between the effects of 15(*R*)-15-methylprostaglandin $E_2$ (arbaprostil) on gastric blood flow (GBF) and its protective effects on gastric lesions in rats. The GBF of anesthetized rats was measured by two different methods: Total blood flow into the stomach (total GBF) was determined by means of an ultrasonic pulsed Doppler flow meter; and gastric mucosal blood flow (mucosal GBF) was measured by nonradioactive microspheres. Systemic blood pressure (SBP), heart rate (HR) and gastric vascular resistance (GVR) were recorded simultaneously. Arbaprostil (10–100 $\mu$g/kg) given i.v. did not affect resting total or mucosal GBF even though it decreased SBP and GVR. Significant improvement of the total and mucosal GBF decreased by indomethacin pretreatment (10 mg/kg, i.v.) was observed by administration of arbaprostil (10–100 $\mu$g/kg, i.v.) in a dose-dependent manner. Furthermore, i.v.-administration of this agent, in the same dose-range, prevented the formation of gastric lesions induced by indomethacin. The present result suggests that mitigation for the ischemic state of the gastric mucosa may be one of the important mechanisms for the prophylactic and curative effect of arbaprostil on gastric lesions induced by indomethacin.

*Keywords:* Arbaprostil, Gastric blood flow, Indomethacin, Gastric lesion, Nonradioactive microsphere

15(*R*)-15-Methylprostaglandin $E_2$ (arbaprostil), a synthetic prostaglandin $E_2$ analogue, is currently being evaluated as a new antiulcer agent. This agent protects the gastric mucosa against grossly observable injuries caused by a variety of noxious agents and accelerates the healing of chronic gastric ulcers in rats (1, 2). Furthermore, a number of investigators have demonstrated that arbaprostil is useful for the treatment of peptic ulcers in clinical settings (3–5). It has been generally accepted that peptic ulcers result from an imbalance between aggressive and defensive factors; i.e., defensive factors such as gastric blood flow, mucus secretion, mucosal barrier and alkali secretion protect the gastric and duodenal mucosa against the aggressive factors, acid and pepsin (6). Although arbaprostil has been reported to have antisecretory properties in humans (7–9), there have been few reports regarding its effect on gastric blood flow.

The aim of the present study was to examine the relationship between the effects of arbaprostil on gastric blood flow in rats treated or not treated with indomethacin and its protective effects on gastric lesions induced by indomethacin.

## MATERIALS AND METHODS

Male Sprague-Dawley rats (300–350 g), kept in individual cages with raised mesh bottoms, were fasted overnight with access to water. The animals were anesthetized with an i.p. pentobarbital sodium (55 mg/kg), supplemented with a continuous infusion (17 mg/kg/hr) into the left femoral vein. The rectal temperature was maintained at 36 ± 1°C by intermittent heating with an infrared lamp throughout the experiments. A polyethylene cannula was intubated into the trachea to maintain a patent airway. For drug administration, a polyethylene catheter (PE-10) was inserted into the right femoral vein. Through the right femoral artery, a

catheter was advanced into the abdominal aorta to measure systemic blood pressure (SBP) by means of a pressure transducer (TP-200T, Nihon Kohden, Tokyo, Japan). Heart rate (HR) was measured by means of a heart rate counter (AT-601G, Nihon Kohden).

*Determination of total blood flow into the stomach (total GBF)*

Total GBF was determined using an ultrasonic pulsed Doppler flowmeter (model VF-1, Valpey-Fisher Corp., MA, U.S.A.) at 20 MHz. A midline laparotomy was made, and the celiac artery was isolated carefully from the surrounding tissue. The common hepatic artery and the splenic artery, as well as the associated branch arteries and vessels, were all ligated so that the blood in the celiac artery could flow selectively into the left and right gastric artery (10). Then a miniatured Doppler flow probe (DBF 1.0, ID 1.0 mm) was sutured loosely around the celiac artery for the total GBF measurement. Gastric vascular resistance (GVR) was calculated by dividing the mean SBP by the Doppler shift in kHz as previously described (11). All data were recorded on a thermal pen writing recorder (WR-3101, Graphtec, Tokyo, Japan). According to our preliminary experiments which indicated that all hemodynamic parameters reached stable levels 20–30 min after completion of the surgical procedure, a minimum of 30 min was allowed for equilibration of the preparation after the operation. After this stage, a stable condition of the preparations was maintained for over 2 hr. Arbaprostil was administered i.v. for 30 sec in a volume of 0.5 ml/kg. Indomethacin was also given into the vein for 30 sec in a volume of 1 ml/kg, which was subsequently flushed in with 0.9% saline. Drug effects were expressed as percent changes from the preadministration control level.

*Determination of gastric mucosal blood flow (mucosal GBF)*

Mucosal GBF measurement by nonradioactive microspheres (12) was performed according to the standard technique using radioactive microspheres (13). The rat was anesthetized, and a polyethylene cannula (PE-50) was threaded into the left ventricle through the right carotid artery. The position of the cannula was verified by the presence of a left ventricular pressure pattern and by inspection at necropsy. Approximately one million microspheres (E-Z Trac, Los Angeles, CA, U.S.A.) of 15.3 ± 0.17 $\mu$m (mean ± S.D.) in diameter were injected into the left ventricle over a 15 to 20-sec period. A reference blood sample was withdrawn (0.4 ml/min) for 90 sec from the left femoral artery, just 5 sec before microsphere injection. The animal was killed painlessly by i.v.-injection of potassium chloride (5 min after microsphere injection), and the stomach was removed. The gastric mucosal layer was bluntly separated and weighed. By means of sequential collagenase and sodium hydroxide digestion, the spheres were extracted from the reference blood and the gastric mucosal sample. The extracted spheres were counted with the use of a hemocytometer. Mucosal GBF was calculated by means of a standard formula (12):

$$Q_m = (C_m \times Q_r)/C_r \times 100$$

Where $Q_m$ is the mucosal GBF (ml/min/100 g), $C_m$ is the microsphere count per gram of the gastric mucosa specimen, $Q_r$ is the withdrawal rate of the reference blood sample (0.4 ml/min) and $C_r$ is the microsphere count in the reference blood sample.

Microsphere injections were performed at 2 and 5 min after arbaprostil administration in rats not treated and treated with indomethacin, respectively, because the maximal changes in total GBF occurred at these times.

*Induction of gastric lesions*

The rats (230–250 g) were deprived of food (but not water) for 24 hr prior to the experiment. The gastric lesions were produced according to the method described by Takeuchi et al. (14) with a modification. Indomethacin, suspended in 0.9% saline with a few drops of Tween 80, was given s.c. to five groups of ten rats each at a dose of 30 mg/kg in a volume of 5 ml/kg body weight. Approximately 4 hr later, the animals were killed under deep ether anesthesia, and the stomach was removed, inflated by injecting 12 ml of 2% formalin, and immersed in 2% formalin for 10 min. Then, the stomach was incised along the greater curvature. The total length (mm) of gastric lesions of each stomach induced by indomethacin was measured under a dissecting microscope (×10) by an observer unaware of the treatment, and this was used as a lesion index. Either arbaprostil (10–300 $\mu$g/kg) or 0.9% saline containing 0.5% ethanol (control) in a volume of 0.5 ml/kg was injected into the left lateral saphenous vein just before indomethacin administration.

*Drugs*

15(*R*)-15-Methylprostaglandin $E_2$ (arbaprostil) was a gift from the Upjohn company (Kalamazoo, MI, U.S.A.). Indomethacin was purchased from Sigma (St. Louis, MO, U.S.A.). Arbaprostil was first solubilized into absolute ethanol and then diluted with 0.9% saline to make a final ethanol concentration of 0.5%. Indomethacin was dissolved into 100 mM $Na_2CO_3$ solution and the pH was adjusted to 7.5–8.0 with diluted HCl.

*Statistical analysis*

Data are expressed as the mean ± S.E. Statistical analysis was made by one-way analysis of variance (ANOVA) coupled with Dunnett's test. In the case of analysis of the difference in two groups, the *t*-test of Aspin-Welch was used to determine the statistical significance of the data. P values less than 0.05 were considered statistically significant.

## RESULTS

*Total blood flow into the stomach (total GBF) in rats not treated with indomethacin*

Basal values of hemodynamic parameters prior to i.v.-administration of arbaprostil are presented in Table 1. Arbaprostil had no significant effects on total GBF, whereas it produced a dose-dependent reduction of mean SBP, in parallel with that of GVR accompanied by slight changes in HR (Fig. 1). At the largest dose (100 μg/kg), arbaprostil decreased mean SBP and GVR by about 20% from the pretreatment level at 2 min after administration. The changes in these hemodynamic parameters diminished within 20 min after administration.

*Total GBF in rats treated with indomethacin*

Basal values of hemodynamic parameters before injection of indomethacin are shown in Table 2. The i.v.-injection of indomethacin had no effect on total GBF at a dose of 3 mg/kg, but produced a sustained decrease in total GBF at a dose of 10 or 30 mg/kg (Fig. 2). The significant decrease in total GBF induced by indomethacin lasted for approximately 30 and 60 min in a dose of 10 and 30 mg/kg, respectively. SBP and GVR were increased dose-dependently by indomethacin administration (Fig. 2).

Arbaprostil given i.v. 15 min after the treatment with indomethacin (10 mg/kg, i.v.) dose-dependently produced an increase in total GBF, accompanied by decreases of GVR and SBP, without affecting HR (Fig. 3). Administration of 100 μg/kg of arbaprostil significantly increased total GBF to the level of the basal flow rate prior to indomethacin administration. Arbaprostil at a dose of 10 or 30 μg/kg also produced an increase in total GBF, even enough its effect was not significant compared with the 0.9% saline containing 0.5% ethanol administration (control) group. It is confirmed that the basal flow rate improved by arbaprostil was maintained over 60 min in doses of 30 and 100 μg/kg.

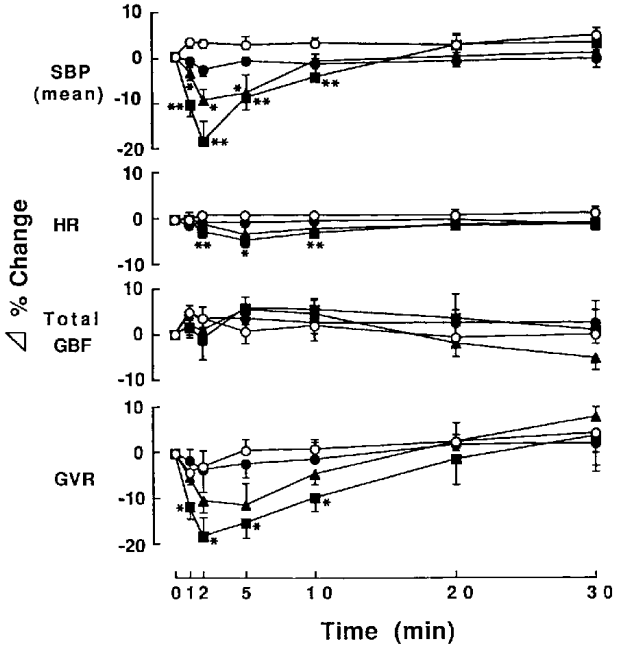


**Fig. 1.** Dose-related effects of arbaprostil (● 10 μg/kg, ▲ 30 μg/kg, ■ 100 μg/kg) given i.v. on systemic blood pressure (SBP, mean), heart rate (HR), total blood flow into the stomach (total GBF) and gastric vascular resistance (GVR) in rats not treated with indomethacin. Each point represents the mean of 6 observations of 6 preparations. Vertical bars show ± S.E. *P < 0.05, **P < 0.01, compared with the control group (○) treated with 0.9% saline containing 0.5% ethanol at the same time.

**Table 1.** Basal values of hemodynamic parameters prior to i.v.-administration of test drugs in rats not treated with indomethacin

| Experimental group | SBP (mean) (mmHg) | HR (beats/min) | Total GBF (kHz) | GVR (mmHg/kHz) |
|---|---|---|---|---|
| 0.9% Saline | 122 ± 4 | 387 ± 7 | 7.2 ± 1.1 | 20.9 ± 3.5 |
| Arbaprostil 10 μg/kg | 129 ± 5 | 408 ± 10 | 5.7 ± 0.8 | 26.5 ± 4.4 |
| Arbaprostil 30 μg/kg | 125 ± 4 | 401 ± 14 | 6.9 ± 0.7 | 20.1 ± 2.1 |
| Arbaprostil 100 μg/kg | 124 ± 5 | 398 ± 10 | 6.3 ± 0.7 | 22.4 ± 2.5 |

SBP, systemic blood pressure; HR, heart rate; Total GBF, total blood flow into the stomach; GVR, gastric vascular resistance. Values presented are means ± S.E. from 6 preparations in each group. None of the values are significantly different compared with the corresponding value from the 0.9% saline-injected group.

**Table 2.** Basal values of hemodynamic parameters prior to i.v.-administration of test drugs in rats treated with indomethacin

| Experimental group | | SBP (mean) (mmHg) | HR (beats/min) | Total GBF (kHz) | GVR (mmHg/kHz) |
|---|---|---|---|---|---|
| 100 mM $Na_2CO_3$ | | 123 ± 5 | 388 ± 10 | 5.1 ± 0.3 | 24.3 ± 1.0 |
| Indomethacin | 3 mg/kg | 118 ± 4 | 393 ± 4 | 4.4 ± 0.5 | 26.6 ± 2.8 |
| Indomethacin | 10 mg/kg | 117 ± 4 | 382 ± 9 | 5.8 ± 0.8 | 22.1 ± 2.9 |
| Indomethacin | 30 mg/kg | 123 ± 4 | 388 ± 10 | 5.3 ± 0.6 | 24.2 ± 3.0 |
| Indomethacin (10 mg/kg) | | | | | |
| + 0.9% Saline | | 121 ± 4 | 420 ± 17 | 5.0 ± 0.5 | 25.8 ± 2.6 |
| + Arbaprostil | 10 μg/kg | 127 ± 2 | 427 ± 6 | 4.6 ± 0.6 | 30.3 ± 3.6 |
| + Arbaprostil | 30 μg/kg | 116 ± 3 | 398 ± 10 | 4.6 ± 0.5 | 26.9 ± 3.5 |
| + Arbaprostil | 100 μg/kg | 131 ± 6 | 428 ± 13 | 4.8 ± 0.4 | 27.6 ± 1.9 |

SBP, systemic blood pressure; HR, heart rate; Total GBF, total blood flow into the stomach; GVR, gastric vascular resistance. Values presented are means ± S.E. from 6 preparations in each group. None of the values are significantly different compared with the corresponding value from the 100 mM $Na_2CO_3$-injected group.

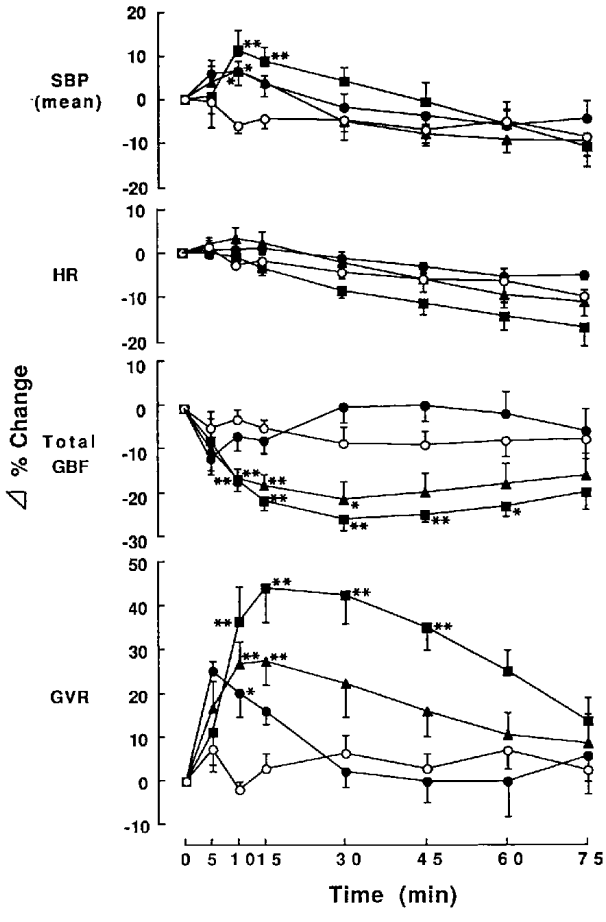


**Fig. 2.** Dose-related effects of indomethacin (● 3 mg/kg, ▲ 10 mg/kg, ■ 30 mg/kg) given i.v. on systemic blood pressure (SBP, mean), heart rate (HR), total blood flow into the stomach (total GBF) and gastric vascular resistance (GVR) in rats. Each point represents the mean of 6 observations of 6 preparations. Vertical bars show ± S.E. *P < 0.05, **P < 0.01, compared with the control group (○) treated with 100 mM $Na_2CO_3$ at the same time.

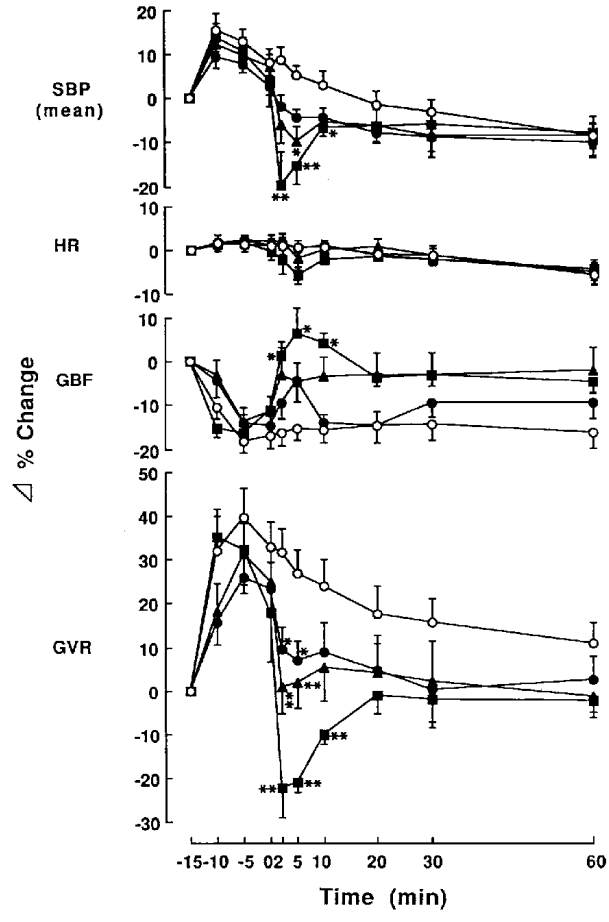


**Fig. 3.** Dose-related effects of arbaprostil (● 10 μg/kg, ▲ 30 μg/kg, ■ 100 μg/kg) on systemic blood pressure (SBP, mean), heart rate (HR), total blood flow into the stomach (total GBF) and gastric vascular resistance (GVR) in rats treated with indomethacin. Either arbaprostil or 0.9% saline containing 0.5% ethanol (control) was given i.v. 15 min after the i.v.-treatment of indomethacin (10 mg/kg). Each point represents the mean of 6 observations of 6 preparations. Vertical bars show ± S.E. *P < 0.05, **P < 0.01, compared with the control group (○) treated with 0.9% saline containing 0.5% ethanol at the same time.

*Gastric mucosal blood flow (mucosal GBF)*

Figure 4A indicates the mucosal GBF determined using the nonradioactive microsphere technique in rats not treated with indomethacin. Mucosal GBF at the stable resting state before administration of any stimulating drugs and 2 min after 0.9% saline containing 0.5% ethanol injection (control) were 59.6 ± 4.5 and 64.3 ± 5.2 ml/min/100 g, respectively (N = 6, each). No significant difference was observed between the values from each group. Arbaprostil did not cause any significant effects on resting mucosal GBF at 2 min after administration even at the highest dosage examined (100 μg/kg, i.v.).

As shown in Fig. 4B, i.v.-administration of indomethacin (10 mg/kg) significantly decreased mucosal GBF from 61.6 ± 6.3 ml/min/100 g in rats treated with vehicle (100 mM $Na_2CO_3$) to 35.2 ± 5.8 ml/min/100 g (N = 6, each). Arbaprostil given i.v. 15 min after administration of indomethacin improved the depressed mucosal GBF in a dose-dependent manner, and the effect of the highest dose of arbaprostil (100 μg/kg) was significant compared with the 0.9% saline-treated group.

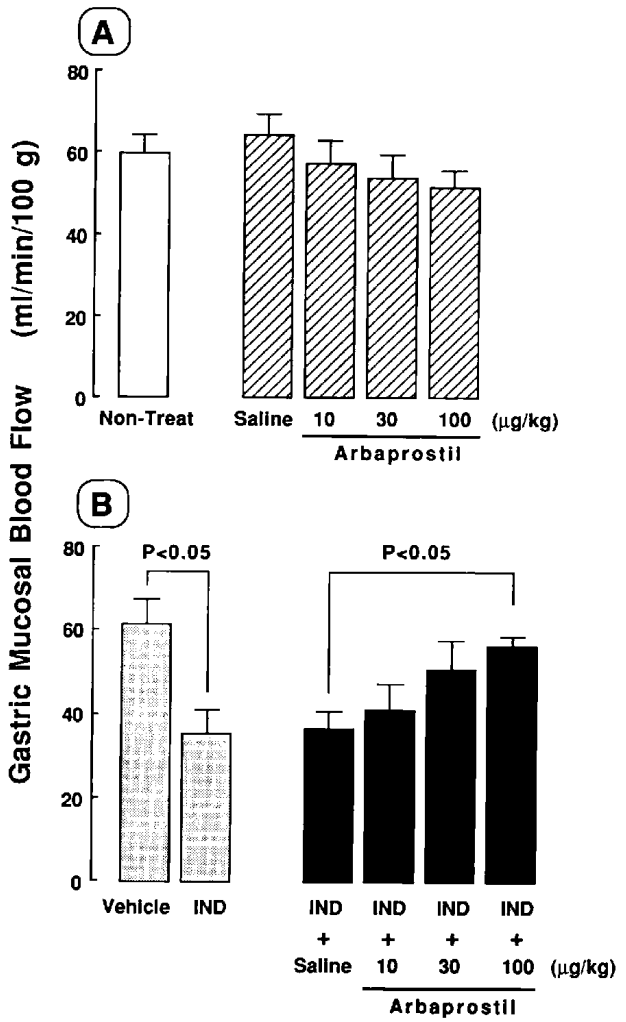


**Fig. 4.** Dose-related effects of arbaprostil on gastric mucosal blood flow in rats not treated [A] and treated [B] with indomethacin. Open column, microsphere injection was performed during the stable resting state before administration of any stimulating drug. Hatched column, microspheres were injected at 2 min after administration of arbaprostil or 0.9% saline containing 0.5% ethanol (control) in rats not treated with indomethacin. Dotted column, microspheres injection was performed at 15 min after i.v.-administration of indomethacin (IND, 10 mg/kg) or its vehicle (100 mM $Na_2CO_3$). Closed column, microspheres were injected at 5 min after administration of arbaprostil or 0.9% saline containing 0.5% ethanol (control) in rats treated with indomethacin. Indomethacin (10 mg/kg, i.v.) was pretreated 15 min before administration of arbaprostil or 0.9% saline. Each column represents the mean of 6 observations of 6 preparations. Vertical bars show ± S.E.

*Indomethacin-induced gastric lesions*

Administration of indomethacin (30 mg/kg, s.c.) produced gross mucosal lesions in the stomach within 4 hr, exclusively in the glandular portion, and the lesion index was 13.2 ± 2.9 mm (N = 10). Pretreatment of the animals with i.v.-administered arbaprostil (10–300 μg/kg) dose-dependently reduced the formation of gastric lesions induced by indomethacin (Fig. 5). The inhibition obtained by arbaprostil was 63.6% and 70.5% at the dose of 100 and 300 μg/kg, respectively, which were both significantly different ($P < 0.05$) from the control.

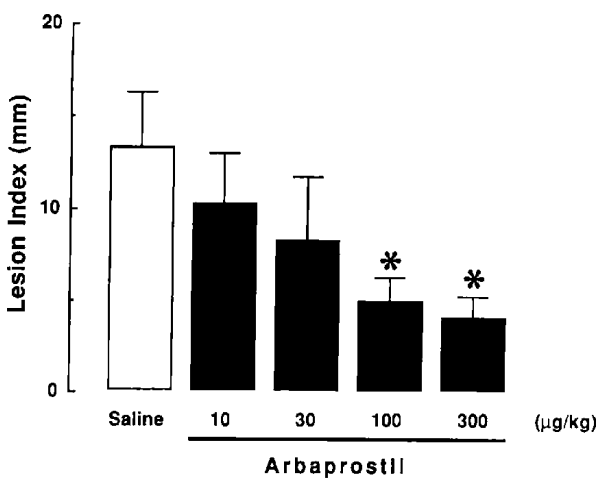


**Fig. 5.** Dose-related effects of arbaprostil on indomethacin-induced gastric lesions. Either arbaprostil or 0.9% saline containing 0.5% ethanol (control) was given into the left lateral saphenous vein just before indomethacin treatment (30 mg/kg, s.c.). The animals were killed 4 hr after the administration of indomethacin. Each column represents the mean of 10 rats per group. Vertical bars show ± S.E. *$P < 0.05$, compared with the control group treated with 0.9% saline.

## DISCUSSION

The present experiment demonstrates that arbaprostil given i.v. dose-dependently improves total blood flow into the stomach (total GBF) and gastric mucosal blood flow (mucosal GBF) decreased by indomethacin pretreatment in rats even though it did not affect resting total or mucosal GBF in rats not treated with indomethacin. Furthermore, in the same dose-range, pretreatment with i.v.-arbaprostil significantly reduces the formation of gastric lesions induced by indomethacin.

In the present study, i.v.-administration of indomethacin caused marked reductions of total and mucosal GBF, accompanied by a rise of gastric vascular resistance (GVR) and systemic blood pressure (SBP), without affecting heart rate (HR). The hemodynamic changes induced by indomethacin were improved by i.v.-injection of arbaprostil. That is, arbaprostil reversed SBP and GVR increased by indomethacin and clearly remedied decreases in total GBF. In addition, decreases in mucosal GBF by indomethacin were significantly improved to the level of the basal flow rate prior to indomethacin administration by i.v.-injection of arbaprostil in a dose of 100 $\mu$g/kg.

A number of investigations have demonstrated that indomethacin produces lesions in the stomach of animals (15, 16) and humans (17), although the pathogenetic mechanism underlying these lesions is not yet known. According to the report of Kauffman et al. (18), i.v.-administration of indomethacin decreases GBF in dogs. It seems that the decrease in GBF is one of major factors related to the indomethacin-induced gastric lesions. Indeed, there have been a number of investigations showing that decreases in GBF may be one of the causative factors in the manifestation of acute gastric lesions (19–21). Kamada et al. (19) reported that the reduction of mucosal blood volume precedes the development of acute gastric lesions in patients with thermal or head injuries. Kitagawa et al. (20) and Hase and Moss (21) have observed that significant decreases in GBF can be manifested prior to the appearance of gastric lesions under the stressed state in rats. Taking these together into consideration, it seems very likely that the ischemic state of the gastric mucosa could induce ulcergenic changes; that is, focal devitalization of tissue, alteration of the mucus barrier and digestion of devitalized tissue by acid and pepsin.

In the present study, resting total or mucosal GBF was not significantly affected by i.v.-arbaprostil. Even though the lack of increase in resting GBF may be a secondary response related to the fall of SBP, the result coincides with previous observations (22, 23) that $PGE_2$ and 16,16-dimethyl $PGE_2$ did not increase resting GBF. Interestingly, the sustained decreases in total and mucosal GBF produced by indomethacin were clearly improved to the level of the basal flow rate prior to indomethacin administration by i.v.-arbaprostil in a dose of 100 $\mu$g/kg. It is also noticed that the basal flow rate of total GBF improved by arbaprostil was maintained over 60 min. At this dosage or above, the gastric mucosal injury induced by indomethacin was significantly alleviated by i.v.-arbaprostil. In spite of the effectiveness, arbaprostil, even at the highest i.v.-dose (300 $\mu$g/kg), did not cause any diarrhea in the present study (data not shown), even though it has been well-known as a common side effect of PG derivatives experimentally (24) and clinically (25). The present data suggest that protective effects of arbaprostil against gastric injury may partly be explicable in terms of mitigation of depressed GBF (that is, to maintain rather than increase GBF) induced by indomethacin. Leung et al. (23) and Guth et al. (26) have come to a similar conclusion that prophylactic effects of 16,16-dimethyl $PGE_2$ on gastric lesions of rats may be due to a maintainance rather than an increase in GBF.

It has also been reported that various antisecretory agents prevent the formation of gastric lesions in response to indomethacin (27), and that arbaprostil exhibits gastric antisecretory activity after oral administration in humans (7–9) and topical application to the gastric mucosa in dogs (28). However, as previously demonstrated (29), parenteral administration of arbaprostil (300 $\mu$g/kg) to rats failed to reveal any significant antisecretory effects: this agent develops a potent antisecretory action due to its epimerization to 15(*S*)-15-methyl $PGE_2$, which has a potent antisecretory activity, by gastric acid in the stomach. So, it is unlikely that the mucosal protection by i.v.-arbaprostil in this study was accounted for by its antisecretory activity.

In conclusion, i.v.-administration of arbaprostil dose-dependently improved total and mucosal GBF decrements by indomethacin. Arbaprostil also protected the gastric mucosa from acute injuries induced by indomethacin. These results suggest that the improvement of the ischemic state of the gastric mucosa may play some role in the prophylactic and curative activity of arbaprostil on gastric lesions.

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