The Regional Difference of Relaxations Induced by Various Vasodilators in Isolated Dog Coronary and Mesenteric Arteries

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Abstract—Relaxant responses to vasodilators, including nitroglycerin, sodium nitroprusside, prostaglandin I₂ sodium salt (PGI₂), prostaglandin E₁ (PGE₁), diltiazem hydrochloride and adenosine, were compared in helical strips of dog coronary arteries of different sizes and in coronary and mesenteric arterial strips. The relaxant responses to nitroglycerin, sodium nitroprusside, diltiazem and adenosine were significantly greater in coronary arteries than in mesenteric arteries, whereas the responses to PGI₂ and PGE₁ in these arteries did not significantly differ. In coronary arteries of different sizes, the relaxation induced by nitroglycerin was in the order of large > medium > small-size, while in contrast, the relaxations by adenosine, PGI₂ and PGE₁ were greatest in the small-size arteries and least in the large-size arteries. The relaxant responses to sodium nitroprusside and diltiazem did not differ in the coronary arteries of different sizes. Nitroglycerin, sodium nitroprusside and diltiazem appear to dilate coronary arteries more predominantly than mesenteric arteries. The preferential dilator action of PGI₂ and PGE₁ on distal coronary arteries, like that of adenosine, may lead more blood to re-distribute to the non-ischemic region of the heart in anginal patients.

Vasodilators have recently been used in patients with congestive heart failure to reduce systemic vascular resistance or left ventricular afterload with resultant improvement of left ventricular function (1, 2). Vasodilators have potential abilities to dilate not only the systemic vascular bed but also the coronary artery. It has been recognized that nitroglycerin acts mainly on the proximal, large coronary artery, whereas dipyridamole preferentially dilates the distal coronary artery, resulting in a decrease in total coronary vascular resistance (3, 4). However, there is little direct documentation concerning the regional difference in coronary artery responses to various vasodilator agents.

Thromboxane A₂ (TXA₂) has been postulated to be one of vasoactive endogenous substances related to coronary

artery spasm (5). Carbocyclic TXA₂ (6), a stable analog of TXA₂, remarkably contracts isolated dog and monkey arteries (7). Accordingly, in isolated dog large, medium and small coronary arteries or in coronary and mesenteric arteries maximally contracted with carbocyclic TXA₂, we compared the relaxant responses to nitroglycerin, sodium nitroprusside, prostaglandin I₂, prostaglandin E₁, diltiazem or adenosine.

Materials and Methods

Subjects: Mongrel dogs of either sex, weighing 6 to 21 kg, were anesthetized with intravenous injections of pentobarbital in a dose of 30 mg/kg and were killed by bleeding from the common carotid arteries. The heart was rapidly removed, and left anterior descending and circumflex branches (epicardial location) of the left coronary artery of different sizes were isolated. Inside diameters were greater than 1.5 mm in large, proximal coronary arteries, 0.5 to 0.8 mm in the arteries of the medium-size arteries and

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less than 0.3 mm in small, distal arteries. The mesenteric artery (0.35 to 0.5 mm) was also resected. The arteries were cleaned and cut helically into strips, approximately 20 mm long. Endothelial cell functions were determined by testing a dose-dependent relaxation induced by acetylcholine (8). Each strip was fixed vertically between hooks in a muscle bath containing the nutrient solution which was aerated with a mixture of 95% O₂ and 5% CO₂ and maintained at 37±0.5°C. The hook anchoring the upper end of the strips was connected to the lever of a force-displacement transducer (Nihon Kohden Kohgyo, Co., Tokyo, Japan). The maximum contraction was obtained at a passive tension of 1.5 g in strips of the medium-size coronary artery and the mesenteric artery (9). Cross-sectional areas of large, medium and small coronary arteries, calculated by the ratio of wet weight and length of strips, were 1.17±0.10 mm² (n=31), 0.65±0.05 mm² (n=31) and 0.22±0.02 mm² (n=31), respectively (10). Therefore, the resting tension was adjusted to 3.0 g for large arteries, 1.5 g for medium-size arteries, 0.6 g for small arteries and 1.5 g for mesenteric arteries. Constitutions of the nutrient solution were as follows (mM): Na⁺: 144.7, K⁺: 5.4, Cl⁻: 131.5, Ca⁺⁺: 2.2, Mg⁺⁺: 1.0, HCO₃⁻: 25.0, dextrose: 5.6. The pH of the solution was 7.25–7.35. Before the start of experiments, all preparations were allowed to equilibrate for 60–90 min in the control media, during which time the fluids were replaced every 10–15 min.

Vasodilator dose-response curves: Iso-metric contractions and relaxations were displayed on an inkwriting oscillograph (San-ei Instrument Co., Tokyo). The contractile response to KCl (30 mM) was first obtained, the average values in large, medium and small coronary arteries being 2.07±0.25 (n=31), 2.93±0.31 (n=31) and 2.46±0.38 (n=31) g/mm² cross sectional areas, respectively. The preparations were then washed repeatedly and equilibrated for 30–40 min. Before the dose-response curve for vasodilators was obtained, arterial strips had been contracted with carbocyclic TXA₂ (10⁻⁷ M), a stable analog of TXA₂, in large, medium and small coronary arteries, and the

contractions averaged 3.00±0.41 (n=17), 3.81±0.60 (n=17) and 2.48±0.53 (n=17) g/mm² cross sectional area, respectively. There was no significant difference in the contractions of large, medium and small coronary arteries induced by KCl (30 mM) or carbocyclic TXA₂ (10⁻⁷ M). The vasodilators were added directly to the bathing media in cumulative concentrations. At the end of each series of experiments, papaverine in a concentration of 10⁻⁴ M was added to attain the maximum relaxation. Relaxations induced by vasodilators relative to papaverine-induced relaxations are presented. The contraction induced by KCl (30 mM) was taken as a standard for the contractile response. Paired comparisons were made in the responses to vasodilators of large, medium and small coronary arteries isolated from the same dogs. Paired comparisons in the responses of coronary arteries of medium-size and mesenteric arteries were also made.

Statistical analysis: All data are expressed as mean values±standard errors of the means. Statistical comparisons were performed by one-way analysis of variance with repeated measures and the Newman-Keuls test for multiple comparisons (11, 12) to evaluate possible differences between dose-response curves (Figs. 1, 2 and 5, and Table 1). Student's *t*-test was also used to determine the significance in maximum relaxations or median effective concentrations (ED50's).

Drugs: Drugs used were carbocyclic TXA₂ (Ono Co., Osaka, Japan), nitroglycerin (Nihon Kayaku Co., Tokyo, Japan), sodium nitroprusside (Nakarai Kagaku, Kyoto, Japan), PGI₂ sodium salt (Ono Co.), PGE₁ (Ono Co.), diltiazem hydrochloride (Tanabe Co., Osaka), adenosine (Kohjin Co., Tokyo) and papaverine hydrochloride.

Results

All six drugs including nitroglycerin, sodium nitroprusside, PGI₂, PGE₁, diltiazem and adenosine relaxed dog coronary arteries of different sizes and mesenteric arteries in a dose-dependent manner, except for PGE₁ in low dose which contracted large coronary arteries. Nitroglycerin (10⁻⁹–10⁻⁶ M), sodium nitroprusside (10⁻⁹–10⁻⁵ M), PGI₂ (10⁻¹⁰–

10^{-6} M), PGE_1 (10^{-7} – 2×10^{-6} M) and adenosine (10^{-8} – 10^{-4} M) rapidly relaxed the arteries; thus, a series for the dose-response relationship was completed within 15 min. On the other hand, the diltiazem (10^{-8} – 10^{-4} M)-induced relaxation slowly developed; it took over 40 min to complete the dose-response relationship. This relaxation was sustained for over 1 hr, while relaxations induced by the other drugs were sustained only for a few minutes. Mean values of the apparent median effective concentration (ED_{50}) of each drug in dog mesenteric arteries and coronary arteries of different sizes are summarized in Table 1.

Relaxant responses to vasodilators in coronary and mesenteric arteries: Dose-relaxant response relationships of vasodilators in coronary and mesenteric arteries are shown in Figs. 1 and 2. Relaxant responses to nitroglycerin, sodium nitroprusside, diltiazem and adenosine were significantly larger in coronary arteries than in mesenteric arteries. Relaxant responses to PGI_2 and PGE_1 of these arteries did not significantly differ. Maximum relaxations induced by nitroglycerin, sodium nitroprusside and diltiazem were significantly larger ($P < 0.01$ with nitroglycerin and sodium nitroprusside; $P < 0.02$ with diltiazem) in coronary arteries than in mesenteric arteries. ED_{50} values of nitroglycerin, sodium nitroprusside and adenosine were significantly less in coronary arteries than in mesenteric arteries (Table 1).

Relaxant responses to vasodilators in coronary arteries of different sizes: There were significant differences in the relaxant responses of large, medium and small coronary arteries to nitroglycerin, PGI_2 , PGE_1 or adenosine. Typical recordings of relaxant responses to PGI_2 are shown in Fig. 3. Greater relaxations induced by PGI_2 as well as adenosine are seen in the small-size arteries than in the large arteries. In contrast, nitroglycerin produced a greater relaxation in the large coronary artery, as shown in Fig. 4. Quantitative data on the relaxations of coronary arteries of different sizes are summarized in Figs. 5 and 6. The ED_{50} values of nitroglycerin were in the order of large < medium < small coronary arteries, and the values of PGI_2 and adenosine were in the order of large > medium > small coronary arteries (Table 1). PGE_1 in a low dose (10^{-7} M) contracted the large arteries and at the higher doses produced a relaxation. The administration of PGE_1 elicited only relaxation in medium and small arteries. The maximum relaxation by PGE_1 was significantly larger ($P < 0.05$) in small coronary arteries than in large arteries. The ED_{50} value of PGE_1 was significantly larger ($P < 0.05$) in large coronary arteries than in small arteries (Table 1). There was no significant regional difference in the coronary artery relaxation induced by sodium nitroprusside and diltiazem.

Table 1. Mean values of apparent median effective concentration (ED_{50}) of vasodilators

	N	$\text{ED}_{50} (\times 10^{-8} \text{ M})$					
		Coronary artery					
		L	M	S	Coronary artery	Mesenteric artery	
NG	10	0.82 ± 1.31^a	2.08 ± 0.44	4.53 ± 0.62^a	12	2.01 ± 0.41	6.36 ± 0.98^d
NP	7	1.71 ± 0.38	2.38 ± 0.46	1.59 ± 0.47	7	2.38 ± 0.46	10.19 ± 0.28^d
DZ	13	9.77 ± 1.66	7.16 ± 1.75	6.21 ± 1.48	13	7.16 ± 1.75	8.17 ± 1.94
PGE_1	7	4.97 ± 1.15	3.42 ± 1.12	1.13 ± 1.02^c	7	3.42 ± 1.12	1.91 ± 0.82
PGI_2	12	2.35 ± 0.34^b	1.27 ± 0.48	0.58 ± 0.20^c	12	1.27 ± 0.48	1.51 ± 0.65
AD	8	17.11 ± 3.51^a	4.65 ± 0.68	2.33 ± 0.59^a	7	4.47 ± 0.80	7.36 ± 1.75^c

N=number of preparations used, L=large-size artery, M=medium-size artery, S=small-size artery. NG=nitroglycerin, NP=sodium nitroprusside, DZ=diltiazem, PGE_1 =prostaglandin E_1 , PGI_2 =prostaglandin I_2 , AD=adenosine. Significantly different from values in medium-size artery: ^a $P < 0.01$; ^b $P < 0.05$. Significantly different from values in large-size artery: ^c $P < 0.05$. Significantly different from values in coronary artery: ^d $P < 0.01$; ^e $P < 0.05$. Only the values significantly different by the Newman-Keuls test for multiple comparisons are included.

Fig. 1. Dose-response curves of nitroglycerin (NG), sodium nitroprusside (NP) and diltiazem (DZ) in isolated dog coronary and mesenteric arteries. Preparations were contracted with carbocyclic TXA₂ (10^{-7} M). Relaxation induced by 10^{-4} M papaverine was taken as 100%; mean absolute values in coronary arteries were 1280 ± 120 mg ($n=12$), 1410 ± 180 mg ($n=7$) and 1460 ± 240 mg ($n=13$), respectively, and those in mesenteric arteries were 1830 ± 260 mg ($n=12$), 1290 ± 1100 mg ($n=7$) and 1470 ± 360 mg ($n=13$), respectively. Vertical bars represent the S.E.M. Relaxant responses induced by NG, NP and DZ were significantly greater in coronary arteries ($P < 0.01$ with NG and NP, $P < 0.05$ with DZ) than in mesenteric arteries.

Fig. 2. Dose-response curves of PGE₁, PGI₂ and adenosine (AD) in isolated dog coronary and mesenteric arteries. Preparations were contracted with carbocyclic TXA₂ (10^{-7} M). Relaxation induced by 10^{-4} M papaverine was taken as 100%; mean absolute values in coronary arteries were 1330 ± 160 mg ($n=7$), 1620 ± 230 mg ($n=12$) and 1010 ± 100 mg ($n=7$), respectively, and those in mesenteric arteries were 1220 ± 180 mg ($n=7$), 1470 ± 310 mg ($n=12$) and 1520 ± 200 mg ($n=7$), respectively. Vertical bars represent the S.E.M. Relaxant responses induced by AD were significantly greater in coronary arteries ($P < 0.05$) than in mesenteric arteries, but no significant differences were found in the relaxation induced by PGE₁ and PGI₂.

RELAXATION BY PGI_2 (c-TXA₂ CONTRACTED) RELAXATION BY NG (c-TXA₂ CONTRACTED)

Fig. 3. Comparison of dose-related responses to PGI_2 of dog coronary arterial strips of different sizes. Concentrations from 1 to 4: 10^{-9} , 10^{-8} , 10^{-7} and 10^{-6} M, respectively. Before the addition of PGI_2 , the strips were contracted with 10^{-7} M carbocyclic TXA₂. PA: 10^{-4} M papaverine. The absolute values of the maximum relaxation in large, medium and small-size arteries were 4630, 2840 and 270 mg, respectively.

Fig. 4. Comparison of dose-related responses to nitroglycerin (NG) of dog coronary arterial strips of different sizes. Concentrations from 1 to 5: 10^{-9} , 10^{-8} , 10^{-7} , 10^{-6} and 10^{-5} M, respectively. Before the addition of nitroglycerin, the strips were contracted with 10^{-7} M carbocyclic TXA₂. PA: 10^{-4} M papaverine. The absolute values of the maximum relaxation in large, medium and small-size arteries were 2090, 1160 and 350 mg, respectively.

Fig. 5. Dose-response curves of nitroglycerin (NG), sodium nitroprusside (NP) and diltiazem (DZ) for isolated dog coronary arteries of different sizes. Preparations were contracted with carbocyclic TXA₂ (10^{-7} M). Relaxation induced by 10^{-4} M papaverine was taken as 100%; mean absolute values in large arteries were 3040 ± 490 mg ($n=10$), 3820 ± 910 mg ($n=7$) and 3210 ± 430 mg ($n=13$), respectively; those in medium-size arteries were 2020 ± 430 mg ($n=10$), 2440 ± 330 mg ($n=7$) and 2120 ± 170 mg ($n=13$), respectively; and those in small-arteries were 560 ± 110 mg ($n=10$), 580 ± 190 mg ($n=7$) and 810 ± 220 mg ($n=13$), respectively. Vertical bars represent the S.E.M. Relaxant responses induced by NG were significantly greater in large arteries ($P < 0.05$) and less in small arteries ($P < 0.01$) than in medium arteries. There were no significant regional differences in the relaxations induced by NP and DZ.

Fig. 6. Dose-response curves of PGE_1 , PGI_2 and adenosine (AD) in isolated dog coronary arteries of different sizes. Preparations were contracted with carbocyclic TXA_2 (10^{-7} M). Relaxation induced by 10^{-4} M papaverine was taken as 100%; mean absolute values in large arteries were 2430 ± 610 mg ($n=7$), 3370 ± 330 mg ($n=12$) and 3460 ± 650 mg ($n=8$), respectively; those in medium-size arteries were 2020 ± 330 mg ($n=7$), 2390 ± 220 mg ($n=12$) and 1870 ± 170 mg ($n=8$), respectively; and those in small arteries were 250 ± 50 mg ($n=7$), 790 ± 190 mg ($n=12$) and 280 ± 40 mg ($n=8$), respectively. Vertical bars represent S.E.M. Relaxant responses induced by PGE_1 , PGI_2 and AD were significantly greater in small arteries ($P < 0.01$ with PGE_1 , $P < 0.05$ with PGI_2 and AD) and less in large arteries ($P < 0.01$ with PGE_1 , PGI_2 and AD) than in medium-size arteries.

Discussion

The results of our experiments with isolated dog arteries revealed that some of the vasodilators produced a different magnitude of relaxations in the proximal, large coronary arteries and the distal, small arteries. Nitroglycerin dilated proximal coronary arteries to a greater extent than the distal arteries, whereas adenosine produced a greater relaxation in the distal arteries. These findings are consistent with those in the *in vitro* study of Schnaar and Sparks (13) using isolated dog coronary arteries of 2 mm o.d. as large arteries and arteries of 550 μ o.d. as small ones. The inside diameters of small coronary arteries used in the present study are under 300 microns, being less than those used in the study of Schnaar and Sparks (13). Fam and McGregor (4) and Winbury et al. (3) also found similar results in cannulated large and small coronary arteries in *in vivo* dog experiments. Cohen and Kirk (14) using cannulated dog coronary vessels have shown that nitroglycerin

preferentially reduces large coronary artery resistance under normal and ischemic conditions, and adenosine has a main action on resistive coronary vessels under normal perfusion, resulting in a reduction of the total coronary vascular resistance. Therefore, the isolated small coronary arteries that we used appear to share functional characteristics with resistant arterioles *in vivo*.

Drug-induced changes in large vessel tone would be important in patients with spasm of proximal coronary arteries. Coronary arterial spasm with or without fixed organic stenosis is considered to be closely related to the pathophysiology of not only variant angina but also of other ischemic heart disease including some of rest angina, effort angina and myocardial infarction (15–17). Mechanisms by which coronary arterial spasm is triggered are not fully known, but in recent days, great attention is paid to TXA_2 derived from platelets in blood (5). Our results using coronary artery strips contracted with carbocyclic TXA_2 , a stable analog of TXA_2 (6), indicate that nitro-

glycerin may be most effective in remission of vasoconstriction in the large coronary arteries. On the contrary, exogenous PGI₂ as well as PGE₁ do not appear to effectively inhibit coronary artery vasoconstriction. In fact, PGI₂ given intravenously suppressed attacks evoked spontaneously or by ergonovine only in one out of 9 patients with variant angina (18).

Another clinical implication of the regional differences is related to the effects on the patients with ischemic heart disease who have significant organic stenosis in coronary arteries. Nitroglycerin is reported to dilate epicardial large coronary arteries and would contribute to the redistribution of the coronary blood flow (19–21). In contrast, adenosine, a potent metabolic coronary vasodilator, preferentially relaxed the distal portion (13, 22). The peripheral arteries which are expected to dilate maximally under the ischemic condition could not be dilated any more by vasodilators, while they dilate vessels in the healthy region, resulting in decrease of regional blood flow to ischemic areas (23, 24). Dipyridamole (25), an adenosine potentiator, is a drug potentially causing transient myocardial ischemia by such "coronary steal" due to its vasodilating action on coronary arterioles in patients with significant organic stenosis. Both PGI₂ and PGE₁ may cause "coronary steal" because of their preferential actions on small arteries, like those of adenosine. Mehta et al. (26) reported that intravenous PGI₂ did not alter the regional blood flow across the fixed stenosis produced by an external occluder, but increased the flow in the non-ischemic area in dogs.

Both sodium nitroprusside and diltiazem did not show selective dilator actions on large and small coronary arteries. Diltiazem produced progressive and sustained relaxations, which were different from those induced by the other vasodilators used.

Our data also demonstrated that nitroglycerin, sodium nitroprusside, diltiazem and adenosine relaxed coronary arteries to a greater extent than mesenteric arteries when contracted with carbocyclic TXA₂. Feldman et al. (27) reported that nitroglycerin in low doses dilated coronary arteries without

influencing systemic blood pressure in man. Similar results with sodium nitroprusside were also obtained by Yeh et al. (28). Nakajima et al. (29) also demonstrated that in helical strips of rabbit coronary arteries, vasodilator action of diltiazem is more predominant than in the other arteries. The fact that the profound contraction induced by a high concentration of carbocyclic TXA₂ was reversed by diltiazem predominantly in coronary arteries suggests that this Ca⁺⁺ antagonist may be particularly effective in the treatment of coronary vasospasm. Both PGI₂ and PGE₁ relaxed mesenteric arteries to a significantly greater extent than coronary arteries contracted with PGF_{2α} (30). These data may indicate that PGI₂ and PGE₁ contribute to a reduction of afterload.

We clearly demonstrated a regional difference in vasodilator actions in isolated dog arteries. Clinical evaluations are required to determine whether such a different action is true in patients with angina pectoris, acute heart failure and hypertension.

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