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Original Research

Endothelin-1 releases endothelium-derived endoperoxides and thromboxane A_2 in porcine coronary arteries with regenerated endothelium[1]

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KEY WORDS coronary vessels; endothelin-1; indomethacin; prostaglandin-endoperoxide synthase; nitric oxide; thromboxane A_2; vascular endothelium

ABSTRACT

AIM: To determine the role of endothelium-derived contracting factor (EDCF) in the response to endothelin-1 in arteries with regenerated endothelium. **METHODS**: Rings of porcine coronary arteries, with and without endothelium of previously deendothelialized left anterior descending coronary arteries and native left circumflex coronary arteries, were suspended in conventional organ chambers for the measurement of isometric force. **RESULTS**: In quiescent rings of the previously deendothelialized left anterior descending coronary artery treated with the NO-synthase inhibitor nitro-*L*-arginine, endothelin-1 caused contractions which were larger in rings with than that in those without endothelium. Under the same experimental conditions, in the left circumflex coronary artery, the contractions to endothelin-1 were augmented markedly by the removal of the endothelium. In rings with endothelium of the previously deendothelialized left anterior descending coronary artery, indometacin (inhibitor of cyclooxygenase) and ridogrel (thromboxane A_2 receptor antagonist and inhibitor of thromboxane synthase) inhibited contractions to endothelin-1. Dazoxiben (inhibitor of thromboxane synthase) inhibited, to the same extent as indometacin and ridogel, the response to higher concentrations of endothelin-1. The endothelium-dependent component of the response to lower concentrations of endothelin-1 was inhibited by indometacin and ridogrel, but not by dazoxiben. In rings without endothelium of both previously deendothelialized left anterior descending and native left circumflex coronary arteries, indometacin and ridogrel did not affect the contractions to endothelin-1. **CONCLUSION**: These findings suggest that in regenerated endothelium, high concentrations of endothelin-1 stimulate the release of thromboxane A_2. Endoperoxides generated by activation of endothelial cyclooxygenase may be the endothelium-derived contracting factor(s) released in regenerated endothelium by lower concentrations of the peptide.

INTRODUCTION

Endothelin-1 is a potent vasoconstrictor substance that causes slow and long-lasting conctractions of isolated blood vessels[1,2]. The aorta of the spontaneously hypertensive rat is characterized by the occurrence of endothelium-dependent contractions[3-7]. In this preparation, endothelin-1 stimulates the release of a cyclooxygenase-dependent, endothelium-derived contracting factor (EDCF), presumably thromboxane A_2[3,4,8]. Similar conclusions have been reached in the pulmonary artery of the rat[9] human placental vessels[10] and afferent arterioles of the SHR[11].

Following balloon deendothelialization, porcine

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coronary arteries with regenerated endothelial cells exhibit not only selectively impaired pertussis-toxin sensitive endothelium-dependent relaxations, but also augmented endothelium-dependent contractions to serotonin, norepinephrine and platelets[12-16]. This dysfunction of regenerated endothelium may play an important role in the pathogenesis of vasospasm[15-16]. The present study was designed to determine whether or not the response to endothelin-1 is modulated by regeneration of the endothelium in the porcine coronary artery.

MATERIALS AND METHODS

Male Yorkshire pigs [8 wk of age (n = 5; 20 - 25 kg)] were used. The animals were anesthetized with Telaxol (a mixture of tiletamine hydrochloride, arylaminocycloalkanone, and zolazepam hydrochloride, 100 mg/animal, im) and atropine (0.4 mg, im) followed by inhalation of halothane (2 L/min). Using aseptic surgical technique, the left carotid artery was dissected free and a 7F guiding catheter (hockey stick or multipurpose) was introduced into the left coronary ostium under fluoroscopic guidance. Before denudation, heparin (100 $\mu g \cdot kg^{-1}$) and lidocaine HCl (20 mg) were administered via the arterial sheath. During the procedure, the arterial blood pressure and the electrocardiogram (ECG, lead Ⅱ, avL) were monitored continuously. A 2.5 or 3 mm sized balloon catheter (USCI, over-the guide wire system) was advanced through the guiding catheter into the left anterior descending coronary artery. The balloon was then gently rubbed against the proximal 3 to 4 cm of the arterial endothelium. Successful denudation of the coronary endothelium was confirmed by ischemic ECG changes (0.1 mV of ST segment depression or elevation) and/or decreases in luminal diameter changes upon intracoronary injection of serotonin (10 $\mu g \cdot kg^{-1}$)[8-15,17]. The animals were then housed individually in temperature-controlled animal quarters and fed regular chow. The daily food intake was limited to an amount equal to 3 % of the body weight to prevent excessive weight gain. The organ chamber experiments were performed after 4 wk of feeding. All procedures were in accordance with institutional guidelines.

Organ chamber experiments After 4 wk, the pigs were anesthetized with Telazol (100 mg im) and sodium pentobarbital (12.5 $mg \cdot kg^{-1}$ iv). The hearts were then removed. Both left coronary [anterior descending coronary artery (LAD) and circumflex (LCX)] arteries were dissected free, immersed in cold modifed Krebs-Ringer bicarbonate solution [consisting of ($mmol \cdot L^{-1}$) NaCl 118.3, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, glucose 11.1, and calcium disodium edetate 0.026 at pH 7.4 (control solution)], and cleaned of connective tissue. They were cut into rings (3 to 4 mm lengh). The proximal 3 to 4 cm portions of the LAD were used for the organ chamber experiments, and the same anatomic portions of the LCX were used as controls. In some rings, the endothelium was removed mechanically by inserting the tip of a watchmaker's forceps into the lumen and gently rolling the preparation back and forth over a paper tissue wetted with cold control solution. The rings were suspended horizontally in organ chambers filled with 25 mL of control solution (37 ℃), gassed with 95 % O_2 + 5 % CO_2 (pH 7.4), and stretched to the optimal point of their length-active tension relation as determined by the contractile response to KCl (60 $mmol \cdot L^{-1}$) at progressive levels of stretch. The tissues were allowed to equilibrate for 60 min before beginning the experiments. The presence of the endothelium was confirmed by the occurrence of relaxations to bradykinin (0.01 $\mu mol \cdot L^{-1}$) in rings contracted with prostaglandin $F_{2\alpha}$ (2 $\mu mol \cdot L^{-1}$). Rings with and without endothelium of the same coronary arteries were studied in parallel. After one hour of equilibration concentration-response curves to endothelin-1 (0.0001 to 0.1 $\mu mol \cdot L^{-1}$) were obtained by cumulative addition of the peptide either in control solution or after incubation (45 min) with indometacin (10 $\mu mol \cdot L^{-1}$; inhibitor of cyclooxygenase), dazoxiben (100 $\mu mol \cdot L^{-1}$; inhibitor of thromboxane synthase), or ridogrel (1 $\mu mol \cdot L^{-1}$; antagonist of thromboxane A_2 receptors and inhibitor of thromboxane synthase)[19] where indicated. Certain experiments were performed in the presence of nitro-*L*-arginine (100 $\mu mol \cdot L^{-1}$) to prevent the production of nitric oxide (NO).

Drugs The following drugs were used: bradykinin, endothelin (ET)-1, indometacin, potassium chloride, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) (all from Sigma Chemical Company, St Louis Mo. USA); dazoxiben (Pfizer, Groton, Conn); N^G-nitro-*L*-arginine

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(Aldrich, Milwaukee, WIS); and ridogrel (Janssen Pharmaceutica, Beerse, Belgium). All drugs were prepared with distilled water on the day of the study, except indometacin which was dissolved in water and Na_2CO_3, and sonicated. Na_2CO_3 had no effect at the concentration of 5 μmol·L^{-1}. The concentrations of the drugs are expressed as final molar (M) concentration in the bath solution.

Statistical analysis The results are expressed as $\bar{x} \pm s_{\bar{x}}$. Unless otherwise specified, n refers to the number of animals studied. Statistical evaluation of the data was performed with t-test for either paired or unpaired observations (two tailed). Values were considered to be statistically different when P was less than 0.05.

RESULTS

In the experiments which were performed in the presence of nitro-*L*-arginine, nitro-*L*-arginine induced an increase in tension, which averaged 0.88 ± 0.12 g in both left anterior descending and circumflex coronary arteries with endothelium.

Native endothelium In quiescent rings of left circumflex coronary arteries (control arteries), endothelin-1 caused concentration-dependent contractions, which were markedly less in rings than that in those without endothelium (Fig 1, left panel).

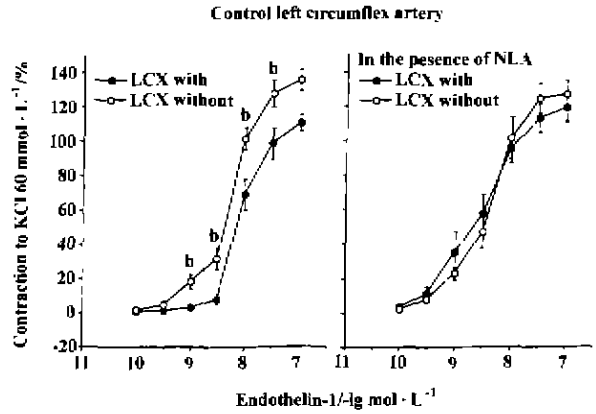

Fig 1. Cumulative concentration-response curves to endothelin-1 (0.0001 – 0.1 μmol·L^{-1}) in quiescent rings, with and without endothelium, of control left circumflex porcine coronary arteries (LCX) in control solutions (left panel), and in the presence nitro-*L*-arginine (NLA 100 μmol·L^{-1}) right panel). Data shown as $\bar{x} \pm s_{\bar{x}}$ (n = 5 pigs), and expressed as percent of a reference contraction to KCl (60 mmol·L^{-1}). $^bP < 0.05$ *vs* with endothelium group.

However, in the presence of nitro-*L*-arginine, the contractions in rings with and without endothelium were comparable (Fig 1, right panel).

In the presence of nitro-*L*-arginine, inhibitors of the arachidonic acid cascade did not affect the contractions to endothelin-1 in rings with and without endothelium (Tab 1).

Tab 1. Effect of indometacin, dazoxiben and ridogrel on contractions evoked by endothelin-1 in porcine coronary arteries with and without endothelium.

	ED_{50}/ − lg mmol·L^{-1}		Maximal contraction/ %	
	Denuded LAD	LCX	Denuded LAD	LCX
Rings with endothelium				
Control	8.68 ± 0.05	8.73 ± 0.20	145 ± 5^c	119 ± 8
Indometacin, 10 μmol·L^{-1}	8.28 ± 0.03^b	8.46 ± 0.15	114 ± 2.7^b	119 ± 6
Dazoxiben, 100 μmol·L^{-1}	9.32 ± 0.09^b	8.96 ± 0.14	109 ± 7^b	118 ± 4
Ridogrel, 1 μmol·L^{-1}	8.31 ± 0.07^b	8.49 ± 0.10	115 ± 4^b	118 ± 7
Rings without endothelium				
Control	8.48 ± 0.11	8.57 ± 0.17	117 ± 3	126 ± 8
Indometacin 10 μmol·L^{-1}	8.34 ± 0.15	8.52 ± 0.17	128 ± 5	122 ± 6
Dazoxiben, 100 μmol·L^{-1}	8.79 ± 0.23	8.86 ± 0.22	103 ± 6	116 ± 5
Ridogrel, 1 μmol·L^{-1}	8.35 ± 0.09	8.55 ± 0.11	130 ± 7	123 ± 6

Data are expressed as $\bar{x} \pm s_{\bar{x}}$; n = 5 pigs. ED_{50}: effective concentration producing 50 % of the maximal response to KCl 60 mmol·L^{-1}. Maximal contraction: maximal contraction to KCl 60 mmol·L^{-1}. Denuded: previously balloon endothelial denuded; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery. $^bP < 0.05$ compared with controls. $^cP < 0.05$ compared with LCX. All experiments were performed in the presence of nitro-*L*-arginine 100 mmol·L^{-1}.

Regenerated endothelium In quiescent rings of previously deendothelialized left anterior descending coronary arteries, endothelin-1 (0.0001 – 0.1 μmol · L^{-1}) caused concentration-dependent, comparable contractions in rings with and without endothelium (Fig 2, left panel).

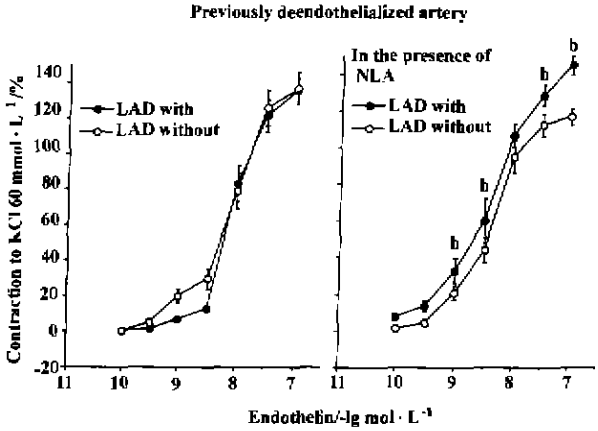

Fig 2. Cumulative concentration-response curves to endothelin-1 (0.0001 – 0.1 μmol · L^{-1}) in quiescent rings with and without endothelium of previously deendothelialized porcine left anterior descending coronary arteries (LAD) in control solution (left panel), and in the presence of nitro-*L*-arginine (NLA 100 μmol · L^{-1}) (right panel). Data shown as $\bar{x} \pm s_{\bar{x}}$ ($n = 5$ pigs), and expressed as percent of a reference contraction to KCl (60 mmol · L^{-1}). $^{b}P < 0.05$ *vs* rings without endothelium.

Contractions to endothelin-1 (0.3 – 0.1 μmol · L^{-1}) in rings of LAD with regenerated endothelium were markedly larger than those in LCX with native endothelium (Fig 1, 2, Tab 1). In the presence of nitro-*L*-arginine, endothelin-1 caused markedly larger contractions in rings than that in those without endothelium (Fig 2, right panel). In rings with endothelium of the previously deendothelialized LAD, indometacin and ridogrel caused a markedly reduced contraction, the ED_{50} was increased (Fig 3, Tab 1).

Dazoxiben did, markedly augmented the response to low, but caused a significant decrease in the response to high concentrations of endothelin-1 (0.3 – 0.1 μmol · L^{-1}) (Fig 3, Tab 1). In rings without endothelium, inhibitors of the arachidonic acid cascade did not affect the contractions to endothelin-1 (Tab 1).

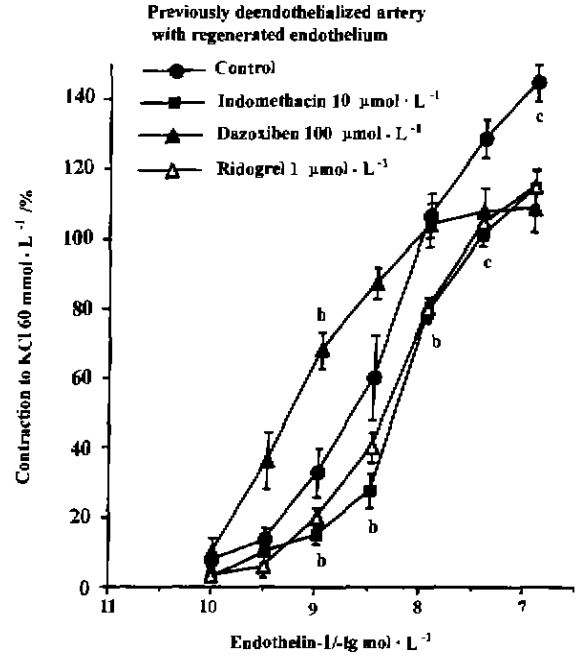

Fig 3. Effect of indometacin, dazoxiben, BQ-123 and ridogrel on contractions evoked by endothelin-1 in the presence of nitro-*L*-arginine (100 μmol · L^{-1}) in quiescent rings with endothelium of previously deendothelialized left anterior descending coronary arteries. Data shown as $\bar{x} \pm s_{\bar{x}}$ ($n = 5$ pigs), and expressed as percent of a reference contraction to KCl (60 mmol · L^{-1}). $^{b}P < 0.05$, $^{c}P < 0.01$ *vs* control.

DISCUSSION

The present study suggests that endothelin-1 releases endothelium-dependent contracting factors in porcine coronary arteries with regenerated endothelium. Two endothelin receptors have been cloned; one shows high specificity for endothelin-1 and is expressed mainly in vascular smooth muscle (ET_A receptor)[18], and the other binds equally to all isoforms of the peptide and is found preferentialy on the endothelium (ET_B receptor). The latter mediates the release of prostacyclin and endothelium-derived relaxing factor (EDRF)[19]. The removal of the endothelium and treatment with an inhibitor of nitric oxide synthase augments contractions evoked by endothelins[20-22].

In the present study, in rings with previously deendothelialized regenerated endothelium, contractions to endothelin-1 were greater than those in rings with native endothelium. This can be explained by the

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depressed release of endothelium-derived relaxing factor(s), or by the release of endothelium-derived contracting factors from the regenerated endothelium, or both. In control left circumflex arteries, the contractions to endothelin in rings with endothelium were less than that in those without endothelium, and the inhibitor of NO synthase (nitro-*L*-arginine) resulted in greater contractions in rings with endothelium. These findings indicate that endothelin-1 stimulates the release of EDRF in the porcine coronary artery or, alternatively, that the basal release of EDRF attenuates the contractile response to endothelin-1. However, there was no evidence of release of cyclooxygenase-dependent contracting factors from native endothelium and vascular smooth muscle.

In chronic regenerated endothelium from previously deendothelialized LAD, the inhibitor of nitric oxide synthase (nitro-*L*-arginine) also results in greater contractions in rings with regenerated endothelium. This suggests that either the basal release of endothelium-derived relaxing factor is preserved in regenerated endothelium, or that the regenerated endothelium releases EDRF in response to endothelin-1. The effects of indometacin (inhibitor of cyclooxygenase) and ridogrel (antagonist of thromboxane A_2 receptors and inhibitor of thromboxane synthase) indicate that endothelin-1 induces the production of a cyclooxygenase-dependent, endothelium-derived contracting factor(s) by the regenerated endothelium, the action of which is mediated by a endoperoxide/thromboxane receptor on the vascular smooth muscle.

In response to lower concentrations of endothelin-1, the augmented contractions were inhibited by indometacin and ridogrel, but not by dazoxiben (inhibitor of thromboxane synthase). These observations suggest that in response to lower concentrations of endothelin-1, endoperoxides rather than thromboxane A_2 may be the cyclooxygenase-dependent, endothelium-derived contracting factor(s), as is the case in the SHR aorta [for acetylcholine and serotonin[5-7,23]]. In fact, dazoxiben augmented the endothelium-dependent contraction in response to endothelin-1 1 nmol·L^{-1}. This may be due to blockade of thromboxane synthesis resulting in accumulation of endoperoxides in the vascular smooth muscle. Endoperoxides can cause contraction of vascular smooth muscle by activation of endoperoxide/thromboxane receptors[24,25]. However, in response to higher concentrations of endothelin-1, dazoxiben had a comparable inhibitory effect to those of indomethacin and ridogrel. Thus, it is logical to conclude that higher concentrations of endothelin-1 stimulate the release of cyclooxygenase-dependent, endothelium-derived contracting factor(s) which most likely is thromboxane A_2. The present findings suggest that cyclooxygenase-dependent, endothelium-derived contracting factors, thromboxane A_2 and endoperoxides, contribute to the augmented contractions to endothelin-1 in porcine coronary arteries with regenerated endothelium.

Pathophysiological implications Circulating endothelin-1 levels are increased in various ischemic heart diseases including acute myocardial infarction[26-28]. Endothelins are potent activators of most vascular smooth muscle. However, they by themselves are not likely to contribute to acute endothelium-dependent changes in tension as they are not stored in endothelial cells. Any augmented release would require de novo protein synthesis. Thus, it is likely that endothelin-1 may be involved in long-term regulation of vascular tone[29]. However, threshold concentrations of endothelin-1 potentiate the contractile response to norepinephrine and serotonin[30], which may be important mediators of coronary vasospasm. These observations taken in conjunction with the present findings imply that locally increased levels of endothelin-1 may indirectly contribute to the enhanced vasoconstrictor responses through the release of EDCF.

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内皮素-1 促进猪冠状动脉再生内皮释放内皮衍生内过氧化物和血栓素 A_2[1]

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关键词 冠状血管; 内皮素-1; 吲哚美辛; 前列腺素内过氧化物合酶; 一氧化氮; 血栓素 A_2; 血管内皮

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