newborns.

Furthermore, we need to pay careful attention to administering U46619 into newborns, because neonatal pulmonary hypertension (PPHN) is characterized by pulmonary vasoconstriction, due in part to hypoxia-induced TP hyperresponsiveness[25, 26]. Although PPHN is induced by intravenous infusion of U46619 (~2μg/kg/min)[27, 28], further investigation is required to examine whether a bolus injection of U46619 at a low concentration induces PPHN or not.

Taken together, the present study demonstrated that low-dose TP stimulation induced vasoconstriction of the DA with minimal systemic adverse effects when U46619 is administered at a concentration of up to 0.05μg/g. Although COX inhibitors such as indomethacin and ibuprofen are the current unique pharmacological treatment for PDA[1, 3], the frequent failure rate of COX inhibitors is clinically problematic. COX inhibitors also share the similar adverse effects with U46619. Therefore, we propose that low-dose TP stimulation can be an alternative pharmacological strategy for PDA treatment when COX inhibitors are difficult to be administered.

The mechanism why U46619 constricted the DA more than other vessels is the next important question to be clarified, because a considerable number of *ex vivo* experiments have demonstrated that TP agonists constrict a variety of arteries and veins[7, 29]. We assume that the higher

sensitivity to U46619 in the DA could be due to its artery type (muscular type), because the structure of the DA is considered as a muscular type and most of other arteries that we examined belong to an elastic type. U46619 at a concentration of 0.05μg/g significantly constricted mature fetal DA by ~40% of the control groups, whereas the same dose of U46619 did not reduce the diameter of MA and blood flow of the rat neonatal tail. Because resistant muscular arteries supply the blood flow in the colon and tail, the arterial type may not be the sole reason of the hypersensitivity to U46619 in the DA.

We also examined the abundance of TP expression between the DA and the aorta during development. Although the expression levels of TP mRNA in the DA were higher than those in the aorta in the fetal period, the expression levels of TP protein showed no difference between the DA and the aorta (**Supplemental figure 2**). Therefore, the abundance of TP expression is not the reason of the hypersensitivity to U46619 in the DA. It is then highly possible that TP in the DA has higher binding affinities to TP agonists than that in the other arteries. Several studies have demonstrated that the affinity state of TP is influenced by interaction with $G_{\alpha 13}$ and/or $G_{\alpha q}$[30, 31]. Interestingly, recent studies by Dakshinamurti's group have demonstrated that a change in oxygen tension from normoxia to hypoxia provokes hypersensitivity to TXA_2 in pulmonary arterial myocytes of neonatal piglets[25, 26]. The authors have indicated that hypoxia promotes the membrane localization of TP and increases its ligand

affinity in pulmonary arterial myocytes. The response to oxygen is opposite between pulmonary arteries and other arteries including the DA. The DA is known to be more sensitive than the adjunct arteries to changes in oxygen tension[32]. It should be noted that the response to oxygen is stronger in the mature DA than in the premature DA[33]. The present study also demonstrated that the response to U46619 was stronger in the mature DA than in the premature DA (**Figure 1**). Therefore, this characteristic may be responsible for the DA-specific constriction that results from TP stimulation. Further study is apparently required to understand the mechanism why the DA is hypersensitive to TP stimulation.

In contrast to exogenous TP stimulation by U46619, our data showed that TP inhibition by the TP antagonist SQ29548 did not have a vasodilatory effect on the neonatal rat DA. Consistent with this observation, a previous study has demonstrated that a native TXA_2 was not synthesized in the DA under physiological conditions[34]. In addition, no PDA phenotype has been identified in TP knockout mice to date. Taken together, the evidence suggests that endogenous TXA_2 and TP are likely to play minor roles in the physiological closure of the DA.

In conclusion, our results demonstrate that TP agonists are a selective and potent vasoconstrictor of the fetal and neonatal rat DA with minimal adverse effects when they were administered at lose dose (up to 0.05μg/g). Although further investigation will be apparently required to

clinically use TP agonists for the patient with PDA, we propose that low-dose TP agonists may serve as a possible pharmacological therapeutic strategy for DA closure.

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Figure legends

Figure 1 ***TP stimulation induced vasoconstriction of the fetal rat DA***

(A-F) Effects of U46619 on the fetal rat DA at e19 (A-C) and at e21 (D-F). Each panel showed representative data injected with saline (A, D), U46619 (0.05μg/g: B, E. 5.0μg/g: C, F). Arrows show the constricted DA. Scale bar: 0.2mm. Ao: aorta, LPA: left PA, RPA: right PA.

(G, H) Effects of various doses of U46619 (from 0.0005 to 5.0μg/g) (G) (n=3-12) and I-BOP (0.05 and 5.0μg/g) (H) (n=5-10) on the diameter of the fetal rat DA at e19 and e21. *p* value (vs. saline) $^{\dagger}p<0.05$, $^{*}p<0.01$, $^{*}p<0.001$. (e19 vs. e21) $^{\ddagger}p<0.05$. (n=3-12).

Figure 2 ***TP stimulation caused DA constriction in the premature and hypoxia-induced PDA models***

(A) The ratios of DA constriction in premature rats injected with U46619 (0.0005, 0.05, or 5.0μg/g). The diameter of the DA was measured 10, 20, and, 30min after injection. *p* value (vs. each saline group) $^{\dagger}p<0.05$, $^{*}p<0.001$ (n=4-9).

(B) The ratios of DA constriction in hypoxia-induced PDA model rats injected with U46619 and indomethacin (indo). *p* value (vs. saline on hypoxia) $^{\dagger}p<0.05$, $^{*}p<0.001$, (vs. indomethacin on hypoxia) $^{**}p<0.01$. (n=3-4)

Figure 3 ***TP stimulation caused no vasoconstriction of adjunct arteries and veins***

(A, B) Constrictive effect of U46619 on the aorta (Ao) (A) (n=3-9) and the pulmonary artery (PA) (B) (n=4-10) in e19 and d0.

(C-F) Constrictive effect of U46619 on the vertebral artery (VA) (C) (n=4-5), the renal artery (RA) (D) (n=4-8), the portal vein (PV) (E) (n=4-8), and the marginal artery of the colon (MA) (F) (n=3-6) in d0. *p* value (vs. saline) $^{*}p<0.001$

Figure 4 ***U46619 did not decrease peripheral blood flow in neonatal rats***

(A-F) Representative images of blood flow at lower part of the neonates. Left (A, C, E) and right panels (B, D, F) indicate relative blood flow "pre-treated" and "post-treated" U46619 injection, respectively. Upper (B), middle (D), and lower (F) panels indicate U46619-injected group at dose of 0.0005, 0.05, and 5.0μg/g, respectively.

(G) Effect of U46619 on peripheral blood flow in the tails. "pre" indicates "pre-treated" *p* value (vs. pre) $^{\dagger}p<0.05$, (vs. 5.0μg/g) $^{*}p<0.01$ (n=5).

Figure 5 ***U46619-induced isometric tension of the DA and aorta vascular rings***

(A, B) Isometric tension of the DA and aorta rings at e19 (A) or e21 (B), stimulated by various doses of U46619 (10^{-8}, 10^{-7}, and 10^{-6} M). Squares and circles indicate the DA and aorta rings, respectively. *p* value (DA vs. aorta) $^{*}p<0.001$, $^{**}p<0.01$ (n=4-5).

Figure 6 ***Thrombosis formation in the microvasculature of the rat lung***

(A-C) Rat lung sections from PM20, injected with saline (A), U46619 (B), and arachidonic acid (AA) (C). Arrows indicate thrombosis formation. Scale bar: 0.1mm.

(D): The ratio of thrombosis formation in all pulmonary capillary arteries. *p* value (vs. saline) $^{*}p<0.001$ (n=4).

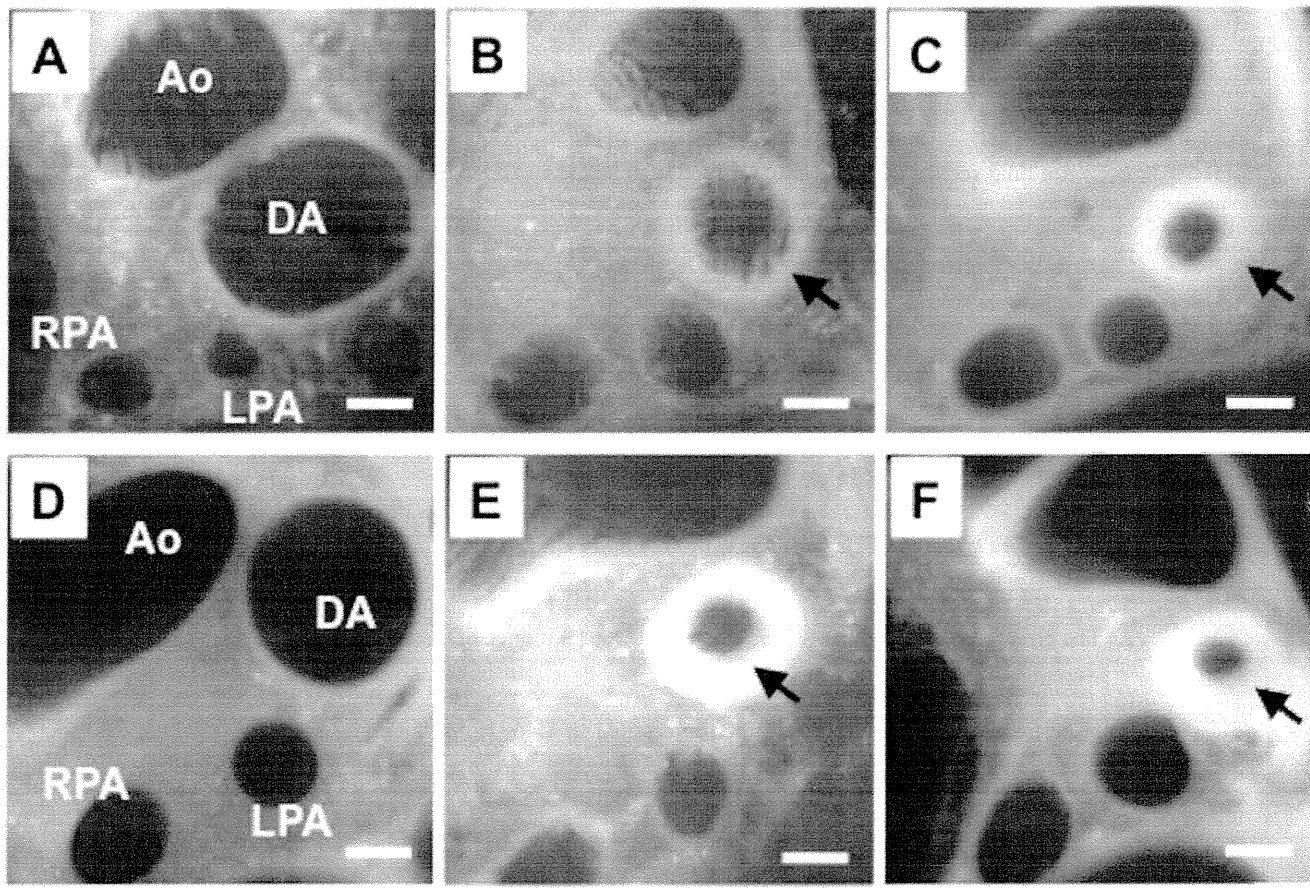
Figure 7 ***The effect of TP inhibition on the neonatal rat DA***

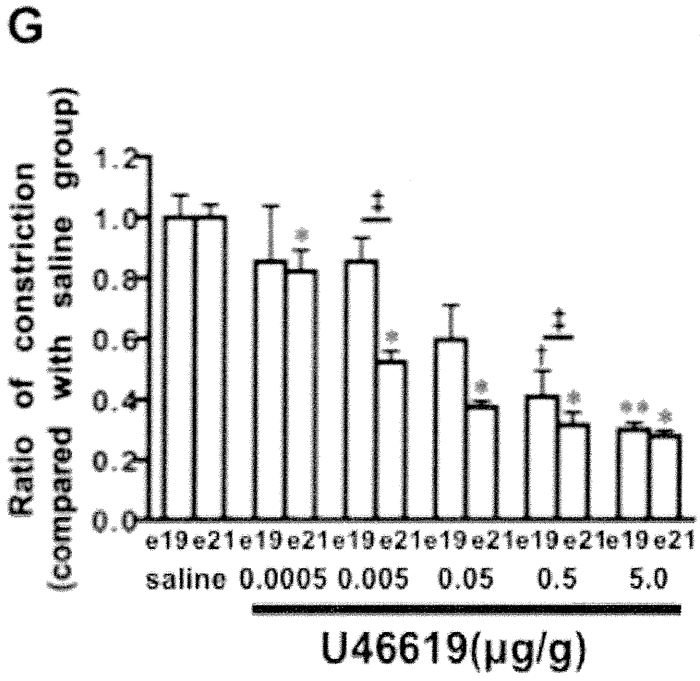
(A) The effect of TP antagonist SQ29548 on the U46619-induced DA constriction. SQ+U indicates the group pretreated with SQ29548 and then injected with U46619. *p* value (vs. saline) $^{**}p<0.05$, (vs. SQ+U) $^{\ddagger}p<0.05$ (n=3-4)

(B) The effect of the TP antagonist SQ29548 on the DA in rat neonates. PGE_2 was injected as a positive control. Circle, square, and triangle indicate group of SQ29548, PGE_2, and saline, respectively. *p* value (vs. saline) $^{*}p<0.001$ (n=3-4).

(C) Effect of a different dosage of SQ29548 (10μg/g) on the DA diameter. *p* value (vs. saline) $^{*}p<0.001$ (n=7-8).

Figure 1


A
Ao
DA
RPA
LPA
B
C
D
Ao
DA
RPA
LPA
E
F


G
Ratio of constriction (compared with saline group)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
e19 e21 e19 e21 e19 e21 e19 e21 e19 e21 e19 e21
saline 0.0005 0.005 0.05 0.5 5.0
U46619(μg/g)

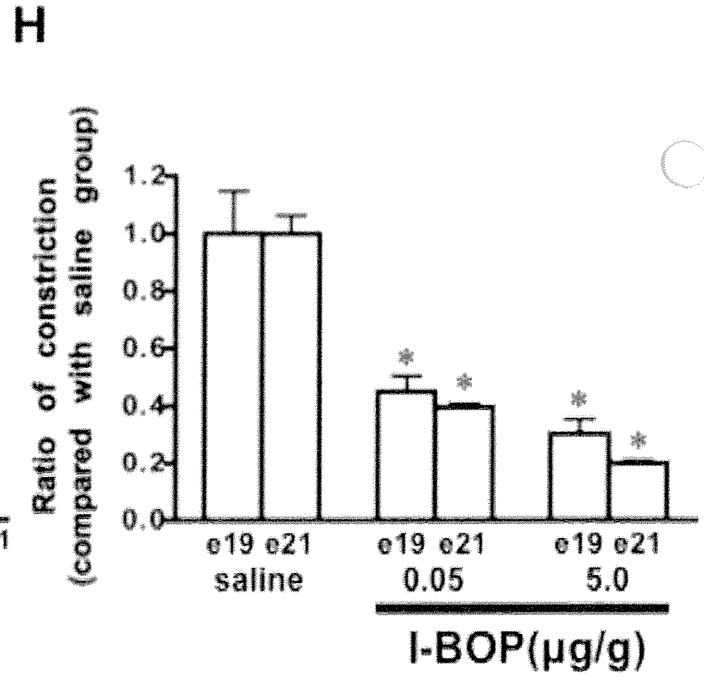

H
Ratio of constriction (compared with saline group)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
e19 e21
saline
e19 e21
0.05
e19 e21
5.0
I-BOP(μg/g)

Figure 2

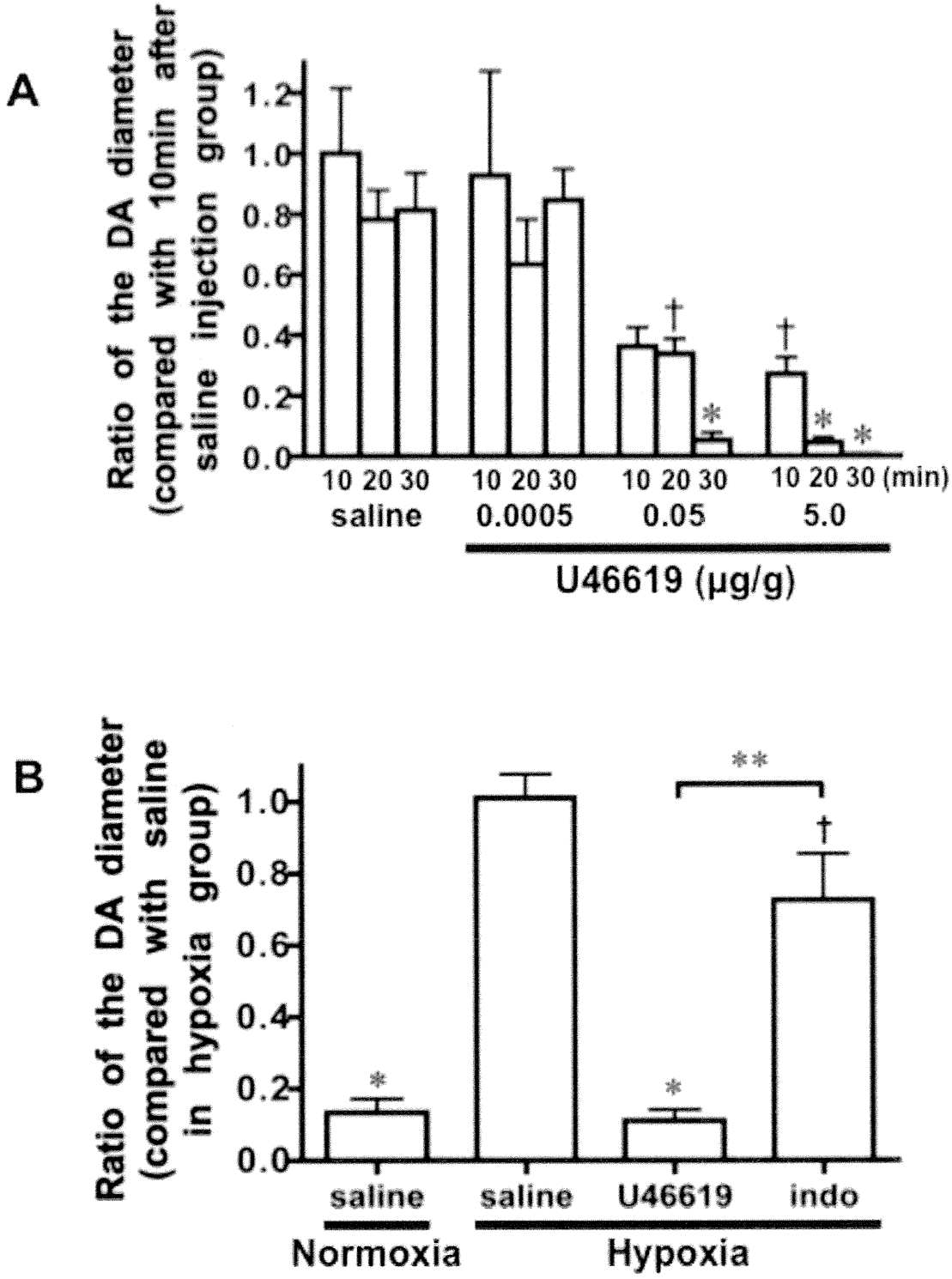

A
Ratio of the DA diameter (compared with 10min after saline injection group)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
10 20 30
saline
10 20 30
0.0005
10 20 30
0.05
10 20 30 (min)
5.0
U46619 (μg/g)
B
Ratio of the DA diameter (compared with saline in hypoxia group)
1.0
0.8
0.6
0.4
0.2
0.0
saline
saline
U46619
indo
Normoxia
Hypoxia

Figure 3

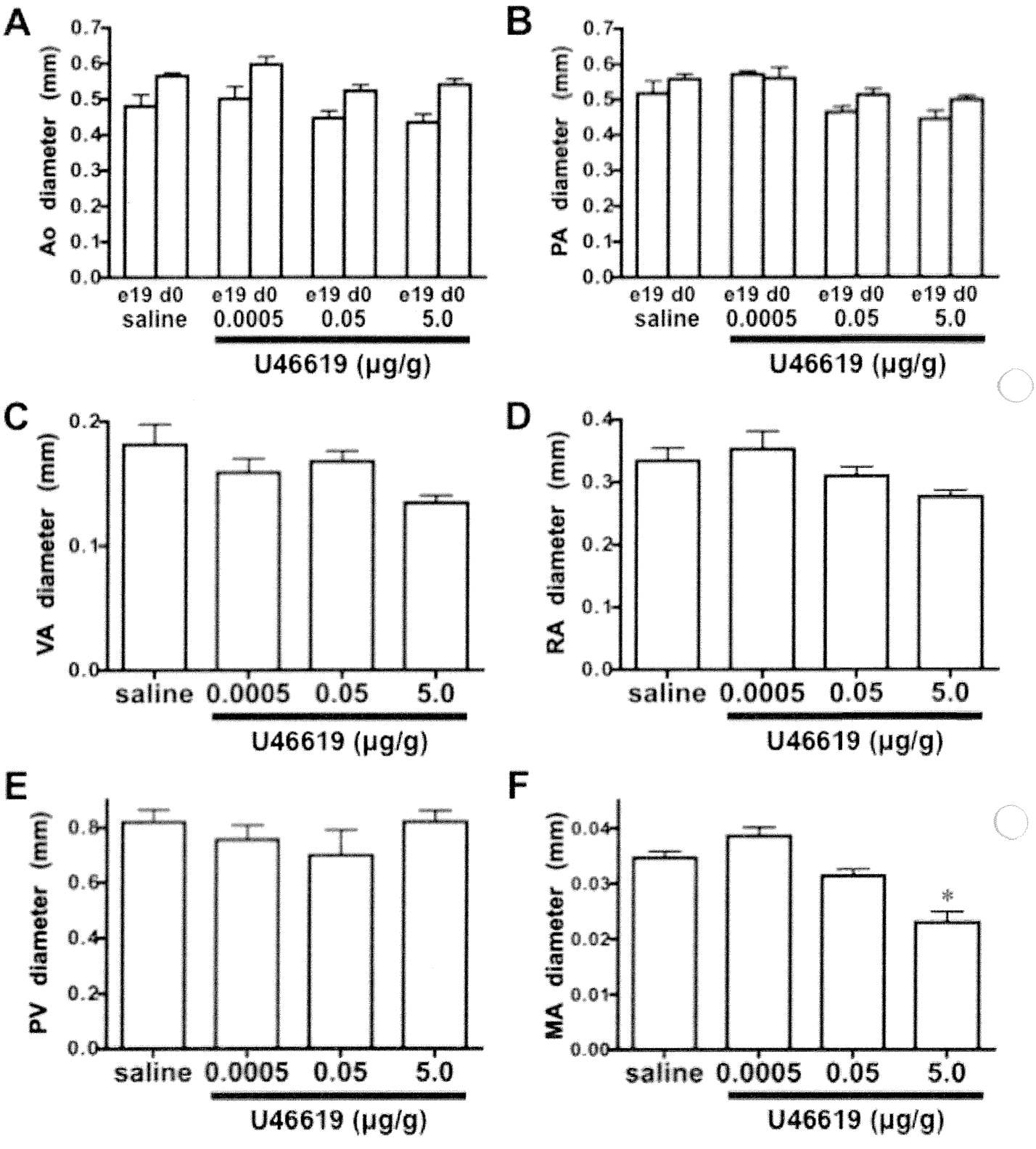
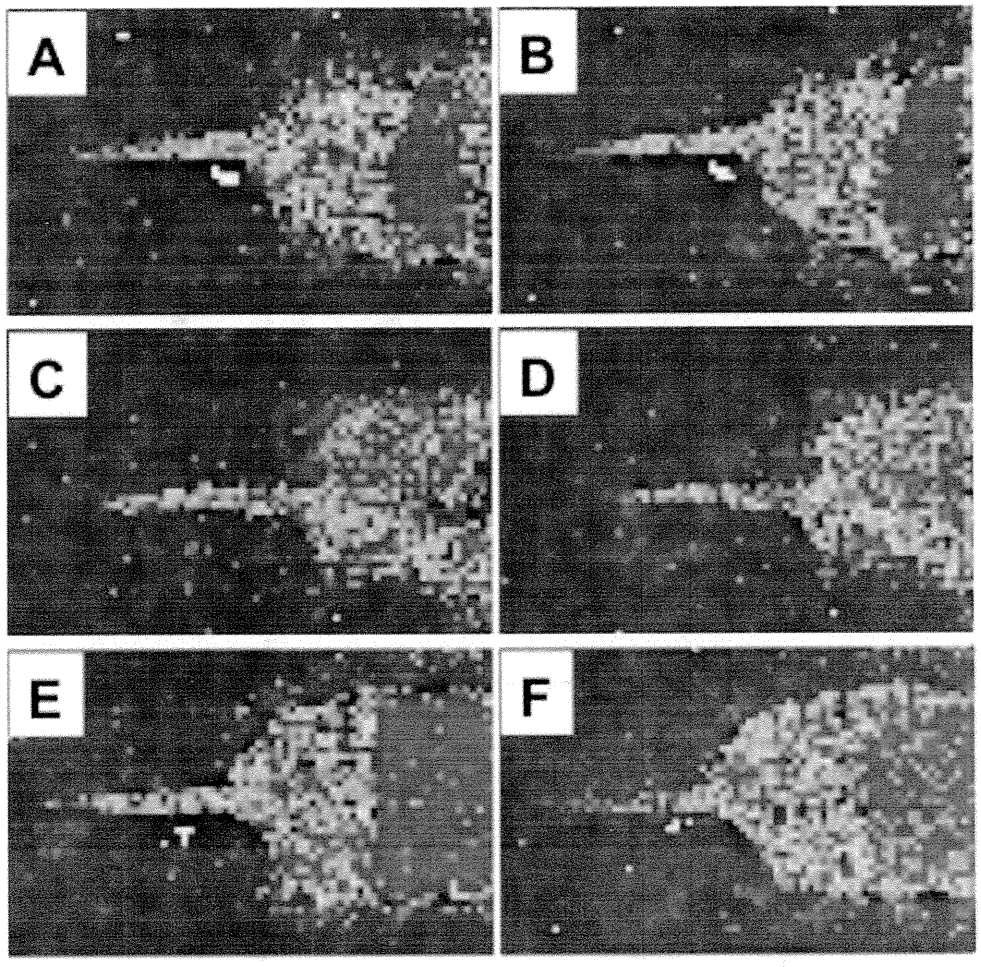

A
Ao diameter (mm)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
e19 d0
saline
e19 d0
0.0005
e19 d0
0.05
e19 d0
5.0
U46619 (µg/g)
B
PA diameter (mm)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
e19 d0
saline
e19 d0
0.0005
e19 d0
0.05
e19 d0
5.0
U46619 (µg/g)
C
VA diameter (mm)
0.2
0.1
0.0
saline
0.0005
0.05
5.0
U46619 (µg/g)
D
RA diameter (mm)
0.4
0.3
0.2
0.1
0.0
saline
0.0005
0.05
5.0
U46619 (µg/g)
E
PV diameter (mm)
0.8
0.6
0.4
0.2
0.0
saline
0.0005
0.05
5.0
U46619 (µg/g)
F
MA diameter (mm)
0.04
0.03
0.02
0.01
0.00
*
saline
0.0005
0.05
5.0
U46619 (µg/g)

Figure 4


A
B
C
D
E
F
T

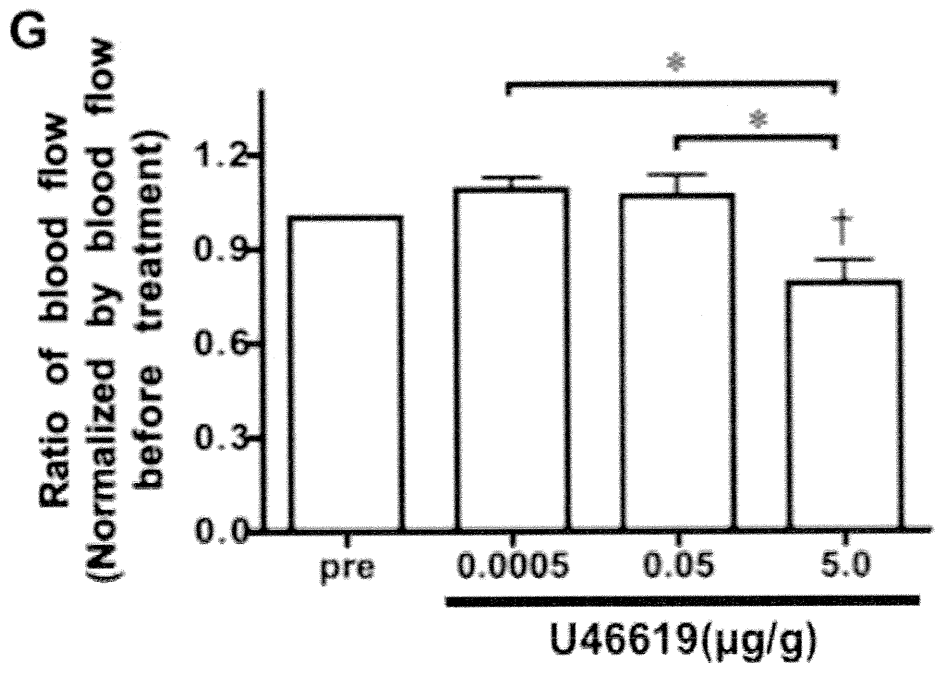

G
Ratio of blood flow
(Normalized by blood flow
before treatment)
1.2
0.9
0.6
0.3
0.0
*
*
†
pre
0.0005
0.05
5.0
U46619(μg/g)

Figure 5

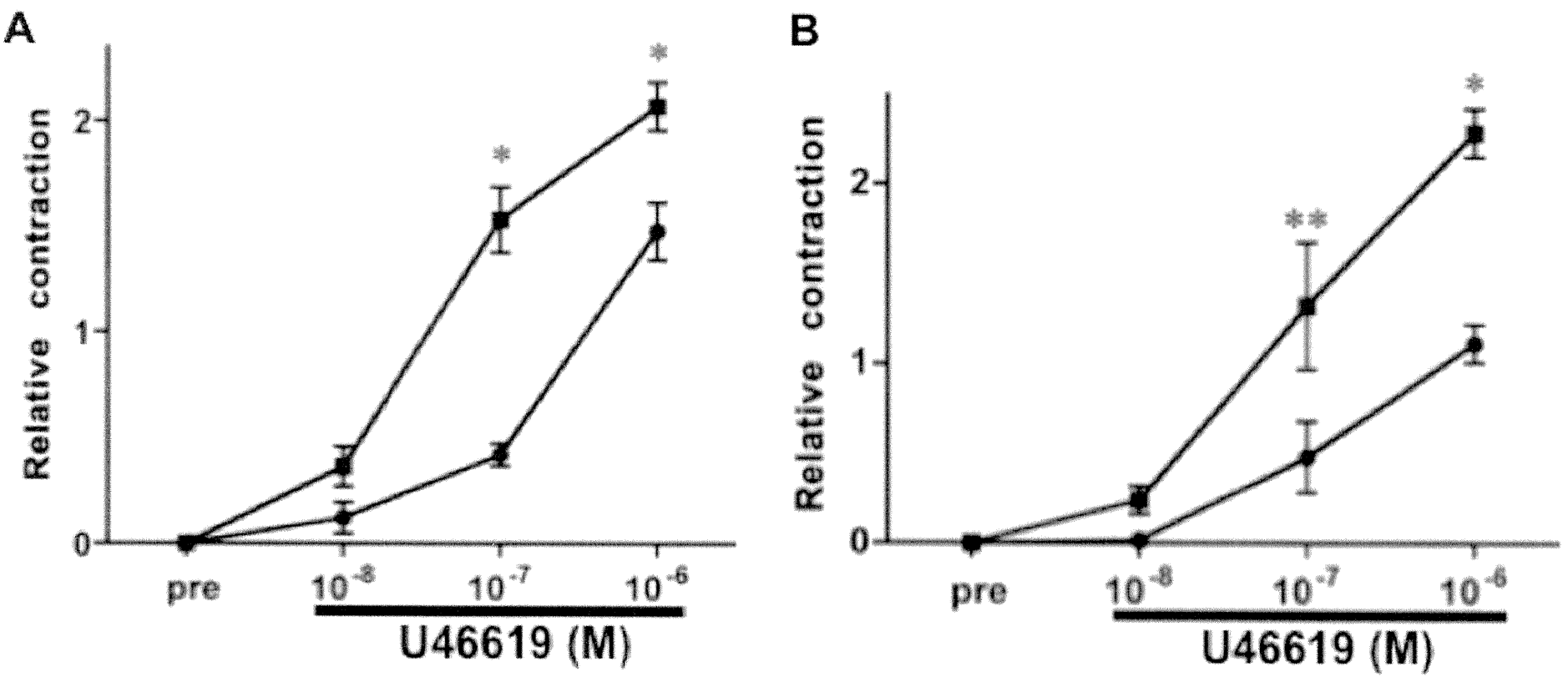

A
Relative contraction
2
1
0
*
*
pre
10-8
10-7
10-6
U46619 (M)
B
Relative contraction
2
1
0
**
*
pre
10-8
10-7
10-6
U46619 (M)

Figure 6

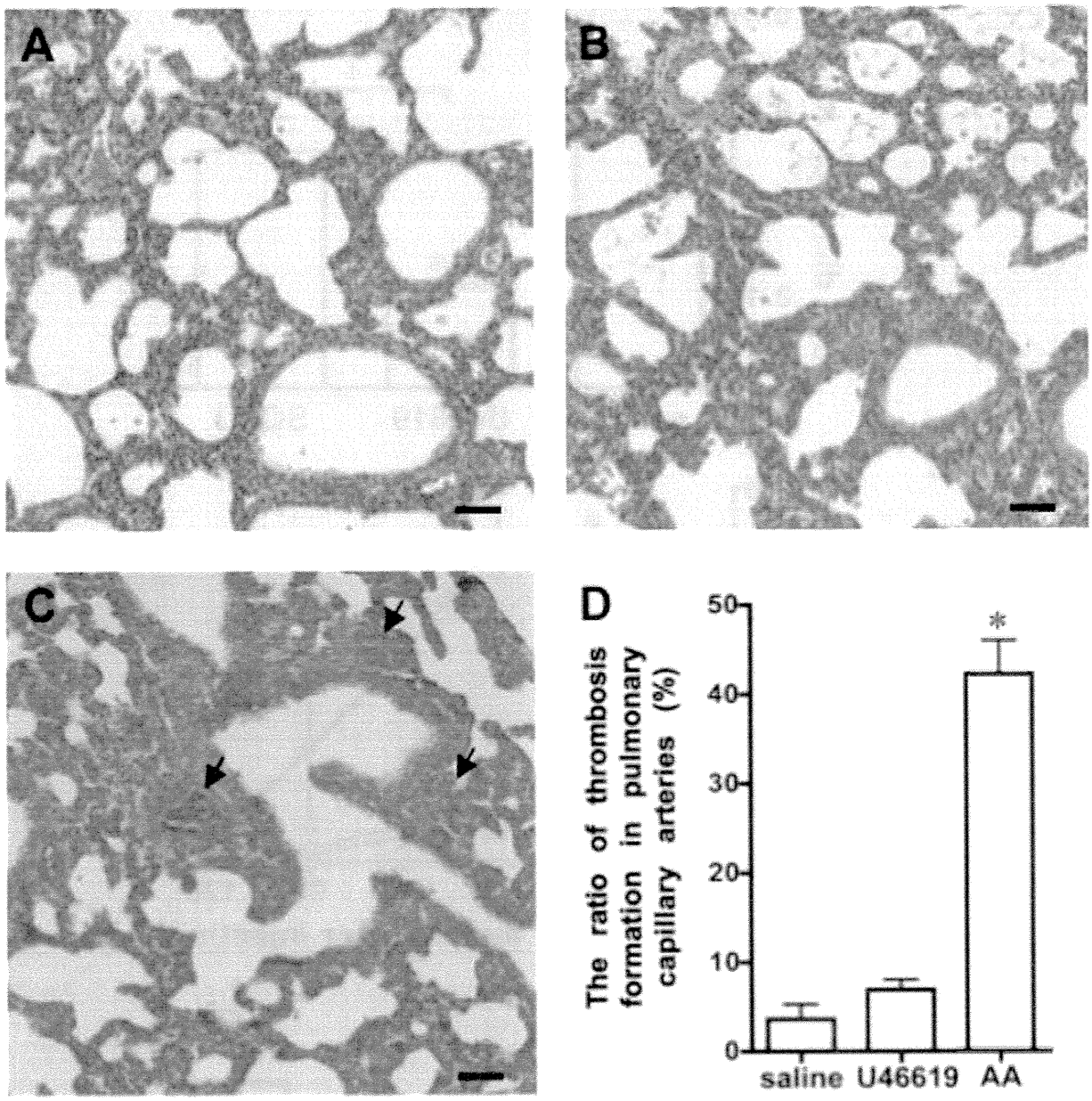
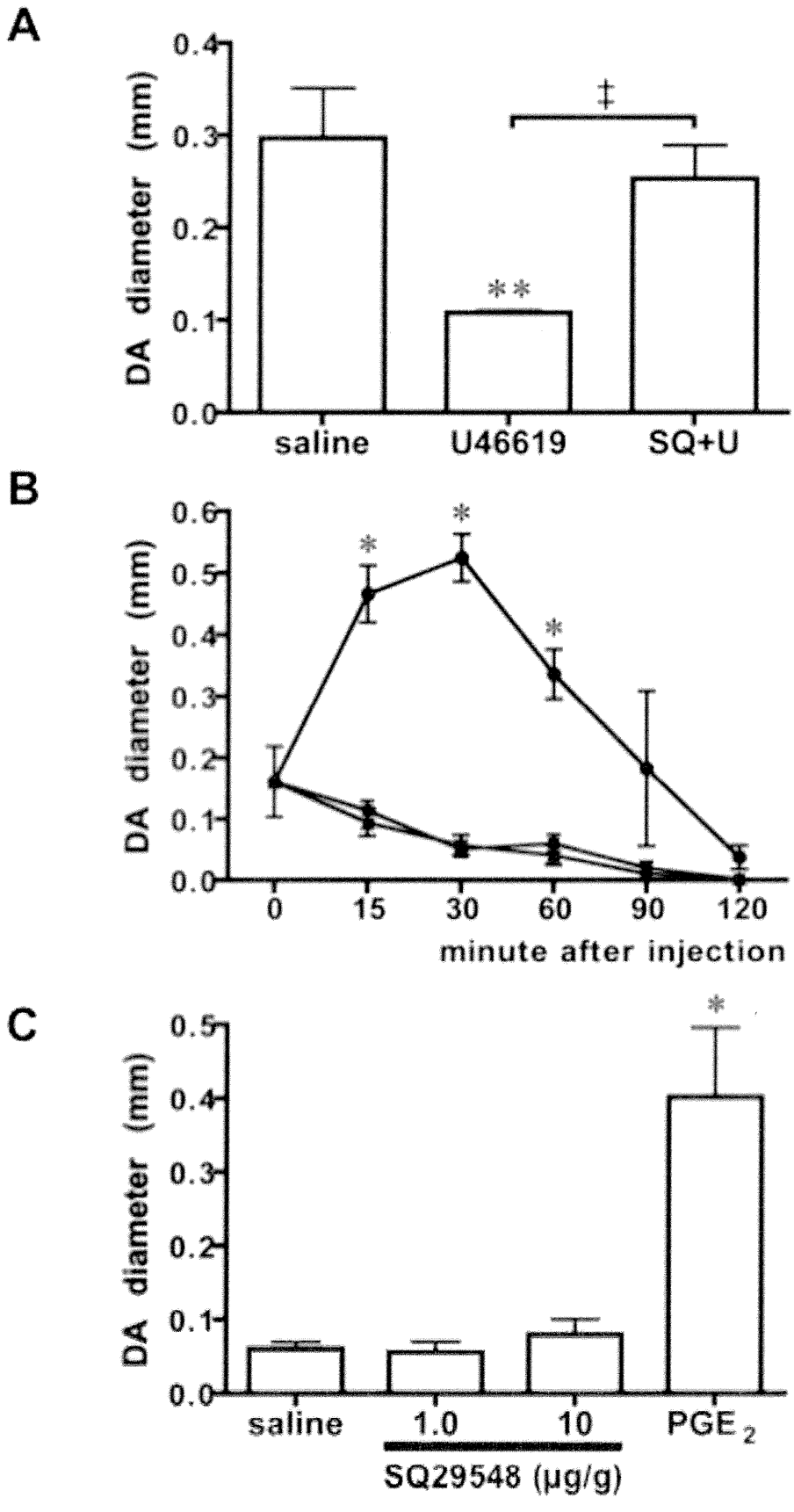

A
B
C
D
The ratio of thrombosis formation in pulmonary capillary arteries (%)
50
40
30
20
10
0
*
saline
U46619
AA

Figure 7


A
DA diameter (mm)
0.4
0.3
0.2
0.1
0.0
‡
**
saline
U46619
SQ+U
B
DA diameter (mm)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
*
*
*
0
15
30
60
90
120
minute after injection
C
DA diameter (mm)
0.5
0.4
0.3
0.2
0.1
0.0
*
saline
1.0
10
PGE2
SQ29548 (µg/g)

Table

Incidence of complete DA closure

time after injection (min)	Percent incident (no. complete closed DA/no. DA analyzed)			
		U46619 (μg/g)		
	saline	0.0005	0.05	5
10	0% (0/8)	0% (0/7)	0% (0/8)	11% (1/9)
20	0% (0/8)	0% (0/7)	0% (0/8)	86% (6/7)
30	0% (0/4)	0% (0/4)	75% (6/8)	100% (7/7)

Inhibition of EP4 Signaling Attenuates Aortic Aneurysm Formation

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Abstract

Background: Aortic aneurysm is a common but life-threatening disease among the elderly, for which no effective medical therapy is currently available. Activation of prostaglandin E_2 (PGE_2) is known to increase the expression of matrix metalloproteinase (MMP) and the release of inflammatory cytokines, and may thus exacerbate abdominal aortic aneurism (AAA) formation. We hypothesized that selective blocking of PGE_2, in particular, EP4 prostanoid receptor signaling, would attenuate the development of AAA.

Methods and Findings: Immunohistochemical analysis of human AAA tissues demonstrated that EP4 expression was greater in AAA areas than that in non-diseased areas. Interestingly, EP4 expression was proportional to the degree of elastic fiber degradation. In cultured human aortic smooth muscle cells (ASMCs), PGE_2 stimulation increased EP4 protein expression (1.4±0.08-fold), and EP4 stimulation with ONO-AE1-329 increased MMP-2 activity and interleukin-6 (IL-6) production (1.4±0.03- and 1.7±0.14-fold, respectively, $P<0.05$). Accordingly, we examined the effect of EP4 inhibition in an $ApoE^{-/-}$ mouse model of AAA infused with angiotensin II. Oral administration of ONO-AE3-208 (0.01–0.5 mg/kg/day), an EP4 antagonist, for 4 weeks significantly decreased the formation of AAA (45–87% reduction, $P<0.05$). Similarly, $EP4^{+/-}/ApoE^{-/-}$ mice exhibited significantly less AAA formation than $EP4^{+/+}/ApoE^{-/-}$ mice (76% reduction, $P<0.01$). AAA formation induced by periaortic $CaCl_2$ application was also reduced in $EP4^{+/-}$ mice compared with wild-type mice (73% reduction, $P<0.001$). Furthermore, in human AAA tissue organ cultures containing SMCs and macrophages, doses of the EP4 antagonist at 10–100 nM decreased MMP-2 activation and IL-6 production (0.6±0.06- and 0.7±0.06-fold, respectively, $P<0.05$) without increasing MMP-9 activity or MCP-1 secretion. Thus, either pharmacological or genetic EP4 inhibition attenuated AAA formation in multiple mouse and human models by lowering MMP activity and cytokine release.

Conclusion: An EP4 antagonist that prevents the activation of MMP and thereby inhibits the degradation of aortic elastic fiber may serve as a new strategy for medical treatment of AAA.

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Introduction

Aortic aneurysm is the 13th leading cause of death in the United States, with roughly 15,000 deaths per year [1]. After rupture occurs, the probability of mortality is greater than 60% [1]. Ultrasonography screening studies of men over 60 years old have shown that a small abdominal aortic aneurysm (AAA), i.e., 3 to 5 cm in diameter, is present in 4% to 5% of patients [2,3]. When patients with a small AAA were followed for up to 6 years, AAA diameter had increased in 55% of patients. The rate of increase in diameter was more than 1 cm per year in 23% of patients, and AAA diameter had expanded to 6 cm in 9% of patients, at which point the risk of rupture significantly increases [3]. Although AAAs typically continue to expand, increasing the likelihood of rupture and consequent mortality, no effective pharmacological therapy to prevent the progression of AAA is currently available.

The hallmarks of AAA are the presence of an inflammatory infiltrate within the vascular wall, which is followed by proteolytic degradation of extracellular matrixes (ECM) [4]. Proinflammatory cytokines play an important role, particularly in the initiation of