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## Asthma causes inflammation of human pulmonary arteries and decreases vasodilatation induced by prostaglandin I<sub>2</sub> analogs

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### ABSTRACT

**Objective:** Asthma is a chronic inflammatory disease associated with increased cardiovascular events. This study assesses the presence of inflammation and the vascular reactivity of pulmonary arteries in patients with acute asthma. **Methods:** Rings of human pulmonary arteries obtained from non-asthmatic and asthmatic patients were set up in organ bath for vascular tone monitoring. Reactivity was induced by vasoconstrictor and vasodilator agents. Protein expression of inflammatory markers was detected by western blot. Prostanoid releases and cyclic adenosine monophosphate (cAMP) levels were quantified using specific enzymatic kits. **Results:** Protein expression of cluster of differentiation 68, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and cyclooxygenase-2 was significantly increased in arteries obtained from asthmatic patients. These effects were accompanied by an alteration of vasodilatation induced by iloprost and treprostinil, a decrease in cAMP levels and an increase in prostaglandin (PG) E<sub>2</sub> and PGI<sub>2</sub> synthesis. The use of forskolin (50 µmol/L) has restored the vasodilatation and cAMP release. No difference was observed between the two groups in reactivity induced by norepinephrine, angiotensin II, PGE<sub>2</sub>, KCl, sodium nitroprusside, and acetylcholine. **Conclusion:** Acute asthma causes inflammation of pulmonary arteries and decreases vasodilation induced by PGI<sub>2</sub> analogs through the impairment of cAMP pathway.

### ARTICLE HISTORY

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### KEYWORDS

Asthma; prostaglandins; pulmonary arteries; vasoconstriction; vasodilatation

### Chemical compounds studied in this article

Acetylcholine (PubChem CID: 187), angiotensin II (PubChem CID: 172198), forskolin (PubChem CID: 47936), iloprost (PubChem CID: 5311181), norepinephrine (PubChem CID: 439260), prostaglandin E<sub>2</sub> (PubChem CID: 5280360), U46619 (PubChem CID: 5311493), RO1138452 (PubChem CID: 9839644), sodium nitroprusside (PubChem CID: 11963622), treprostinil (PubChem CID: 6918140)

### Introduction

Asthma is an inflammatory disease involving airway remodeling and a decline in lung function with recurrent bouts of cough, wheezing, chest tightness, shortness of breath, and reversible airway obstruction [1,2]. Airway remodeling is characterized by the loss of epithelial integrity and denudation of the basement membrane, subepithelial fibrosis, hyperplasia and hypertrophy of smooth muscle cells, hyperplasia and hypertrophy of submucosal glands with mucus production, obstruction and thickening of the airway walls, loss of cartilage integrity, and angiogenesis [3].

Various epidemiological studies have demonstrated an increased incidence of cardiovascular disease in patients

with asthma [4,5]. Over the past decade, there has been an evolution in the perception of asthma as a systemic disease associated with inflammation extending beyond the airways. In view of this, multiple mechanisms have been proposed implicating various systemic proinflammatory mediators common to the pathophysiology of both asthma and atherosclerosis. Further studies are required to evaluate whether attenuation of systemic inflammation will decrease cardiovascular events [6].

Prostaglandins (PG) and thromboxane (Tx), also called prostanoids, are known to be implicated in inflammatory diseases such as asthma and atherosclerosis [2,7,8]. These mediators are derived from arachidonic acid via cyclooxygenase (COX) activity. Two isoforms of this enzyme have been described: The constitutive isoform, COX-1, expressed in normal physiological conditions and COX-2 isoform which is expressed under inflammatory conditions. PGE<sub>2</sub> and PGI<sub>2</sub> are preferentially synthesized by human vascular cells under inflammatory conditions [9,10]. In vessels, PGE<sub>2</sub> induces vasodilatation through the activation of EP1 and EP3 receptors and vasodilatation via the activation of EP2 and EP4 receptors, while PGI<sub>2</sub> activates preferentially IP receptor and produces vasodilatation.

In view of the above, we aimed to assess whether patients with acute asthma have increased inflammation in pulmonary arteries, especially those nearby airways. This pathological situation may alter the vascular tone.

## Methods

### *Subjects and tissue preparation*

This study was approved by our local ethics committee and has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Young and nonsmoking population less than 45 years old was included in this study. Additional exclusion criteria included the presence of diabetes or chronic obstructive pulmonary disease was applied. Subjects who had used systemic corticosteroids, theophylline, long-acting  $\beta_2$ -agonists, leukotriene antagonists, or antihistamines within 4 months before the study were also excluded, as subjects who had histories of respiratory tract infection within the previous 8 weeks or immunotherapy within the previous 12 months.

Human lung tissues, confirmed as “tumor-free,” were obtained from consenting patients under chemotherapy treatments (14 males and 11 females) who had undergone surgery for lung carcinoma. The arteries were removed from pulmonary parenchyma adjacent to alveolar ducts and divided in three parts: one for western blot analysis in order to verify the expression of inflammatory mediators, a second part for the measurement of cyclic adenosine monophosphate (cAMP) levels, and the last part was used for vascular reactivity monitoring.

### *Western blot analysis*

Approximately 100 mg of frozen artery tissue was homogenized mechanically using potter glass homogenizer and immediately transferred to the RIPA buffer (in mmol/L: Tris:50, pH: 8; NaCl: 150; Triton X-100: 1%; sodium desoxycholate 1%; SDS (sodium dodecyl sulfate) 0.1%; EDTA: 5) with a protease inhibitor cocktail. The homogenate was centrifuged at 10,000 g for 10 minutes at 4°C. Proteins were quantified by Lowry's method. Approximately 50  $\mu$ g of total protein extracts was run per lane on 10–15% SDS PAGE at 80 V for about 2 hours. Proteins present on gels were transferred to nitrocellulose membranes using Biorad apparatus during 2 hours at 250 mA. Membranes were incubated in 5% non-fat dry milk/Tris Buffered Saline solution for 1 hour at room temperature to block non-specific binding, then overnight at 4°C with specific primary antibodies against Cluster of Differentiation 68 (CD68), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), COX-2, IP receptor, and  $\beta$  actin diluted at

1:200 or 1:500. Subsequently, blots were washed with Tris Buffered Saline/Tween-20 and then incubated for 1 hour at room temperature with HRP (horseradish peroxidase)-conjugated secondary antibodies diluted in 5% milk and Tris Buffered Saline solution in a 1:2000 ratio. Membranes were washed 5 times with Tris Buffered Saline/Tween-20. Bands were visualized by chemical luminescence plus system (Amersham Biosciences) and photographic films.

### *Vascular reactivity studies*

Artery samples cut as rings were placed in vertical chambers (internal volume 15 mL) filled with Krebs–Henseleit solution (mmol/L): NaCl 110.8,  $\text{CaCl}_2$  2.49,  $\text{NaHCO}_3$  25.0, KCl 5.9,  $\text{MgSO}_4$  1.07,  $\text{NaH}_2\text{PO}_4$  2.33 and glucose 11.51, oxygenated with carbogen gas (95%  $\text{O}_2$ /5%  $\text{CO}_2$ ) at 37°C under a tension of 1.0 g, for 1 hour to equilibrate. Initial vasoconstriction was induced by a single dose of U46619 (0.1  $\mu$ mol/L). Vascular preparations were washed with Krebs–Henseleit solution until they returned to the resting tone. Subsequently, these preparations were incubated (30 minutes) with NO synthase inhibitor (L- $\text{N}^G$ -Nitroarginine methyl ester, 1 mmol/L) and non-selective COX inhibitor (Salicylic acid, 100  $\mu$ mol/L) to avoid any effect related to endogenous NO and PG releases. In some protocols, Forskolin (50  $\mu$ mol/L) was added to this incubation period as indicated in Table 3. Subsequently, acetylcholine (ACh), angiotensin II (Ang II), iloprost, KCl, norepinephrine (NE),  $\text{PGE}_2$ , U46619 an analog of  $\text{TxA}_2$ , sodium nitroprusside (SNP), or treprostinil were added in a cumulative fashion to the baths (0.1 nmol/L–10  $\mu$ mol/L). A precontraction was induced by a single dose of U46619 (0.1  $\mu$ mol/L) before vasodilatation protocols. To investigate artery viability response, KCl (1 mmol/L) or papaverine (100  $\mu$ mol/L) were added at the end of experiments. Mechanical activities were recorded by isometric force transducer and a personnel computer equipped with an analog-to-digital converter board.

### *Measurement of $\text{PGE}_2$ and 6-keto-PGF $_{2\alpha}$ releases*

The releases of  $\text{PGE}_2$  and 6-keto-PGF $_{2\alpha}$ , a stable metabolite of PGI $_2$  were measured in samples collected from organ bath mediums after 1 hour of equilibration. Measurements were performed using specific enzyme-immunoassay kits (Cayman Chemical).

### *Measurement of cAMP levels*

Samples of human pulmonary arteries weighed on an electrobalance were cultured in RPMI medium containing antibiotics, iloprost (1  $\mu$ mol/L), forskolin (50  $\mu$ mol/L), and/or RO1138452 (0.1  $\mu$ mol/L) and placed for 12 hours

**Table 1.** Clinical characteristics of patients.

|                  | Non-asthmatic (n = 15) | Asthmatic (n = 10) | p      |
|------------------|------------------------|--------------------|--------|
| Age mean (years) | 39.1 ± 2.1             | 42.0 ± 2.8         | NS     |
| BMI mean         | 25.8 ± 1.5             | 25.3 ± 2.3         | NS     |
| Gender (M/F)     | 9/6                    | 5/5                | NS     |
| FEV1% baseline   | 97.2% ± 2.0            | 76.9% ± 1.7        | <0.001 |
| FEV1% post ECT   | 98.1% ± 1.4            | 66.2% ± 1.5        | <0.001 |

NS: not significant, BMI: body mass index, M: male, F: female, FEV1%: percent of predicted forced expiratory volume in the first second, ECT: exercise challenge test.

in an incubator at 37°C and 5% CO<sub>2</sub>. After the incubation period, vascular preparations were immersed in cold 6% trichloroacetic acid for 15 min. Subsequently, tissues were homogenized using a potter glass homogenizer at 4°C and centrifuged at 12,000 g for 10 minutes at 4°C. The supernatants were washed five times with 5 mL of water saturated with diethyl ether solution (50:50). cAMP quantification was performed using enzyme-immunoassay commercial kit (cAMP direct Biotrak EIA, GE Healthcare Bio-Sciences).

### Data analysis

Acquisition of the reactivity changes data was performed with the Powerlab software. The data expressed in grams (g) are positive for vasoconstrictions and negative for vasodilations. E<sub>max</sub> value correspond to the maximal effect measured. The pEC<sub>50</sub> values were calculated as the negative log of the half-maximum effective concentration (EC<sub>50</sub> values). The concentration-response was expressed in percent (%) to the initial U46619 vasoconstriction. All data are presented as means ± standard error of mean (SEM) derived from (n) patients. The concentration-response curves were analyzed by two-way analysis of

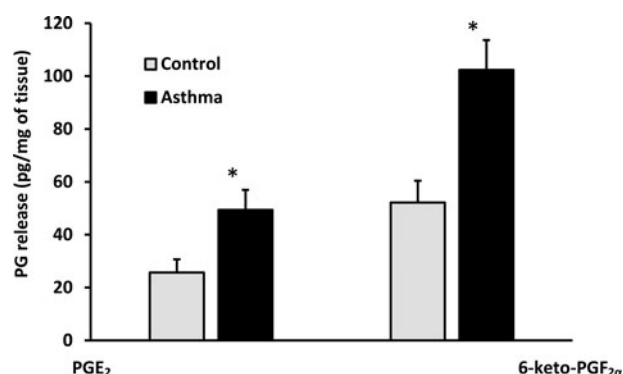


**Figure 2.** Vasodilation induced by iloprost (A) and sodium nitroprusside (SNP, B) on human pulmonary arteries obtained from non-asthmatic (Control, n = 8) and asthmatic (Asthma, n = 6) patients. Results are expressed as percent of precontraction induced by U46619 (0.1 μmol/L). (\*) indicates results are different from control (p < 0.05, Student's paired t-test).

variance (ANOVA). The pEC<sub>50</sub> and E<sub>max</sub> were analyzed by paired Student's t-test. A p-value < 0.05 was considered statistically significant.

## Results

### Study population

The baseline clinical characteristics of all subjects are shown in Table 1. There was no significant difference between the asthmatic and the non-asthmatic control group for age, gender, and body mass index (BMI). Percent of predicted forced expiratory volume in the first second (FEV1%) baseline and FEV1% post exercise challenge test were significantly lower in asthmatic patients compared to non-asthmatic patients (Table 1).

### Expression of CD68, ICAM-1, VCAM-1, COX-2, IP, and β actin proteins

A representative result of western blot analysis using artery samples from four asthmatic and five non-asthmatic patients is presented in Figure 1. The use

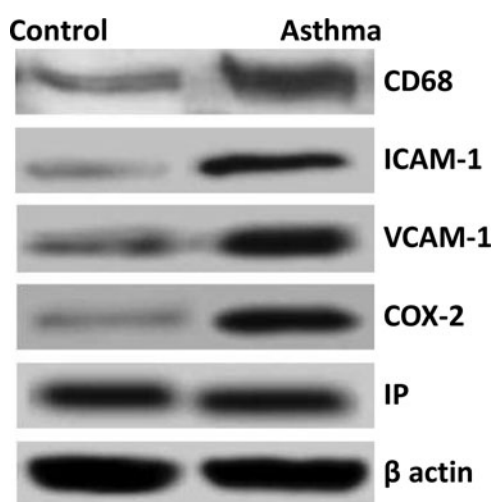


**Figure 1.** Representative of western blot analysis for Cluster of Differentiation 68 (CD68), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), cyclooxygenase-2 (COX-2), IP receptor, and β actin in human pulmonary arteries obtained from non-asthmatic (Control, n = 5) and asthmatic (Asthma, n = 5) patients.

**Table 2.** E<sub>max</sub> and pEC<sub>50</sub> values of vasoconstriction induced by selective agonists in human pulmonary arteries from non-asthmatic (Control, n = 8) and asthmatic (Asthma, n = 6) patients.

| Agonists                     | Control           |                      | Asthma            |                      |
|------------------------------|-------------------|----------------------|-------------------|----------------------|
|                              | pEC <sub>50</sub> | E <sub>max</sub> (g) | pEC <sub>50</sub> | E <sub>max</sub> (g) |
| Norepinephrine               | 7.01 ± 0.20       | 1.67 ± 0.24          | 6.99 ± 0.39       | 1.72 ± 0.28          |
| Angiotensin II               | 8.03 ± 0.29       | 1.46 ± 0.19          | 8.07 ± 0.16       | 1.56 ± 0.22          |
| KCl                          | NC                | 3.02 ± 0.22          | NC                | 2.99 ± 0.35          |
| Prostaglandin E <sub>2</sub> | 7.51 ± 0.13       | 1.20 ± 0.39          | 7.25 ± 0.17       | 1.10 ± 0.42          |
| U46619                       | 7.63 ± 0.29       | 4.62 ± 0.90          | 7.70 ± 0.34       | 4.34 ± 1.01          |

Values are means ± s.e.mean derived from (n) different patients.

E<sub>max</sub> indicates maximal vasoconstriction effect. (NC) indicates not calculable.

Rings were treated for 30 minutes with L-N<sup>G</sup>-nitroarginine methyl ester (1 mmol/L) and salicylic acid (100 μmol/L) before vasoconstriction protocols.

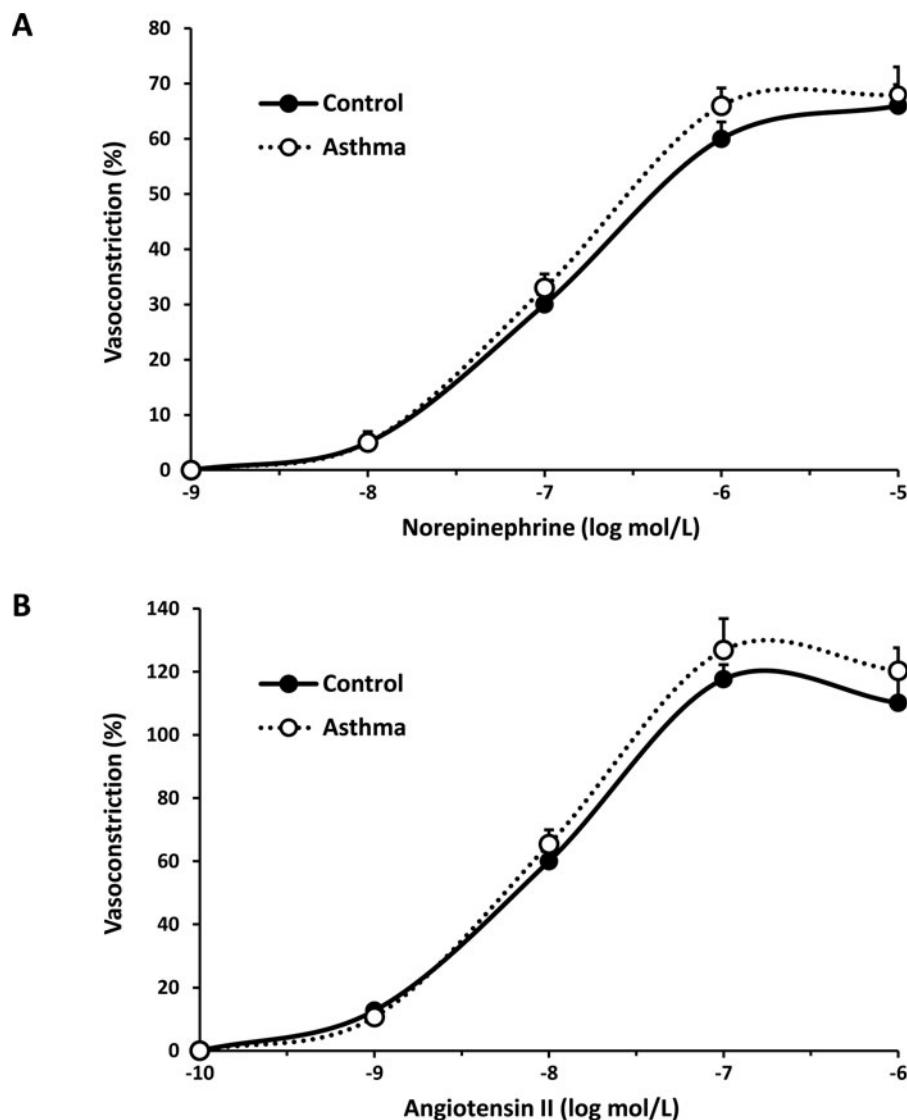


**Figure 3.** Measurement of prostaglandin (PG)  $E_2$  and 6-keto- $PGF_{1\alpha}$  released by human pulmonary arteries into the media of organ bath experiments. The results derived from non-asthmatic (Control,  $n = 5$ ) and asthmatic (Asthma,  $n = 5$ ) patients; (\*) indicates data significantly different from their respective control ( $p < 0.05$ , Student's paired  $t$ -test).

**Table 3.**  $E_{max}$  and  $pEC_{50}$  values of vasodilatation induced by selective agonists in human pulmonary arteries obtained from asthmatic (Asthma,  $n = 8$ ) and non-asthmatic (Control,  $n = 6$ ) patients.

| Agonist      | Treatments | Control         |                  | Asthma          |                    |
|--------------|------------|-----------------|------------------|-----------------|--------------------|
|              |            | $pEC_{50}$      | $E_{max}$ (g)    | $pEC_{50}$      | $E_{max}$ (g)      |
| SNP          | S + L      | $8.02 \pm 0.79$ | $-2.10 \pm 0.24$ | $7.88 \pm 0.91$ | $-2.03 \pm 0.18$   |
| Iloprost     | S + L      | $7.31 \pm 0.32$ | $-1.62 \pm 0.25$ | $6.79 \pm 0.36$ | $-1.10 \pm 0.29$ * |
| Iloprost     | S + L + F  | $7.81 \pm 0.55$ | $-1.90 \pm 0.53$ | $6.91 \pm 0.44$ | $-1.48 \pm 0.31$   |
| Treprostinil | S + L      | $6.78 \pm 0.28$ | $-1.26 \pm 0.43$ | $6.11 \pm 0.39$ | $-0.96 \pm 0.12$ * |
| ACh          | S + L      | $6.92 \pm 0.32$ | $-1.85 \pm 0.19$ | $6.55 \pm 0.51$ | $-1.92 \pm 0.42$   |

Values are means  $\pm$  s.e.mean derived from ( $n$ ) different patients.

$E_{max}$  indicates maximal vasodilatation effect. (NC) indicates not calculable.

(\*) indicates data significantly different from respective control values ( $p < 0.05$ , Student's paired  $t$ -test).

ACh: acetylcholine, F: forskolin (30 minutes, 50  $\mu$ mol/L), L: L- $N^G$ -Nitroarginine methyl ester (30 minutes, 1 mmol/L), S: salicylic acid (30 minutes, 100  $\mu$ mol/L), SNP: sodium nitroprusside.

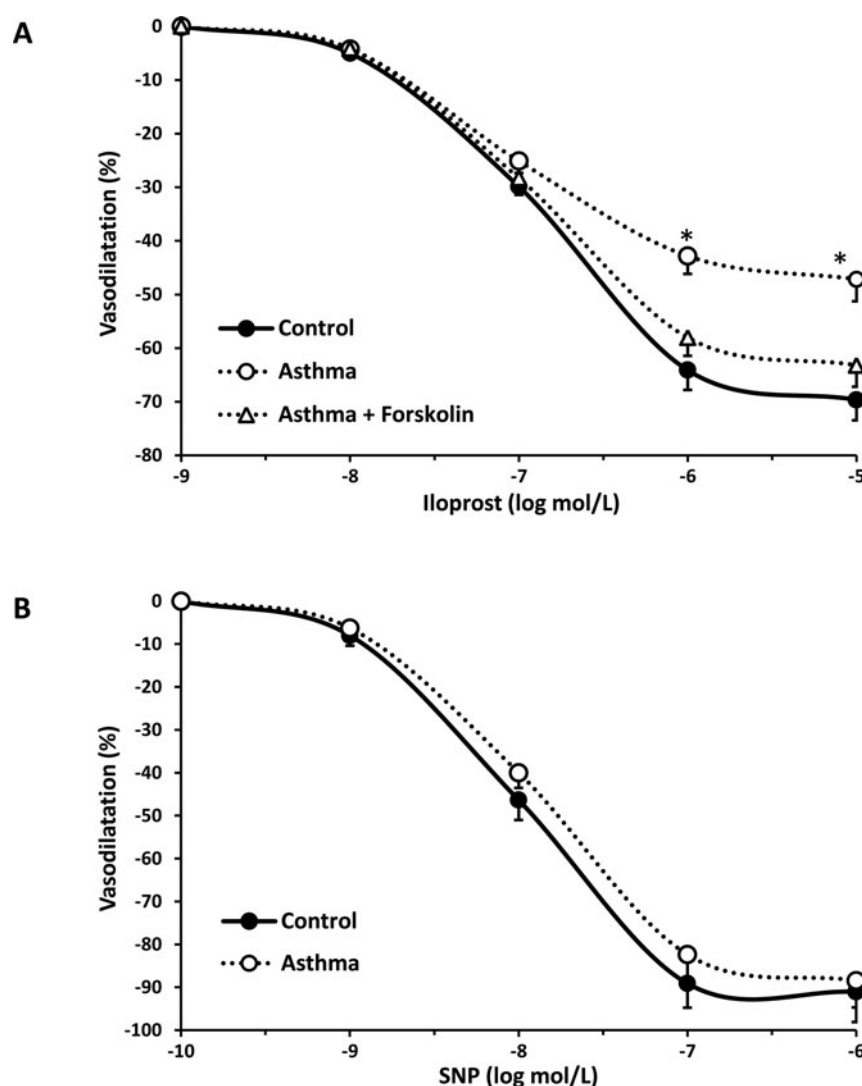


**Figure 4.** Vasoconstrictions induced by norepinephrine (A) and angiotensin II (B) on human pulmonary arteries from normal (Control,  $n = 8$ ) and asthmatic (Asthma,  $n = 6$ ) patients. Results are expressed as percent of precontractions induced by U46619 ( $0.1 \mu\text{mol/L}$ ). (\*) indicates results are different from Control ( $p < 0.05$ , Student's paired  $t$ -test).

of specific antibodies demonstrated that CD68, ICAM-1, VCAM-1, and COX-2 were markedly expressed in vascular preparations obtained from asthmatic patients in comparison to non-asthmatic patients. Expressions of IP receptor and  $\beta$  actin were not different between both groups. To check the purity of artery samples, the surfactant protein B was checked as a marker of alveoli using a specific antibody (Abcam, UK). The results show an absence of surfactant protein B expression in human pulmonary arteries used for this study ( $n = 4$ , data not shown).

#### Vascular reactivity of isolated pulmonary arteries

Vasoconstrictions induced by NE,  $\text{PGE}_2$ , Ang II, and KCl are presented in Figure 2 and Table 2. No difference in vasoconstrictions was observed between asthmatic and non-asthmatic groups.

Vasodilations induced by SNP, iloprost, treprostinil, and ACh are presented in Figure 3 and Table 3. No difference in vasodilations induced by SNP and ACh was observed between both groups. However, vasodilations induced by iloprost and treprostinil were significantly lower in pulmonary arteries obtained from asthmatic in comparison to non-asthmatic patients. The treatment of asthmatic arteries with forskolin ( $50 \mu\text{mol/L}$ , 30 minutes) prior reactivity protocols increases and restores vasodilatation induced by iloprost (Figure 3 and Table 3). The IP antagonist (RO1138452,  $0.1 \mu\text{mol/L}$ ) completely blocked vasodilations induced by iloprost and treprostinil (data not shown).

#### Release of $\text{PGE}_2$ and $\text{PGI}_2$

The release of  $\text{PGE}_2$  and 6-keto- $\text{PGF}_{2\alpha}$ , a stable metabolite of  $\text{PGI}_2$ , was significantly greater in mediums obtained from asthmatic than non-asthmatic groups (Figure 4).

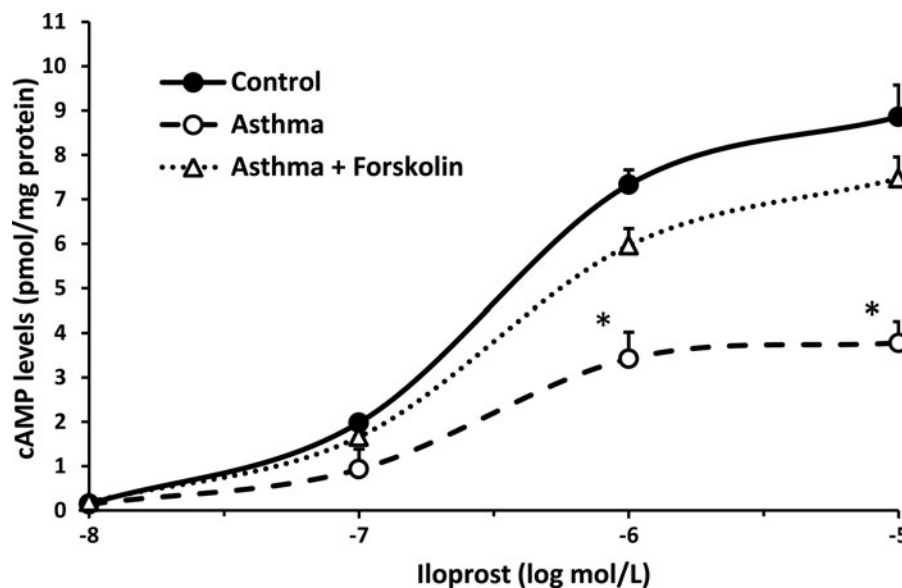


**Figure 5.** cAMP levels measured in human pulmonary arteries obtained from non-asthmatic (Control,  $n = 8$ ) and asthmatic (Asthma,  $n = 6$ ) patients after treatment with increased doses of iloprost in presence or absence of forskolin ( $50 \mu\text{mol/L}$ ). (\*) indicates results are different from control ( $p < 0.05$ , Student's paired  $t$ -test).

#### Effect of iloprost, forskolin, and RO1138452 on cAMP levels

Iloprost causes an increase in cAMP levels in pulmonary arteries (Figure 5, Table 4). This effect was significantly lower in arteries obtained from asthmatic in comparison to non-asthmatic patients (Figure 5, Table 4). No difference was observed after treatment with forskolin ( $50 \mu\text{mol/L}$ ). The IP receptor antagonist (RO1138452,  $0.1 \mu\text{mol/L}$ ) blocked the cAMP release in both groups.

#### Discussion

The current study demonstrates that lung patients with acute asthma have increased arterial inflammation compared to carefully matched individuals without asthma. This inflammatory condition is associated with a decrease in vasodilatation induced by  $\text{PGI}_2$  analogs.

**Table 4.** cAMP levels measured in human pulmonary arteries obtained from non-asthmatic (Control,  $n = 8$ ) and asthmatic (Asthma,  $n = 6$ ) patients after treatment with iloprost ( $1 \mu\text{mol/L}$ ) for 30 minutes in presence or absence of forskolin ( $50 \mu\text{mol/L}$ ) or RO1138452 ( $0.1 \mu\text{mol/L}$ ).

|         | Without         | Iloprost             | Iloprost + forskolin | Iloprost + RO 1138452 |
|---------|-----------------|----------------------|----------------------|-----------------------|
| Control | $0.92 \pm 0.25$ | $8.86 \pm 1.14^*$    | $9.23 \pm 1.19^*$    | $0.52 \pm 0.10$       |
| Asthma  | $0.72 \pm 0.20$ | $3.78 \pm 0.59^{*§}$ | $7.47 \pm 0.79^*$    | $0.54 \pm 0.13$       |

Values are expressed as pmol/mg of total proteins.

(\*) indicates data significantly different from respective values without treatment ( $p < 0.05$ , Student's paired  $t$ -test).

(§) indicates data significantly different from respective control values ( $p < 0.05$ , Student's paired  $t$ -test).

The protein expression of CD68, ICAM-1, VCAM-1, and COX-2 and the releases of  $\text{PGE}_2$  and  $\text{PGI}_2$  were investigated in pulmonary arteries as markers of inflammation. The asthmatic pulmonary arteries showed an increase in these markers as reported in several inflammatory models using vascular preparations [11–15]. This effect was confirmed by the increase in  $\text{PGE}_2$  and  $\text{PGI}_2$  releases due to COX-2 induction. These results are in accordance with other studies performed on human vessels. In fact, COX-2 was induced in human mammary arteries after treatment with inflammatory stimuli such as lipopolysaccharide and interleukin- $1\beta$  [9]. This induction was accompanied by an increase in  $\text{PGE}_2$  and  $\text{PGI}_2$ . Other studies show that CD68 and VCAM-1 expressions increased in atherosclerotic coronary arteries due to inflammation [16]. Finally, another study showed an elevation of almost all markers involving inflammation of the endothelial cells in the coronary artery and in epithelial cell lining of the airway in patients with asthma [17].

Our study shows that asthma causes inflammation of pulmonary arteries as observed in bronchial airways. The inflammatory effect of asthma observed in our study seems to not be due to atherosclerosis or cigarette smoke, since all subjects are relatively young and lifelong non-smokers. The development of inflammation is linked closely to the recruitment and accumulation of monocytes. The inflammatory response in airways leads to the expression of chemokines, which are implicated for the recruitment of monocytes into the vessel wall. During inflammation, VCAM-1 is expressed on the surface of endothelial cells leading to monocyte adhesion, while the chemokine chemoattractant protein 1 is released to

mediate cell migration and inflammation. This inflammatory reaction interplays between the multi-cellular infiltrate from airways to parenchymal lung tissue cells and it is orchestrated by a broad network of self-amplifying bioactive mediators, including cytokines, antibodies, and growth factors [18].

The vasorelaxant effect of PGI<sub>2</sub> analogs was previously investigated in human vessels under normal conditions. Iloprost and treprostinil cause potent vasodilatation of isolated human pulmonary arteries through the activation of IP receptor. The inflammatory condition observed in our study affects pulmonary vascular tone. About 20% of vasodilatation induced by PGI<sub>2</sub> analogs was reduced in asthmatic patients. This alteration is not related to IP receptor expression but to an impairment of IP/cAMP pathway in the smooth muscle cells. This explanation is supported by the reestablishment of vasodilatation after treatment with forskolin, an activator of cAMP, and the decrease in intracellular cAMP levels (~2-fold) in samples obtained from asthmatic patients. In addition, the alteration of vascular tone during asthma could be specific to PGI<sub>2</sub>/IP/cAMP pathway. In fact, vasoactive and other vasodilator agents were not altered during asthma.

Our study shows that chronic airway inflammation of asthma may affect adjacent arteries and alter their vasodilatation by the impairment of cAMP pathway in the smooth muscle cells. An attempt could be made to put this study into a clinical perspective for the investigation of the systemic inflammation in asthma, which may cause heart disease.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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