Platelet-activating factor impairs mucociliary transport and increases plasma leukotriene B₄ in man


Platelet-activating factor (PAF) has been shown to cause a wide spectrum of effects including acute bronchoconstriction [1-4], and increased airways reactivity [1, 4-8], as well as vascular events similar to those seen in acute inflammation [9], neutrophil [10] and eosinophil chemotaxis [11], degranulation and mediator secretion [12, 13]. Furthermore, inhaled or intravenously administered PAF causes hypotension in animals and in man [1, 14]. Hence, it is speculated that the generation of PAF may be important to the pathogenesis of asthma and anaphylaxis. However, it is poorly understood whether these pathophysiological events are direct actions of PAF on target tissues like smooth muscle [15] or mediated via secondary generation or release of leukotrienes [13, 16], cyclooxygenase metabolites of arachidonic acid [6, 16, 17], or histamine [4, 18].

Tracheobronchial clearance is impaired in many airway diseases, and reduced mucus transport may have a contributing role in pathogenesis by preventing the clearance of airway secretions [19-21]. Impaired clearance is a typical characteristic of asthma exacerbations induced by allergen, which may be caused by release of autacoid mediators from immunoglobulin E (IgE)-antigen reaction with resident or inflammatory cells in airways. It has been suggested that leukotrienes might be crucial to allergic inhibition of mucus transport [22, 23]. Preliminary studies have also indicated that PAF reduces tracheobronchial mucus velocity in animals [24, 25].

The purpose of the present investigation was, firstly, to assess the effect of inhaled PAF on tracheobronchial clearance and its possible relation to the PAF-induced bronchial hyperresponsiveness in man. Secondly, we were interested in the role of secondary inflammatory mediators and activation of circulating platelets in PAF-induced bronchial responses. Therefore, the level of plasma leukotriene B₄ and the aggregation and the thromboxane B₂ production of platelets were measured during PAF challenge. On the other hand, the significance of cyclooxygenase products of arachidonic acid metabolism in PAF-induced bronchial effects was further evaluated by acetylsalicylic acid pretreatment. Finally, we wanted to delineate whether noradrenaline or adrenaline release play any role in the modulation of pulmonary or circulatory effects of PAF in man.
Methods

Subjects

All subjects were nonsmoking healthy volunteers, recruited from the staff of Tampere University Central Hospital. They gave informed consent according to the Helsinki Declaration, and the study was approved by the Ethical Committee of Tampere University Central Hospital.

The PAF study was conducted on seven subjects, three men and four women (mean age 40 yrs, range 30–58 yrs). Six of them also participated in the second PAF study with acetylsalicylic acid pretreatment, where 500 mg of acetylsalicylic acid was given twice per os, at approximately 12 h and 2 h before the PAF challenge.

In addition to these seven subjects, the baseline (diluent) mucociliary clearance was also tested twice in eight others, at the same time of day at least 2 wks apart. Thus, the repeatability of the method was assessed in 15 subjects, nine women and six men, with a mean age of 36 yrs (range 21–58 yrs). None had a respiratory disease including upper respiratory viral infection within the previous six weeks. No medication was allowed during the previous 2 wks, or caffeine-containing beverages during the 12 h prior to the study.

Method for aerosol delivery

PAF, radioaerosol, and methacholine were delivered with an automatic, inhalation-synchronized dosimeter jet nebulizer (Spira Elektro 2, Respiratory Care Center, Hämeenlinna, Finland). This dosimeter is triggered by a very low inspiratory flow rate (a threshold \( <33 \text{ ml} \cdot \text{s}^{-1} \)), which enables the delivery of the aerosols with tidal breathing.

The volume output of the dosimeter under these operating conditions, and with 0.5 s nebulization periods is 7.1 \( \mu \text{l} \cdot \text{breath}^{-1} \) (mean±0.5 sd) [26].

Nebulization was practised by each subject with saline before the study began. With noseclip and mouthpiece in place, the subject controlled his tidal breathing with the flow indicator so that the inspiratory flow rate of each breath reached but did not exceed 0.5 \( \text{ls}^{3} \), with intra-individual variation in tidal volume of \( \pm 10\% \).

PAF administration

A mixture of C\(_{16}\) and C\(_{18}\) analogues of 1-0-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine (Novabiochem, Läufelfingen, Switzerland) at a ratio 3:1 was diluted to a concentration of 3.6 mg ml\(^{-1}\) with 0.9% saline containing 0.25% human serum albumin (HSA). After the nebulization of this diluent, PAF was delivered with the dosimeter in four successive doubling cumulative doses (1, 2, 6 and 11 inhalations, respectively), from 25 \( \mu \text{g} \) (0.048 \( \mu \text{mol} \)) to 500 \( \mu \text{g} \) (0.96 \( \mu \text{mol} \)), with 3 min interval between each dose.

Monitoring of immediate bronchial obstruction after PAF

After the inhalations of diluent and of 500 \( \mu \text{g} \) of PAF, spirometric measurements (Vitalograph, Buckingham, UK) were performed. At least two technically correct manoeuvres for the forced maximal expiratory flow-volume curves with a variation of less than 5% were done, and the best curve with the greatest sum of forced expiratory volume in one second (FEV\(_{1}\)) and forced vital capacity (FVC) was utilized in obtaining the data.

Measurement of tracheobronchial clearance

Mucociliary transport rate was evaluated by calculating the clearance of inhaled radioaerosol particles according to the method of Taplin et al. [27] as modified by Isawa et al. [28].

For the radioaerosol, \( ^{99m} \text{Tc} \)-traced human albumin particles with MMAD 1.4 \( \mu \text{m} \) were diluted with 0.9% saline to contain 0.25% HSA. Thus, the diluent was identical to that of PAF. The radioactivity of the nebulizer chamber was recorded before the nebulization by a well counter (Capintec CRC 10, Montvale, NJ, USA), and the radioactivity of solution adjusted to about 30 mCi-2 ml\(^{-1}\). The radioaerosol was given as 0.5 s nebulizations during 15 inhalations, which delivered a total amount of 106.5 \( \mu \text{l} \).

The lungs were imaged with a gamma camera (GE 400 A/T Maxicamera, General Electrics, Horsholm, Denmark), in a frontal projection. Data were collected for 10 min immediately after the nebulization (total lung deposition), and again after 1, 2 and 4 h (tracheobronchial clearance) and then repeated after 24 h for 20 min (retention in alveoli and nonciliated airways).

Gamma images were stored onto magnetic disk of Gamma-11 computer-system using 64 \( \times \) 64 matrix. A special computer program was written to analyse the data. Firstly, separate images were moved on the display so that the same region of interest can be used in the study. The program uses the count numbers from manually drawn lung areas for calculations. Corrections of physical decay of \( ^{99m} \text{Tc} \) and differences in collecting times are then carried out. The constant background activity of the room is collected as well. The counts of the 24 h image are then subtracted from the counts of the other images, because this residual activity is supposed to be trapped in the nonciliated part of lungs. Finally, the program computes the fraction of activity still apparent at different time points (retention values).
Methacholine bronchial challenge

Methacholine bronchial challenge was performed according to a dosimeter method described previously [29]. After nebulization of 36 μg of saline to establish a baseline, methacholine was delivered in ten successive cumulative doses from 18 μg to 2,300 μg. The concentration of methacholine was 2.5 mg·ml⁻¹ for the doses 18-180 μg, and 25 mg·ml⁻¹ for the doses 360-2,300 μg.

At least two maximal flow-volume curves (Vitalograph, Buckingham, UK) were measured before and after inhalation of diluent. Each dose of methacholine with the subject seated. The best curve, with the greatest sum of FEV₁ and FVC, was recorded. The challenge was terminated if the maximal expiratory flow when 50% FVC remained to be exhaled (MEF₅₀) fell by at least 35% from the post-saline value. The fall in MEF₅₀ was plotted against dose methacholine on a log scale, and the provocative dose causing a 35% fall in MEF₅₀ (PD₃₅) was calculated.

Blood pressure recording

After the inhalations of diluent, and each dose of PAF, blood pressure in the left brachial artery was measured with the subject seated using a mercury manometer, cuff size 12 x 35 cm. The cuff pressure at which the sounds of Korotkoff were first heard was the systolic pressure. The diastolic pressure was recorded at the fifth phase of the sounds of Korotkoff.

Mediator levels and platelet function

The measurement of leukotriene B₄ (LTB₄), adrenaline and noradrenaline in plasma, secretion of thromboxane B₂ (TXB₂) from thrombocytes and platelet reactivity to adrenaline, adenosine diphosphate (ADP) and PAF were performed from the blood samples taken after the inhalation of diluent, and 20 and 60 min after the inhalation of the first dose of PAF (5 and 45 min after the last dose of PAF).

Concentrations of LTB₄ in plasma

Heparinized plasma was extracted with Amprep C2 minicartridge (Amersham International, Buckinghamshire, UK) and quantitated with radioimmunoassay (RIA) as follows. One ml of plasma, acidified to pH 3.5 with HCl, was placed in the minicartridge prewashed with 2 ml of methanol and 2 ml of distilled water. The column was washed with 5 ml of distilled water, 5 ml of 10% ethanol and 5 ml of hexane and, thereafter, LTB₄ was eluted with 5 ml of methylformiate. The procedure resulted in >85% recovery for LTB₄. The extraction described was tested to be sufficient by comparing LTB₄ concentrations measured from the same samples (n=24) purified with Amprep C2 + high performance liquid chromatography (HPLC) [30] or Amprep C2 alone. Concentrations of LTB₄ were quantitated with RIA using a commercial kit from Amersham International, Buckinghamshire, UK.

Concentrations of adrenaline and noradrenaline in plasma

Adrenaline and noradrenaline concentrations in plasma were measured by HPLC using electrochemical detection with dihydroxybenzylamine as internal standard as described [31].

TXB₂ synthesis in platelets

Five ml of blood was allowed to clot at 37°C for 30 min. The reaction was stopped by cooling in an ice-bath for 10 min. TXB₂ concentrations in diluted serum were assayed by RIA using antibody obtained from Prof. C. Taube, Martin Luther University, Halle, DDR, and 3H-labelled TXB₂ from Amersham International, Buckinghamshire, UK.

Platelet aggregation

Twenty ml of blood was collected in citrate (9 volumes blood and 1 volume 3.8% citrate) and centrifuged at 150 x g for 20 min to obtain platelet-rich plasma. The platelet count was adjusted to 300,000·mm⁻³, 450 μl of the suspension was transferred into measuring cuvette and preincubated at 37°C for 5 min. The aggregation was induced by adding adrenaline (final concentration 0.1-10 μM; Sigma Chemical Co., St. Louis, MO, USA), ADP (0.1-10 μM; Sigma Chemical Co., St. Louis, MO, USA) or PAF-C₁₈ (0.02-20 μM; Novabiochem, Läufelfingen, Switzerland) in 50 μl. The aggregation was measured by Die Kyoto aggregation recorder (Model PA-3210; Kagaku Co. Ltd, Kyoto, Japan) for 5 min against platelet-poor plasma (obtained by centrifugation at 2,500 x g for 20 min).

Statistical evaluation

For statistical analysis, the Student’s t-test for paired observations and analysis of variance was used. A probability value less than 0.05 was considered to be significant. The repeatability of the measurement of mucociliary transport was evaluated by the method of ALTMAN and BLAND [32] by relating the difference between the first and the second measurement with their mean value in log₁₀ units to ensure that within subject variation was independent of the size of the measurement. Further, the intra- and intersubject coefficient of variation were calculated. From the standard deviation of the differences between measurements the 95% range for a single measurement was calculated from the formula \( t_{0.05} (sd)\sqrt{2} \).
Results

Repeatability of the measurement of tracheobronchial clearance

To test the reproducibility of the method, tracheobronchial clearance was measured twice in 15 normal subjects. The intra- and intersubject variabilities of 4 h tracheobronchial clearance were 11 and 22%, respectively. No relationship between within subject variation and the size of the retention of radioaerosol in ciliated airways was found, calculated after logarithmic transformation of the results. The mean difference between replicates was 0.06 (±0.10) at 4 h measurement. The 95% confidence interval of retention % based on a single measurement was the observed value ±0.48 doubling increment.

Effect of PAF on tracheobronchial clearance

After inhalation of PAF, retention of radioaerosol in ciliated airways at 4 h measurement was 80% greater than in the control recording (p<0.005), and the clearance was reduced by 33%. Acetylsalicylic acid had no significant effect on the PAF-induced impairment in mucus transport (fig. 1).

Bronchial obstruction

There were no significant differences between the two groups (with or without acetylsalicylic acid pretreatment) in the measures of baseline airway function determined just prior to the inhalation of PAF (fig. 2). Inhalation of PAF caused an acute, transient bronchial obstruction. FEV_1 decreased by 16% (SEM 3.6) (p<0.01) and MEF_{50} by 27% (SEM 6.8) (p<0.025). Pretreatment with acetylsalicylic acid almost totally abolished this effect of PAF (fig. 2). In both groups, the subjects also had slightly increased coughing for a couple of hours after the inhalation of PAF.

Bronchial responsiveness to methacholine

Control methacholine test showed no bronchial hyperresponsiveness in our seven subjects. The inhalation of 500 μg of PAF caused a marked bronchial hyperresponsiveness in the next day in three out of the seven individuals, PD_{35} MEF_{50}: 350 μg, 250 μg and 1,600 μg, respectively. After acetylsalicylic acid pretreatment, these three subjects still had increased bronchial responsiveness; PD_{35} MEF_{50}: 255 μg, 330 μg and 560 μg, respectively.

Circulatory effects

In all subjects inhalation of PAF caused facial flushing, warmth and a slight decrease in systolic and diastolic blood pressure (p<0.01) (fig. 3). There was a slight increase in heart rate, not however achieving significance. Pretreatment with acetylsalicylic acid did not influence the flushing, warmth nor the decline of blood pressure (fig. 3).

Leukotriene B_4

Both without and with acetylsalicylic acid, plasma LTB_4 levels were increased in the samples taken 20 min after PAF inhalation (240±65.8 and 299±42.5 pg·ml⁻¹, mean±SEM, respectively) as compared to the baseline.

![Graph showing bronchial obstruction](image-url)
EFFECT OF PAF ON AIRWAYS FUNCTION

Fig. 3. - Effect of cumulative doses of inhaled platelet-activating factor (PAF) on systolic and diastolic blood pressure (mean±SEM, n=6–7) without and with acetylsalicylic acid (ASA) treatment. **: p<0.025; ***: p<0.01. Syst.: systolic; Diast.: diastolic; BP: blood pressure.

Fig. 4. - Effect of inhaled PAF on plasma LTB4 concentration (mean±SEM, n=6–7) with and without acetylsalicylic acid (ASA) treatment.

Fig. 5. - Effect of inhaled platelet-activating factor (PAF) on plasma adrenaline (□□□) and noradrenaline (■■■) concentrations (mean±SEM, n=6–7) without and with acetylsalicylic acid (ASA) treatment.

(144±20.5 and 166±17.3 pg·ml⁻¹) or to the values at 60 min after the challenge (133±17.3 and 178±26.5 pg·ml⁻¹; p<0.05, p<0.01, respectively) (fig. 4).

**Catecholamines**

Plasma concentration of noradrenaline but not that of adrenaline increased significantly due to PAF-inhalation when measured at 20 min (p<0.01) (fig. 5) and then declined. This pattern remained unchanged after acetylsalicylic acid pretreatment (fig. 5).

**Thromboxane production by platelets**

Thromboxane B2 released from platelets during 30 min incubation at 37°C remained unchanged at 20 and 60 min after PAF inhalation when compared with the
prechallenge value (fig. 6). In the second study, acetylsalicylic acid pretreatment virtually abolished thromboxane production (fig. 6).

Platelet aggregation

Aggregability of platelets to ADP, PAF and adrenaline was similar whether measured in vitro before, 20 or 60 min after PAF-inhalation (fig. 7). Acetylsalicylic acid pretreatment decreased adrenaline-induced aggregation (p<0.005), but had no clear effects on the responses to ADP or PAF (fig. 7).

Discussion

The present data indicate that inhaled PAF causes secondary generation of LTB₄ and impairs tracheobronchial clearance in man. These phenomena may be
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important contributing factors to PAF-induced airways inflammation, and they are very reminiscent of exacerbations in allergic asthma. Surprisingly, pre-treatment with acetylsalicylic acid attenuated the acute PAF-induced obstruction, indicating the importance of cyclo-oxygenase products of arachidonic acid. But was ineffective on the other recorded changes in bronchial functions or blood pressure. Inhalation of PAF had no effects on aggregation or thromboxane production from platelets in vitro, indicating a very local, intrapulmonary response.

For the measurement of tracheobronchial clearance, we standardized a new system based on the administration of radioaerosol with an inhalation synchronized dosimeter technique, which enabled us to standardize the breathing pattern and minimizes loss of aerosol outside the respiratory tract [26, 29]. Previously, considerable variation in the clearance rates has been found even among healthy subjects [21, 33, 34]. Mucus transport is primarily dependent on the aerosol's initial deposition pattern, i.e. the more central (closer to the mouth) the aerosol is deposited, the faster is the clearance [19, 35]. On the other hand, the degree of aerosol penetration to lower airways is found to depend mainly on the inhalation flow rate [36]. The major factors for standardized aerosol deposition are considered to be quantitative aerosol generation and a controlled and determinable mode of inhalation [37]. With continuous aerosol delivery, intersubject coefficient of variation (CV) has been reported to be 42-43% and intrasubject CV 16-20% [38, 39] in healthy nonsmokers. In the present study, with the use of a dosimeter technique combined with controlled tidal breathing, there seems to be an improved reproducibility. Our data agree with the report by Del Donno et al. [40], who found intersubject CV 13% by using dosimeter technique and controlled deep breaths from functional residual capacity (FRC) followed by 3 s breath-holding.

PAF caused a pronounced impairment on mucus transport. Our findings confirm preliminary data from animal models, in which intratracheally but not intravenously administered PAF in the guinea-pig [24] and aerosolized PAF in the sheep [25] decreased tracheal mucus velocity. In the present study, the decline in mucus transport was more pronounced in smaller airways. This could be explained by the PAF-induced cough, which may have increased the clearance of large airways during the first part of the measurement. The PAF-induced impairment of tracheobronchial clearance may be due to a direct "ciliotoxic" effect or an increase in mucus viscosity and volume. Previous reports have shown that PAF increases tracheal mucus and fluid secretion in the ferret in vitro and in vivo [41] and in the pig in vitro [42]. In the guinea-pig, intravenously administered PAF increased the protein content of airway secretions, presumably by causing extravasation of plasma, but there was no increase in mucus secretion [43].

Theoretically, inhaled PAF might also decrease the mucociliary clearance by causing a nonspecific leak in airways. That view is strongly argued by previous animal studies. A specific PAF antagonist, WEB 2086, has been shown to prevent the PAF-induced decrease in tracheal mucus velocity in the sheep [25]. In addition, PAF (10^3 to 10^4 M) has been reported to decrease mean surface liquid velocity and ciliary beat frequency in sheep trachea in a dose-dependent fashion while having no effects on the rheological properties of mucus [44].

Another main finding of our study was the increase of plasma LTB4 following PAF-inhalation. PAF stimulates in vitro the synthesis of leukotrienes in various cell types, including neutrophils [45] and macrophages [46]. The enhanced synthesis has also been found in tissue samples taken from gastrointestinal tract of the rat after PAF-infusion [47]. LTB4 appears to be a major mediator of leukocyte activation [48], is chemotactic for neutrophils and eosinophils [10, 11] and induces adhesion of polymorphonuclear neutrophils (PMNs) to endothelial cells [49]. Thereby an induction of LTB4 secretion by intratracheal PAF might further enhance the PAF-induced (i.e. direct effect) accumulation of inflammatory cells in airways. In addition, the increased secretion of leukotrienes may also contribute to the slowing of the mucociliary transport, as indicated by the previous studies in the sheep [23] and in man [22].

The PAF-induced bronchial obstruction is suggested to be platelet dependent, because at least in two species of experimental animals, PAF elicits bronchoconstriction only if platelets are present [2, 50]. It has also been reported that in isolated human smooth muscle, platelets are required to induce bronchospasm [51]. On the other hand, the bronchial obstruction is not seen in the rat since PAF binding sites in platelets are absent in this species [52]. A plausible cyclo-oxygenase product to mediate the PAF-induced bronchospasm is platelet-derived thromboxane, which is a powerful bronchoconstrictor with a high potency approaching that of the sulphidopeptide leukotrienes [53]. Using a variety of agonists and antagonists, it has recently been shown that thromboxane shares the same receptor on airways smooth muscle with other prostaglandins which mediate constriction [54, 55]. One PAF antagonist, BN52063 has been shown to attenuate PAF-induced bronchoconstriction [56] as well as chlorpheniramine in canine trachealis in vivo [18] and in man [4].

In the present study, PAF caused a marked acute bronchial obstruction, which was attenuated by aspirin pretreatment. Our results are in accordance with a previous report by Anderson et al. [57], who found in the guinea-pig that acetylsalicylic acid, but not indomethacin, attenuated PAF-induced increases in intratracheal pressure. However, Smith et al. [4] found in man that indomethacin did not significantly inhibit PAF-induced bronchoconstriction, although the data presented from their study did show an attenuating tendency for acetylsalicylic acid. Furthermore, chlorpheniramine reduced the PAF-response. On the basis of the present knowledge, PAF induced bronchoconstriction seems to be the result of a cascade of mediators including histamine and cyclo-oxygenase metabolites of arachidonic acid. For instance LTB4, which was increased after
PAF-inhalation in the present study, is spasmogeneric for airway smooth muscle indirectly via stimulated biosynthesis of constrictor cyclo-oxygenase products [58].

One of the interesting properties of PAF is the ability to induce a nonselective increase in bronchial reactivity both in experimental animals and in man [1, 4-8]. The mechanisms underlying PAF-induced hyperreactivity are not clear, but it is of interest that this phenomenon is reducible by selective depletion of platelets in guinea-pigs [9] or neutrophils in the sheep [59], suggesting a link between the activation of inflammatory cells and the induction of bronchial hyperreactivity. Of the platelet-derived mediators, thromboxane A₂ has been implicated in the dog models of induced bronchial hyperresponsiveness [60] and established as a factor of bronchial responsiveness of asthma [61]. On the other hand, in guinea-pigs, acetylsalicylic acid and indomethacin have been reported to enhance airways response to histamine [57] after PAF-infusion.

Unfortunately, the PAF-induced bronchial hyperresponsiveness seems not to be easily repeatable in man, as recently stressed by Horre et al. [62]. Also in our study, only three out of seven subjects showed a bronchial hyperresponsiveness to methacholine after inhaled PAF. Acetylsalicylic acid did not abolish the response in these three subjects, which contradicts the role of thromboxane in the basic mechanism of PAF-induced hyperresponsiveness in man. In addition, our data indicate that the appearance of PAF-induced bronchial hyperresponsiveness is not directly related to slowing of the mucociliary escalator.

In all subjects, inhalation of PAF caused facial flushing, warmth and a decrease in blood pressure confirming the previous studies in animal models [14, 63] and in man [1]. Acetylsalicylic acid did not change these effects. Plasma noradrenaline concentration rose after inhalation of PAF reflecting increased sympathetic nervous activity. No marked changes were found in the plasma adrenaline level. This pattern of noradrenaline and adrenaline release is identical with that seen in bronchoconstriction induced by exercise, hyperventilation, propranolol, inhaled histamine or methacholine, reflecting increased sympathetic nervous activity. No marked changes were found in the plasma adrenaline level. This pattern of noradrenaline and adrenaline release is identical with that seen in bronchoconstriction induced by exercise, hyperventilation, propranolol, inhaled histamine or methacholine, which cause no major adrenomedullary response [64].

PAF is a potent activator of platelet functions, i.e. aggregation and secretion in vitro [65, 66]. Probably phosphatidylinositol turnover resulting in protein phosphorylation is the underlying messenger system, which controls PAF-induced activation of platelets [65]. In the present study, however, inhaled PAF did not change ADP-, PAF- or adrenaline-induced aggregation or thromboxane production from platelets in vitro. Even though intrapulmonary platelets may be responsible for many pulmonary effects of PAF [67], our data suggest that circulating platelets are not activated due to PAF inhalation.

In conclusion, in healthy normal volunteers we observed that PAF reduces mucociliary transport. Whether this is a direct effect of PAF on epithelial cell lining or secondary to activation of recruited inflammatory cells remains to be established. PAF-induced generation of leukotrienes may be a further contributing factor in the slowing of tracheobronchial clearance and in induction of sustained inflammatory response in the airways.

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References


RÉSUMÉ: Nous avons apprécié les effets du facteur activateur des plaquettes (PAF) inhalé sur la clearance trachéo-bronchique, la fonction pulmonaire et la pression sanguine, chez 7 volontaires sains non fumeurs. Après inhalation de 500 μg de PAF, la rétention du radio-aérosol dans les voies aériennes inférieures mesurée à la 4e heure est de 80% supérieure à celle de l'enregistrement de contrôle, et la clearance est réduite de 33% (p<0.005). L'acide acétylsalicylique (1000 mg) n'a pas d'effet sur le freinage de la clearance trachéo-bronchique induit par le PAF. L'inhalation de PAF provoque également une obstruction bronchique aiguë, en diminuant le VEMS de 16% (p<0.01), diminution fortement atténuée par l'acide acétylsalicylique. La chute de pression systolique et diastolique après PAF (p<0.01) n'est pas influencée par l'acide acétylsalicylique. Le taux de noradrénaline plasmatique, mais non celui d'adrénaline, augmente significativement après inhalation de PAF (p<0.01). Le leucotriène B4 (LTB4) est augmenté dans les échantillons sanguins prises 20 minutes après inhalation de PAF (avec et sans acide acétylsalicylique: moyennes 240 et 299 pg/ml respectivement) par comparaison aux valeurs de base (144 et 166 pg/ml) et aux valeurs obtenues 60 minutes après la provocation (133 et 178 pg/ml; p<0.05, p<0.01 respectivement). Seuls 3 des 7 sujets ont montré une hyperréactivité bronchique à la méthacholine, lors d'une mesure réalisée 24 h après l'inhalation de PAF. Nous concluons que l'inhalation de PAF réduit le transport mucociliaire chez l'homme. Le phénomène semble indépendant des produits du type cyclo-oxygénase dus à l'activation de l'acide arachidonique. L'on suggère toutefois que ces autoxidations contribuent à l'obstruction bronchique aiguë après inhalation de PAF. En outre, l'inhalation de PAF entraîne une augmentation transitoire du LTB4 plasmatique, qui pourrait favoriser par ailleurs l'inflammation des voies aériennes induite par le PAF.