Eur Respir J, 1995, 8, 624–631
DOI: 10.1183/09031936.95.08040624
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European Respiratory Journal
ISSN 0903 - 1936

The effect of intravenous phenylephrine on airway calibre in asthma

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ABSTRACT: **Tracheobronchial vasoconstriction and subsequent reduction of airway wall thickness due to the α_1-agonist methoxamine, might be responsible for prevention of exercise-induced asthma, and reduction of bronchial hyperresponsiveness to methacholine increase in exercise performance in patients with impaired left ventricular function. Since bronchial wall oedema plays an important role in asthma, we have now investigated the bronchial response to the intravenously administered α_1-agonist, phenylephrine, in asthma of various severity.**

Increasing noncumulative intravenous phenylephrine doses (100 to 600 μg) were injected in 18 asthmatic subjects (three groups: mild asthma, mild asthma with recent acute attack, severe obstructive asthma) and in 11 control subjects.

Changes in specific airways resistance (sRaw) on phenylephrine were linearly related to the dose administered in 16 out of 18 asthmatic subjects, and in only 3 out of 11 control subjects. In the asthmatic subjects, sRaw increased in 10 patients whose asthma was mild, or bronchial obstruction mild to moderate, and decreased in the remaining 8 asthmatic subjects with more severe disease or with a higher degree of bronchial obstruction. Changes in forced expiratory volume in one second (FEV_1) were consistent with those of sRaw. In the five asthmatic subjects who underwent the protocol twice, results were reproducible. There was no difference in the responses of heart rate between the three groups of asthmatic subjects.

It is likely that phenylephrine acts both *via* airway smooth muscle contraction, an effect which might predominate in mild asthma, and *via* mucosal vasoconstriction, which might overcome the effect on smooth muscle in more severe asthma with bronchial wall oedema. The potential role of a vasoconstrictor agent in asthma treatment deserves further investigation.

Eur Respir J., 1995, 8, 624–631.

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Keywords: α_1-adrenergic agonist
asthma
bronchial wall oedema
phenylephrine

Received: May 18 1994
Accepted after revision December 14 1994

JPC was supported by a scholarship of Ministère des Relations Extérieures, Paris, France.

The contribution of vascular factors to bronchial obstruction in asthma may be directly observed on fibreoptic bronchoscopy [1], and is indirectly documented by use of pharmacological manoeuvres.

Vasodilatation and oedema of the airways wall, in addition to contraction of airway smooth muscle, cause bronchial obstruction in asthma. Several factors contribute to vasodilatation and oedema in airway wall in asthma. Contraction of airway smooth muscle markedly reduces the diameter of the muscular layer, but causes little changes in the external bronchial diameter; thereby, causing distension of the submucosa with a prominent increase in the diameter of small blood and lymphatic vessels [2]. During asthma attacks, the marked fall of inspiratory intrathoracic pressure, with almost no increase in end-expiratory pressure [3], increases the load of the left ventricle [4], thus, facilitating pulmonary and bronchial oedema [5]. Many putative mediators involved in asthma (*e.g.* histamine, sulphidopeptide-leukotrienes and tachykinins) and pharmacological agents used in bronchial provocation tests (*e.g.* histamine and muscarinic agents) are potent vasodilator as well as bronchoconstrictor agents. Finally, clinically, vasodilatation of the tracheobronchial circulation is an important factor of exercise- and hyperventilation-induced asthma [6].

Acute administration of purely or predominantly α_1-adrenergic agonists, such as noradrenaline [7–9] methoxamine [10], or adrenaline [11–13], improve airways obstruction in severe asthma [7, 11–13] or in exercise-induced asthma [8–10]. This effect is best explained by vasoconstrictor-induced reduction of mucosal thickness [14] and plasma extravasation [15], thereby increasing bronchial calibre [16, 17].

However, in stable mild asthmatic subjects with normal or subnormal airway function [18–22], α_1-adrenergic agonists usually cause an acute and severe aggravation of airway obstruction, an effect attributed to the contractile effects of stimulation of α_1-adrenoceptors of airway smooth muscle and to α-adrenergic hypersensitivity [23]. Also, α_1-blocking agents, which are potent vasodilators

and relaxants of airway smooth muscle, prevent acute airway obstruction induced by methoxamine [24], histamine [25], exercise [26], and allergen [27] in asthma, although they have little, if any, beneficial effects on spontaneous asthma [28, 29].

In view of discrepant results regarding the effect of α_1-agonists in asthma, we undertook the present study to determine whether the effects of vasoconstrictor agents in asthma might depend on asthma severity and/or baseline bronchial obstruction. We have studied the effects of intravenous (*i.v.*) phenylephrine (PE), an α_1-adrenergic agonist and potent vasoconstrictor agent, on lung function and blood pressure in control subjects and three distinct groups of asthmatic subjects.

Subjects and methods

Subject

We studied 18 adult asthmatic patients and 11 control subjects (table 1). The diagnosis of asthma was based upon criteria of the American Thoracic Society (ATS) [30]. Five of the asthmatic subjects and four control subjects had a smoking history of <6 pack-years. None of the 29 subjects suffered from cardiovascular disease or high blood pressure. Eleven of the 18 asthmatic subjects were atopic, *i.e.* their skin tests to house dust mite or grass pollens were positive.

Among the 11 control subjects, 9 were healthy and 2 had radiographic sequelae of tuberculosis, although they did not complain of dyspnoea. Lung function of the control subjects was within normal limits (table 1). The two subjects with tuberculosis sequelae had baseline forced expiratory volume in one second (FEV_1) of 72 and 74% predicted [32], respectively.

Among the 18 asthmatic subjects, seven (Nos. 1–7) had mild asthma (<1 asthma attack per week) and were asymptomatic at the time of study with baseline FEV_1 ranging 67–107% predicted (Group 1). Five other subjects also had mild asthma, but had been symptomatic (wheezing and chest tightness, regressing spontaneously or after inhalation of salbutamol 100–300 μg) in the 24 h preceding the study (Group 2, Nos. 8–12). Their FEV_1 ranged 62–82% predicted. The remaining six patients had stable asthma with chronic airway obstruction

Table 1. – Clinical data, baseline lung function and effects of phenylephrine on specific airway resistance

Group Subj No.	Age yrs	Sex	Atopy	Smoking pack-yrs	Base FEV_1 % pred	Base sRaw % pred	Correlation	p-value	ΔsRaw	ΔsRaw rank
Asthmatic subjects										
Group 1										
1	22	M	-	0	101	65	0.83	†	35	9
2	19	F	+	1	76	86	0.89	*	66	11
3	20	M	+	0	107	66	0.99	*	192	18
4	24	F	+	0	105	102	0.99	*	99	12
5	31	M	+	5	93	130	0.98	*	108	13
6	36	M	+	0	84	115	-0.83	†	-40	7
7	21	M	-	0	67	102	-0.94	*	-38	8
Group 2										
8	23	M	+	0	82	223	-0.89	*	-87	5
9	33	M	-	0	62	249	-0.79	NS	-64	6
10	23	F	+	0	73	80	0.89	*	142	16
11	48	M	-	3	58	267	0.70	NS	160	17
12	55	M	-	0	63	63	0.89	*	40	10
Group 3										
13	48	F	+	0	52	373	0.98	*	115	14
14	35	M	-	0	31	680	-0.92	*	-317	3
15	37	F	+	0	33	792	-0.83	†	-453	1
16	34	M	-	6	32	810	-0.99	*	-340	2
17	36	F	+	0	42	878	-0.93	*	-268	4
18	28	M	+	5	68	248	0.96	*	124	15
Control subjects										
19	23	M		2	103	84	-0.60	NS	-18	
20	24	F		0	96	61	0.73	NS	10	
21	23	F		3	98	69	0.98	*	44	
22	34	M		0	135	69	0.61	NS	9	
23	19	M		1	72	70	0.84	†	65	
24	23	M		0	89	46	-0.89	*	-10	
25	23	F		0	81	81	0.40	NS	1	
26	22	F		0	103	70	-0.03	NS	3	
27	25	F		0	109	100	0.56	NS	2	
28	24	M		0	106	133	0.75	NS	100	
29	30	M		5	74	124	-0.35	NS	-32	

M: male; F: female; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted; Base: baseline; sRaw; specific airway resistance; correlation: linear correlation of log sRaw as a function of the dose of PE infused (r=correlation coefficient). †: 0.10>p>0.05; *: p<0.05; NS: nonsignificant. ΔsRaw; sRaw change, *i.e.* maximal change in sRaw on PE in % pred (maximal sRaw value on PE in % pred - baseline sRaw in % pred). ΔsRaw rank is indicated in asthmatics only. Predicted values for sRaw from [31] and for FEV_1 from [32].

(31≤ FEV_1 ≤68% predicted) and complained of daily symptoms (Group 3, Nos. 13–18); 4 of these 6 patients were treated by oral prednisolone on a regular basis. All bronchodilator medications were interrupted 12 h before the study, except for long-acting methyxanthines which were withheld for 24 h (No. 16). Asthma history and treatment at the time of the study are summarized in table 2.

All subjects were fully informed of the design and potential hazards of the study and gave an oral informed consent.

Study design

In all studies, PE (in phosphate buffer, pH 7.4) was infused in a superficial arm vein through an indwelling catheter.

In a preliminary study with four asthmatic and two control subjects, we studied the time-course of changes in airway resistance and systemic circulation caused by *i.v.* infusion of 600 μg of PE over 3 min. Changes of specific airway resistance (sRaw) and arterial systolic blood pressure (SBP) were maximal at 2 min infusion time, and returned to baseline within 7–9 min after cessation of the infusion (within 12% of baseline value in all subjects studied).

Therefore, in the main study, the aim of which was to establish the noncumulative dose response curve of sRaw as a function of increasing doses of *i.v.* PE, infusions of increasing concentrations of 100, 200, 400 and 600 μg of PE were separated by a 10 min interval. Specific airway resistance, arterial SBP and heart rate (HR) were measured before infusion of each concentration and at 2 min infusion time; sRaw was measured immediately after, and then the infusion was discontinued, and infusion of the next concentration was started 10 min later.

After a one hour rest, 10 asthmatic patients (Nos. 2, 3, 5 and 11–17) and five control subjects (Nos. 19, 22, 24, 25 and 27) took part in the second part of the main study. The effect on FEV_1 of the highest PE dose in each subject was studied.

In a subgroup of five asthmatic subjects (Nos. 6, 8, 12, 14 and 17), the study was repeated on another day at the same time of day, in order to test the reproducibility of the effects of *i.v.* PE on sRaw.

All subjects felt restless and complained of a sensation of heat in the chest with the highest dose of PE used. In five of the asthmatic subjects and in one control subject during the study and in two asthmatic subjects during the reproducibility study, these side-effects occurred with the 400 μg dose, and the 600 μg dose was not injected. The mean rise of arterial blood pressure with the highest dose of PE used was 4.6±1.6 mmHg (mean±SD).

Drug

Phenylephrine is an α_1-agonist, with a very close potency and activity to that of methoxamine. However, it is destroyed by catechol-O-methyltransferase. As an α_1- agonist, its predominant activity is on vascular smooth muscle, causing vasoconstriction of systemic vessels and rise in BPsys in humans at low doses. Other effects on human tissues, such as bronchial epithelium [33], might be observed at much higher doses. In the present study, PE has been used in the dose range which elicits dose-dependent systolic effect in humans (100–600 μg). $Alpha_1$-agonist activity of PE is similar to that of epinephrine, with a small β_2-agonist activity, 0.3% that of epinephrine [34].

Technical details

FEV_1 was measured with a heated pneumotachograph (Fleisch No. 4) and the best of three attempts was selected.

Thoracic gas volume (TGV) and airway resistance (Raw) were measured with a pressure-corrected flow bodyplethysmograph (Fenyves and Gut, Bodystar, Basel, CH). Airway resistance was measured with the panting technique at functional residual capacity and expressed as specific airway resistance (sRaw=Raw·TGV). Predicted value for TGV and sRaw were from MATTHYS and RHULE [31].

Statistical analysis

In order to establish the dose-response curve of sRaw as a function of the dose of PE, we expressed sRaw as log sRaw and calculated the linear regression log sRaw=a+b (dose) for all data points in each individual. Rank order of maximal sRaw changes in the three groups of patients were compared using the nonparametric Kruskal-Wallis test. Statistical significance was accepted as $p<0.05$.

Table 2. – Characteristics of asthma in the three groups of patients

	Group 1 n=7	Group 2 n=5	Group 3 n=6
Duration of the disease yrs+	5.2±0.6	6.3±0.4	15.2±4.3*
Hospitalizations in the 5 last yrs+ number per individual	0	0.3±0.05	3.1±0.4*
Drug consumption number of patients per group			
Regular consumption	2/7	3/5	6/6
inhaled steroids	2/7	2/5	6/6
$beta_2$-agonists	0	1/5	4/6
oral steroids	0	0	3/6
anti-allergics	1/7	2/5	3/6
Occasional consumption $beta_2$-agonists	7/7	5/5	6/6

+: Data are presented as mean ±SEM. *: t-test, means in group 3 significantly different from groups 1 and 2.

Results

Clinical and baseline functional data are listed in tables 1 and 2. Individual dose-response curves of sRaw as a function of increasing doses of PE are plotted in figure 1.

Effect of PE on bronchial obstruction

We observed two patterns of directional change of sRaw. Specific airway resistance increased in 10 asthmatic subjects and decreased in the remaining eight. Conversely, sRaw increased in two and decreased in one of three control subjects, in whom changes in sRaw were dose-dependent. In the remaining control subjects, the changes in sRaw were minor (table 1 and figure 1). Maximal sRaw change (maximal sRaw value on PE in % predicted - baseline sRaw in % predicted) was between 35 and 453% predicted in the 18 asthmatic subjects, whereas it was between 1 and 100% predicted in the 11 control subjects.

Ten minutes after the end of the last (400 or 600 μg) infusion of PE, sRaw had returned to baseline value in all subjects, which confirmed the short-term effect of the drug on bronchial tone.

We found dose-related effects of PE on sRaw in 13 of the 18 asthmatic patients. Log sRaw was a linear function of the dose of PE in 13 subjects (Nos. 2–5, 7–8, 10, 12–14 and 16–18; $r \leq 0.89$; $p < 0.05$). In 3 other asthmatic patients (subjects Nos. 1, 6 and 15) $r\ 0.83 > r < 0.89$; with $0.05 < p < 0.10$. Conversely, a linear relationship existed in only two and, possibly, a third of the 11 control subjects (table 1).

Changes of sRaw between days in the five patients who received PE infusions on two different occasions (days 1 and 2) were directionally similar on both instances (fig. 2). In addition, the magnitude of PE-induced changes of sRaw was strongly correlated with baseline sRaw on each study. In subjects Nos. 8, 12 and 14, whose baseline sRaw was similar on both study days, the difference between variation of sRaw on both days was small, which was not the case for subjects 6 and 17. In subjects Nos. 6 and 17 whose baseline sRaw varied between day 1 and day 2, sRaw decrease on PE was greater on the day when they had the greater baseline sRaw (fig. 2).

In the 10 asthmatic subjects who performed forced expiratory manoeuvres, directional changes in FEV_1 were consistent with those in sRaw. FEV_1 increased in the patients in whom sRaw decreased and vice versa (fig. 3). Changes in FEV_1 were small in the five control subjects, but were consistent with those in sRaw.

Factors influencing the response to PE in asthmatics

Disease severity. Maximal sRaw changes were ranked from the smallest (subject No. 14=-453%, rank 1) to the greatest (subject No. 3=+192%, rank 18) (table 1). When the three groups were compared, there was no significant difference between the repartition of the rank order of the values. However, when Group 3 was compared

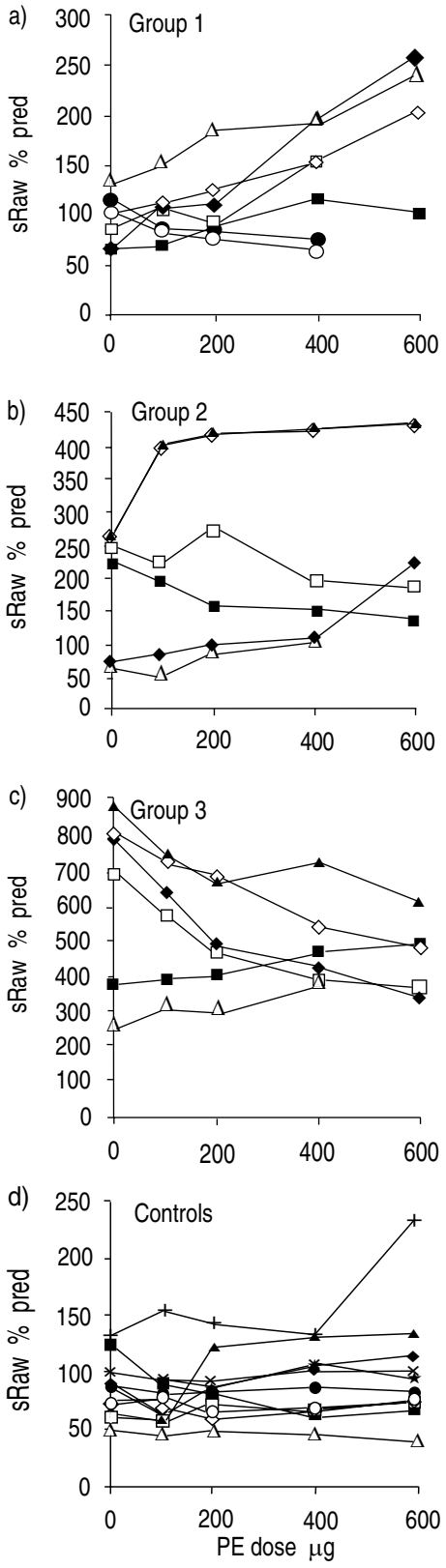

Fig. 1. – Baseline values and dose-response curves of sRaw as a function of increasing doses of PE (100, 200, 400 and 600 μg) in asthmatic patients and 11 control subjects. a) mild asthma (n=7) Group 1; b) mild asthma with recent asthma attack (n=5) Group 2; c) chronic asthma (n=6) Group 3; d) control subjects. Symbols indicate individual subjects. sRaw: specific airways resistance; PE: phenylephrine; % pred: percentage of predicted.

to the sum of Group 1 + Group 2, we found that there was a trend for ranks to be smaller in Group 3 (p=0.092), indicating that in chronic asthma with severe obstruction the change in sRaw on PE more frequently has a large negative value.

Initial airway obstruction. For the entire group of 18 asthmatics (table 1), PE-induced changes in sRaw were a function of baseline airway obstruction. Indeed, the maximal post-PE sRaw change from baseline was negatively correlated to baseline sRaw (r=-0.85; ΔsRaw=a (initial sRaw)+b=-0.530 initial sRaw+134) and positively correlated to FEV_1 (r=0.73; ΔsRaw=5.35 initial FEV_1-388). Patients with the more severe initial obstructive syndrome (Nos. 14–17) also had the maximal decrease in sRaw on PE.

Atopy and airway inflammation. Atopic status had no influence on bronchial response to PE, since among the seven nonatopic subjects, sRaw increased in three and decreased in four, and among the 11 atopic subjects, sRaw increased in seven and decreased in four.

In patients with severe disease (Group 3), changes in sRaw on PE more frequently had large negative values. These patients also had a higher level of anti-inflammatory drug consumption (six out of six were on inhaled steroids, and three out of six on oral steroids).

Steroids. Steroids probably had no pharmacological influence on the bronchial response to PE. In the three patients in whom PE-induced changes in sRaw were significantly correlated to PE dose, and who were receiving prednisolone on a daily basis (Nos. 13–15), sRaw decreased (Nos. 14 and 15, baseline sRaw 680 and 792% pred, respectively) or increased (No. 13). Specific airway resistance also decreased in the patient with a similar degree of baseline airway obstruction who was not receiving steroids at the time of the study (No. 16, baseline sRaw 810% pred). Among subjects receiving inhaled steroids (Nos. 2, 7 and 11–18), sRaw decreased in subjects Nos. 7 and 14–17, but increased in subjects Nos. 2, 11–13 and 18.

Vagal responsiveness. In order to determine the individual vagal response to the rise in systolic arterial pressure due to PE infusion, we correlated PE-induced increase in SBP (mmHg) and decrease in HR (beats·min^{-1}). HR was negatively correlated to BP both in control (HR= -4.3 SBP +128.8; r=-0.649) and asthmatic subjects, whether sRaw increased (HR=-4.0 SBP +124.9; r=0.669) or decreased on PE (HR=-3.3 SBP +112.4; r=-0.570).

Discussion

The main result of our study is that the predominantly α_1-adrenergic agonist, phenylephrine, causes either an increase or a decrease of airway resistance in asthmatic subjects, with dose-dependent improvement of bronchial obstruction being more common in severe asthma and aggravation being more common in mild asthma. Our data confirm that bronchial hyperresponsiveness to α-adrenergic agonists [23] is not a uniform finding in asthma. It is noteworthy that maximal changes in sRaw were ≤100% in all control subjects and in 7 of the 12 subjects with mild asthma. This observation indicates that α_1-adrenergic hyperresponsiveness is not a constant finding in asthma, since the reproducibility of repeated measurements of Raw is within±100%. The dose-dependent rise in sRaw was moderate in four subjects with

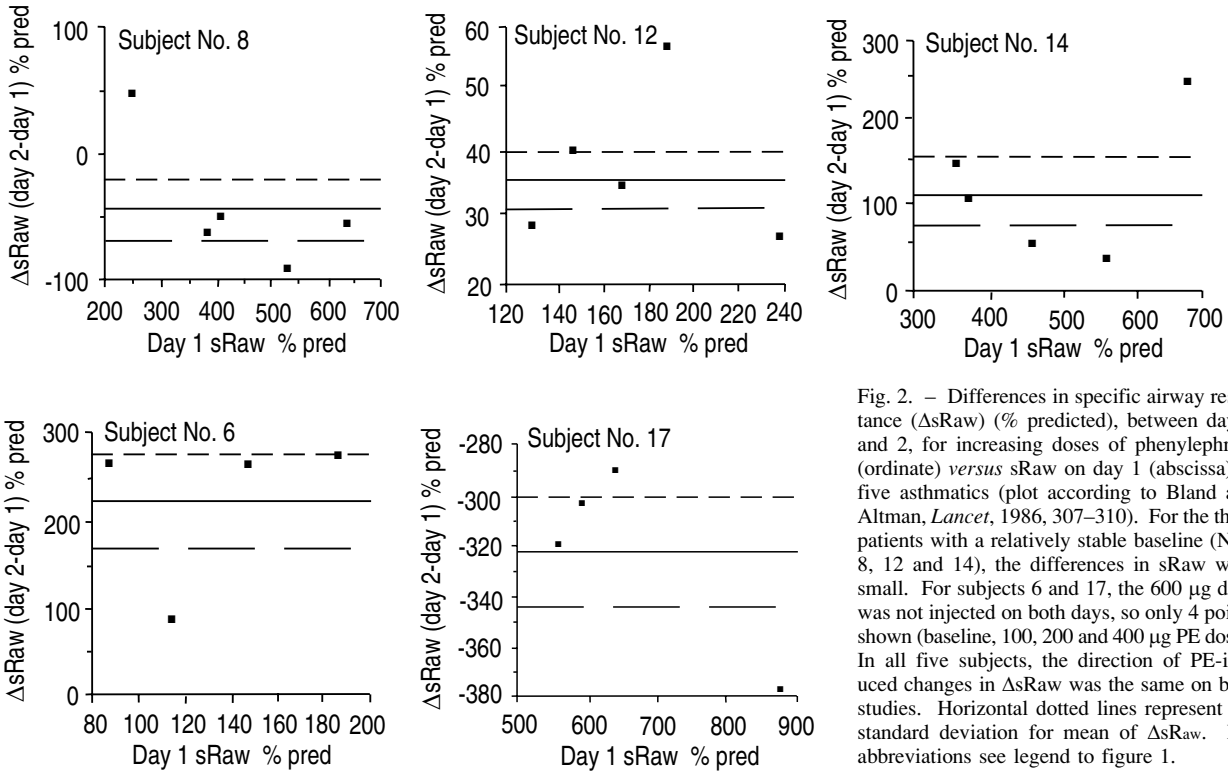

Fig. 2. – Differences in specific airway resistance (ΔsRaw) (% predicted), between day 1 and 2, for increasing doses of phenylephrine (ordinate) *versus* sRaw on day 1 (abscissa) in five asthmatics (plot according to Bland and Altman, *Lancet*, 1986, 307–310). For the three patients with a relatively stable baseline (Nos. 8, 12 and 14), the differences in sRaw were small. For subjects 6 and 17, the 600 μg dose was not injected on both days, so only 4 points shown (baseline, 100, 200 and 400 μg PE doses. In all five subjects, the direction of PE-induced changes in ΔsRaw was the same on both studies. Horizontal dotted lines represent the standard deviation for mean of ΔsR_{aw}. For abbreviations see legend to figure 1.

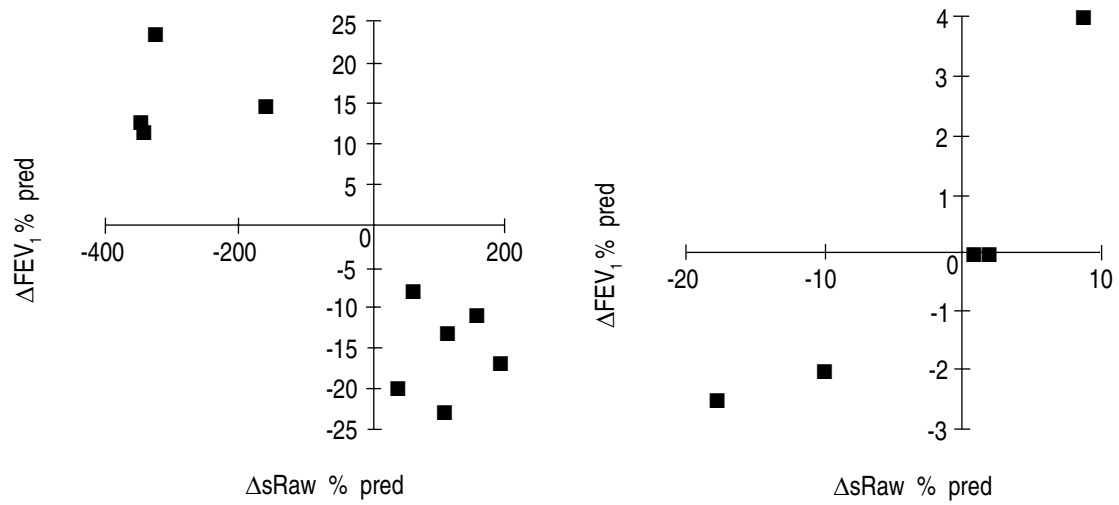

Fig. 3. – Correlation between maximal variations of FEV_1 (ΔFEV_1) and maximal variations of sRaw (ΔsRaw) on PE in: a) 10 asthmatic subjects and b) 5 control subjects. FEV_1: forced expiratory volume in one second. For further abbreviations see legend to figure 1.

mild asthma (Nos. 3, 5, 10 and 11) and in two with severe asthma (Nos. 13 and 18). Conversely, in the remaining four subjects with severe asthma, the maximal PE-induced fall in sRaw was proportionately greater (range -268 to -453%).

Our results are at variance with those of THOMSON *et al*. [35] who found no effects on the bronchi of inhaled PE. Indeed, differential effects on airway patency of inhaled *versus i.v.* or ingested medications is well-documented. Since local concentrations of PE in the work of THOMSON *et al*. [35] and in our own work are unknown, these results are difficult to interpret. However, the lack of effect of inhaled PE in asthmatic subjects might be explained by its inactivation by mucosal catechol-O-methyltransferase [34].

Our most intriguing finding was that *i.v.* PE preferentially caused an increase in airways obstruction in patients with mild sporadic asthma and a decrease in patients with chronic severe asthma. One hypothesis was that this might be due to differences of the cholinergic control of airway smooth muscle tone. However, vagally mediated slowing of heart rate in response to PE-induced rise in blood pressure was similar across the groups of asthmatic subjects studied, irrespective of asthma severity and directional changes in sRaw caused by PE infusion, suggesting that vagal reflexes and/or vagal tone were more or less similar in all groups. Another hypothesis was that the PE-induced, dose-dependent changes in airways obstruction in asthmatic subjects, contrasting with the lack of consistent or significant effects in control subjects, might be ascribed to generalized α-adrenergic hyperresponsivness in the former group [23]. If this had been the case, we anticipated a marked aggravation of airways obstruction on PE in most, if not all, the asthmatic subjects. That airways obstruction improved on PE in a large proportion of them made α-adrenergic hyperresponsiveness an unlikely explanation of our findings.

A third hypothesis was that of dual pharmacological effects of PE on airway smooth muscle. Phenylephrine is a predominant α_1-agonist and a weak β_2-agonist, and, as such, could cause both contraction and relaxation of airway smooth muscle through stimulation of α- or β- adrenergic receptors of airway smooth muscle, respectively. The α-adrenergic effect of epinephrine and phenylephrine occurs at similar dose. At such doses, the β_2-adrenergic effect of phenylephrine is only 0.3% of that of epinephrine [34], and is thus likely to be very small or absent in the present study. Furthermore, it is well-established through studies of functional antagonism, that the more a bronchus is contracted, the higher are the doses of β_2-agonists to reverse bronchoconstriction [36]. It is, therefore, unlikely that the β_2-adrenergic effect could be revealed by severe bronchoconstriction, when it is absent in subjects with no or mild obstruction.

Phenylephrine is not only a contractile agonist of airway smooth muscle, it is also a potent vasoconstrictor agent. It has been shown in animal experiments that PE causes vasoconstriction of the tracheobronchial circulation and reduces mucosal thickness of the trachea [37, 38], thus increasing bronchial calibre [16, 38]. We submit that the differential effects of PE on airway patency can be explained by a predominant contractile effect on airway smooth muscle in mild asthma, and a predominant vasoconstrictor effect in perennial asthma. The role of an imbalance between vasomotor and true bronchomotor effects has already been suggested as an explanation for the increase or decrease of bronchial obstruction caused by prostacyclin in individual asthmatic subjects [39]. It is now generally accepted that chronic inflammation of the airways plays a key role in the occurrence and severity of asthma symptoms in susceptible individuals [40–42], and that vascular congestion and oedema are prominent features of airways inflammation in severe asthma [43]. Our present finding, that the vasoconstrictor agent, phenylephrine, reduced airways obstruction in a dose-dependent manner in a subgroup of asthmatic patients, provided circumstantial evidence that vascular congestion and oedema were major factors of airways obstruction in such patients. Conversely, PE caused an increase in airways resistance in mild, sporadic asthma, suggesting that vascular factors were minimal and

airway smooth muscle contraction predominant in such patients. In so far as asthma severity relates to airway inflammation, it may be suggested that the presence of inflammation might be predictive of possible improvement of airway function on PE.

In summary, our finding that PE tended to reduce airways obstruction in severe asthma and increase it in sporadic asthma suggests that vascular congestion and oedema were relatively more important in the former than the latter.

Acknowledgements: The authors wish to thank J. Hogg and L. Laitinen for helpful comments on the manuscript, and L.M. Capdevielle, I. Broudic, M. Letrait, J.P. Tresca and E. Millon for preparation of the manuscript.

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