Effect of prostaglandin F₂ alpha on lung mechanics in extrinsic asthma

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Summary

In normal subjects inhalation of PGF₂α produced two qualitatively different airways responses. In five subjects there was a significant fall in SG_{aw} without change in maximum expiratory flow rates, FEV₁ or CV. In contrast, the remaining three subjects showed a significant fall in flow rates and FEV₁ together with a significant increase in CV while their SG_{aw} was unaffected. PGF₂α inhalation in six asthmatic patients produced a significant fall in maximum expiratory flow rates, FEV₁ and SG_{aw}. These patients showed a dual response with individual variability in magnitudes of changes. It is suggested that differing responses may reflect the balance between the sympathetic and parasympathetic nervous controls of the airways, and that the diminished β-receptor activity in asthmatic patients may account for heightened bronchoconstrictor response to inhaled PGF₂α both centrally and peripherally in the bronchial tree.

Introduction

Prostaglandin F₂α (PGF₂α), a potent bronchoconstrictor, is released from guinea-pig and rat lungs during anaphylactic reaction and by various chemical and mechanical stimuli (Edmonds, Berry and Wyllie, 1969; Piper and Vane, 1969). This local release of PGF₂α together with the exquisite sensitivity of asthmatic patients has led Mathé *et al.* (1973) to postulate that endogenous, locally formed PGF₂α may play an important part in the pathogenesis of bronchial asthma. This hypothesis is further supported by the report of Green, Hedqvist and Svanborg (1974) who have shown an eight-fold rise in the plasma levels of PGF₂α metabolites in asthmatic patients following allergen challenge. In addition, local release of PGF₂α has been suggested as the mechanism of exercise induced asthma (Paterson, Ahmad and Lefcoe, 1973).

Despite the importance of PGF₂α in asthma, most previous studies of its effect in the human lung have been limited to the measurement of FEV₁ and airways conductance (Mathé *et al.*, 1973; Patel, 1975). In order to obtain additional information on the

effect of PGF₂α on lung mechanics, dynamic and static lung volumes, specific airways conductance and closing volume were measured before and after PGF₂α inhalation in eight normal subjects and seven patients with extrinsic asthma.

Patients and methods

Seven patients aged between 15 and 30 years with extrinsic asthma and reversible airways obstruction were studied. All patients had positive prick tests to inhalant allergens and a blood eosinophilia of over 500 cells/mm³. Simple bronchodilator drugs such as salbutamol and isoproterenol were stopped for at least 24 hr before the tests.

The control group consisted of eight volunteers aged between 18 and 30 years. They had no respiratory disease and there was no personal or family history of bronchial asthma or atopic disease. Five subjects in this group (1, 2, 5, 7 and 8) were light smokers. Informed consent was obtained in each case.

The static lung volumes were measured by helium dilution method in a closed circuit using Godart Pulmotest. Forced expiratory volume in 1 sec (FEV₁), maximum mid-expiratory flow rate (MMFR) and vital capacity (VC) were recorded on a Godart Expirograph. All lung volumes were corrected to body temperature, pressure, saturated with water vapour (BTPS).

Airways resistance (R_{aw}) was measured with a constant volume body plethysmograph (Dubois, Bothelho and Comroe, 1956) at a flow rate of 0.5 l/sec and a panting frequency of 2 Hz. Conductance, the reciprocal of R_{aw}, was divided by the thoracic gas volume at which R_{aw} was measured to give specific airways conductance (SG_{aw}). The mean of four recordings was calculated to give SG_{aw} for the event.

Closing volume (CV) was measured by a single breath nitrogen test as modified by Anthonisen *et al.* (1969). The equipment circuit and procedure has been described previously by Buist and Ross (1973). Both the inspiratory and expiratory flow rates were kept under 0.5 l/sec by close observation of the rate of movement of the pen recording the volume trace on spirometer chart. Throughout the expiration, gas

TABLE 1. Lung function changes in response to inhaled $\text{PGF}_{2\alpha}$ in eight normal subjects

No.	Age	Sex	FEV ₁ (l)		VC (l)		MMFR (l/sec)		SG _{aw} (cm H ₂ O ⁻¹ /sec)		RV (l)		CV/VC%		CC/TLC%	
			B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	30	M	4.71	4.88	6.66	6.68	3.60	4.31	0.265	0.203	1.89	1.53	6.7	8.8	27.3	25.8
2*	35	F	2.89	2.73	4.24	3.98	1.77	1.81	0.211	0.143	1.16	1.55	4.9	8.9	25.3	34.5
3	18	F	3.64	3.74	4.08	4.00	4.08	4.44	0.234	0.132	0.84	0.96	4.8	4.7	21.0	23.1
4*	27	F	3.33	3.06	4.60	4.44	2.30	2.16	0.211	0.113	1.21	1.31	13.0	10.8	31.1	31.5
5*	18	M	4.88	4.72	5.71	5.68	5.72	5.37	0.279	0.152	1.66	1.40	8.2	7.7	28.9	26.0
6*	24	M	5.05	4.59	5.66	5.34	6.29	5.34	0.248	0.258	1.08	0.97	5.3	14.0	20.5	27.2
7*	26	M	3.22	3.01	4.23	4.18	3.25	2.32	0.166	0.149	1.66	1.83	4.6	11.1	31.5	38.1
8	28	M	4.36	3.97	5.65	5.70	3.90	3.56	0.138	0.118	1.80	2.19	4.7	11.8	27.7	36.3
Mean			4.01	3.84	5.10	5.00	3.86	3.66	0.219	0.158	1.46	1.47	6.5	9.7	26.7	30.3
s.e. mean			0.30	0.30	0.33	0.30	0.54	0.45	0.017	0.017	0.11	0.14	1.0	1.00	1.5	2.0
P			<0.05		N.S.		N.S.		<0.025		N.S.		<0.05		=0.05	

* Cigarette smokers; N.S., not significant; B, before $\text{PGF}_{2\alpha}$ inhalation; A, after $\text{PGF}_{2\alpha}$ inhalation.

TABLE 2. Lung function changes in response to inhaled $\text{PGF}_{2\alpha}$ in seven patients with bronchial asthma

No.	Age	Sex	FEV ₁ (l)		VC (l)		MMFR (l/sec)		SG _{aw} (cm H ₂ O ⁻¹ /sec)		RV (l)	
			B	A	B	A	B	A	B	A	B	A
9	24	M	4.64	4.64	6.00	5.98	3.87	4.12	0.167	0.087	1.25	1.63
10	28	M	2.05	1.43	5.21	3.61	0.83	0.40	0.084	0.033	2.64	3.32
11	15	M	3.29	2.80	4.62	3.97	2.25	1.69	0.174	0.056	1.46	1.95
12	22	M	2.05	1.98	3.33	3.16	1.11	1.17	0.051	0.035	1.67	1.87
13	23	F	4.09	3.21	5.89	5.01	2.80	2.00	0.114	0.033	1.65	1.89
14	30	M	3.27	3.11	5.09	4.97	2.55	1.99	0.174	0.054	2.27	2.38
15	29	M	3.32	1.51	6.30	4.28	1.54	0.61	0.102	0.035	2.32	4.82
Mean			3.24	2.67	5.21	4.42	2.13	1.71	0.124	0.048	1.89	2.59
s.e. mean			0.36	0.42	0.38	0.36	0.40	0.46	0.018	0.007	0.19	0.42
P			<0.05		<0.05		<0.05		<0.001		<0.05	

B, Before $\text{PGF}_{2\alpha}$ inhalation; A, after $\text{PGF}_{2\alpha}$ inhalation.

was sampled at the mouth and nitrogen concentration was estimated using a nitrogen meter (Godart Nitrograph). The volume change was recorded using a potentiometer connected to the spirometer pulley. The nitrogen concentration in the expired gas and the VC were recorded on Y and X axis respectively of an X-Y plotter. The volume at which the nitrogen concentration rose sharply from the alveolar plateau (or Phase III) has been termed the closing volume (or Phase IV) and is expressed as the fraction of VC. The term closing capacity (CC) is used for the sum of CV and RV and is expressed as the fraction of total lung capacity (TLC).

Drugs

A sterile stock solution of $\text{PGF}_{2\alpha}$ (as a tromethamine salt), 5 mg/ml, was diluted with normal saline to give a final concentration of 50 $\mu\text{g}/\text{ml}$.

Procedure

After measuring static lung volumes, FEV₁, MMFR, SG_{aw} and CV, each subject inhaled 0.5 ml of $\text{PGF}_{2\alpha}$ solution through a Wright's nebulizer

using compressed air at a flow rate of 8 l/min. The measurements were repeated 5 min after inhalation. The whole procedure in each subject took 30 min to carry out. The test procedure was similar in asthmatic patients; however, satisfactory CV tracings could not be obtained in these patients because of marked bronchoconstrictor response to $\text{PGF}_{2\alpha}$.

Results

$\text{PGF}_{2\alpha}$ inhalation produced coughing and retrosternal tightness in five normal subjects (1-5) whereas the remaining three subjects (6-8) complained of dyspnoea and wheezing. In contrast, all patients with asthma developed more marked and prolonged bronchoconstrictor response following $\text{PGF}_{2\alpha}$ inhalation.

Lung function changes before and after $\text{PGF}_{2\alpha}$ inhalation in normal subjects are given in Tables 1 and 2. Two qualitatively different responses could be distinguished in these subjects depending on the symptoms. In the five subjects with coughing and retrosternal tightness there was a highly significant fall in SG_{aw}, 38%, ($P < 0.001$) whereas FEV₁,

TABLE 3. Lung function changes depending on symptoms following PGF₂α inhalation in normal subjects

	ΔFEV ₁	ΔVC	ΔMMFR	ΔSG _{aw}	ΔRV	ΔCV/VC%	ΔCC/TLC%
Subjects (1-5) with retrosternal tightness and coughing	{ -0.06 (0.08) -1.5% N.S.	{ -0.10 (0.05) -2.0% N.S.	{ -0.02 (0.20) -1.0% N.S.	{ -0.091 (0.012) -38.0% <0.001	{ -0.09 (0.15) +6.6% N.S.	{ +0.67 (1.07) +8.9% N.S.	{ +1.19 (2.19) +4.5% N.S.
<i>P</i>							
Subjects (6-8) with wheezing	{ -0.35 (0.07) -8.3% <0.01	{ -0.11 (0.11) -2.1% N.S.	{ -0.67 (0.17) -15.0% <0.025	{ -0.009 (0.009) -4.8% N.S.	{ +0.17 0.11 +11.2 N.S.	{ +7.40 (0.50) +152.0% <0.01	{ +7.32 0.63 +27.6% <0.01
<i>P</i>							

N.S. = not significant; values in parentheses = 1 s.e. mean; Δ = change.

MMFR and CV/TLC% were unaffected. The second group of subjects (6-8) showed a significant fall in FEV₁, MMFR, together with a significant increase in both CV/VC% and CC/TLC%. The mean fall in FEV₁ and MMFR was 8.3% ($P < 0.01$) and 15% ($P < 0.025$) respectively; and the mean CV/VC% and CC/TLC% increased by 152% ($P < 0.01$) and 27.6% ($P < 0.01$) respectively from the baseline values. However, PGF₂α did not cause a significant change in the mean SG_{aw} in these subjects (Table 3). These differing airways responses did not relate to the smoking habits of the subjects, and time-course experiments in four of these subjects failed to show any relationship to the duration of PGF₂α effect on the bronchial tree.

PGF₂α inhalation in all asthmatic patients but one (9) produced a marked fall in FEV₁, MMFR and SG_{aw} with a significant increase in RV (Table 2). The mean fall in FEV₁, MMFR and SG_{aw} was 17.5% ($P < 0.05$), 19.7% ($P < 0.05$) and 62% ($P < 0.001$) respectively. The mean RV increased by 37% ($P < 0.05$) after PGF₂α inhalation. Apart from one patient (9) who showed a conductance response, all other patients showed a dual response with individual variability in magnitudes of changes.

Discussion

PGF₂α inhalation produced two qualitative different airways responses in normal subjects. Five subjects developed a significant decrease in airways conductance (conductance response) in the absence of flow rate or FEV₁ changes, whereas the remaining three subjects showed a significant reduction in FEV₁ and MMFR (flow rate response) without a change in SG_{aw}. Further, subjects showing predominantly a flow rate response had a significant increase in their CV whereas the subjects with conductance response did not. In contrast, patients with asthma developed a more marked and prolonged bronchoconstriction after PGF₂α inhalation, and the majority of these patients showed a dual response with fall in MMFR, FEV₁ and SG_{aw}. Although satisfactory CV measurements were not possible in asthmatic patients, a significant increase in their RV

following PGF₂α inhalation would suggest that constriction and closure of the peripheral airways did occur in these patients leading to air trapping. These observations in normal subjects are in accord with similar pulmonary responses reported by Bouhuys *et al.* (1970) in cotton workers and healthy subjects following exposure to hemp dust.

The subjective symptoms following PGF₂α inhalation in normal subjects related to the type of airways responses recorded. Subjects who developed coughing and retrosternal discomfort had a conductance response whereas those with breathlessness and wheeze had a flow rate response. However, the type of response did not relate to smoking habits and time course experiments failed to show any relationship to the duration of PGF₂α effect on the bronchial tree. Thus, it seems likely that flow rate and conductance responses reflect a difference in responses between individuals.

It is generally accepted that maximum expiratory flow rates and FEV₁ are predominantly determined by peripheral airways obstruction which contribute little to the total airways resistance (Mead *et al.*, 1967; Macklem, 1971).

In contrast, airways resistance assesses airflow obstruction in central airways, there being little contribution from the peripheral airways to total resistance. Thus, conductance-response would seem to reflect PGF₂α-induced smooth muscle contraction in relatively large airways whereas flow rate response reflects smooth muscle contraction in the peripheral airways. This hypothesis is further supported by observation of a significant increase in the CV in the flow-rate responders, suggesting airways closure and air trapping.

Bouhuys *et al.* (1970) have postulated that individual variations in airways response to histamine or hemp dust is principally determined by variations of sympathetic tone of the airways. According to this hypothesis, a subject with flow rate response may have relatively few sympathetic fibres in peripheral airways so that the β-adrenergic activity might be insufficient to counteract the bronchoconstrictive effect of histamine or hemp dust in

these airways. Conversely, in a subject with conductance response, the sympathetic distribution might be predominantly to the smaller airways. Similarly in dogs, vagal stimulation has been shown to cause bronchoconstriction either centrally or peripherally (Bates, Macklem and Christie, 1971). Reed (1974) has suggested that bronchomotor tone in man is dependent on the balance between the cholinergic and sympathetic divisions of the autonomic nervous system. The observations in man and in dog suggest that the autonomic balance between the sympathetic and parasympathetic system may vary in the different parts of bronchial tree and hence account for differing airways response to histamine, hemp dust, $\text{PGF}_2\alpha$ or vagal stimulation. It is now well recognized that patients with asthma show a diminished β -receptor response to catecholamines (Cookson and Reed, 1963; Middleton and Finke, 1968; Alston, Patel and Kerr, 1974). Hence, a diminished β -receptor function in both the central and peripheral airways in asthmatic patients would explain the marked bronchoconstrictor effect of $\text{PGF}_2\alpha$ at both these sites. In addition, the diminished β -adrenergic responsiveness reflects a failing counter-regulating mechanism against bronchoconstrictor mechanisms and probably accounts for airways hyper-reactivity in asthma (Patel, Alston and Kerr, 1974). In such a situation, $\text{PGF}_2\alpha$ released locally by specific and non-specific stimuli would cause marked bronchoconstriction both in the central and peripheral airways in asthmatic patients with significant air trapping.

Acknowledgments

This work has been supported by a research grant from the Scottish Hospital Endowment Research Trust (HERT-425). I also wish to thank Miss Margaret Roberts and Miss Aileen Roy for secretarial assistance.

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