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BRONCHOCONSTRICTION INDUCED BY REPEATED FORCED VITAL CAPACITY MANOEUVRES

By

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Bronchial hyperreactivity in asthmatics has been demonstrated after inhalation of specific allergen, histamine (6), hyperventilation (26), exposure to cold air (13) or exercise (22). Bronchoconstriction is also sometimes induced by forced breathing during spirometry (24, 11). We report an asthmatic atopic patient who showed this effect after repeated recordings of forced expiratory vital capacity. We have investigated the mechanics of this patient's performance in order to discover the reason for the bronchoconstriction and to study the way in which several drugs prevent it.

SUBJECT AND METHODS

The patient, a 16-year-old boy, had a history of wheezing attacks for about 8 years; he showed skin sensitivity to several antigens. When his forced vital capacity (FVC) and forced expiratory volume in 1 sec (FEV_1) were measured, using a waterless spirometer (Vitalograph®), they were normal on the first occasion; but in successive recordings the measurements fell and were associated with wheezing. At the fifth run FEV_1 was 60 per cent of the initial value. More complete studies were then carried out.

Study 1

The patient sat in a volume displacement body plethysmograph (J. H. Emerson Co.). Airflow was measured at the mouth with a heated pneumotachograph and mouth pressure with a Statham® transducer PR 23-ID-300. Functional residual capacity-(FRC) and airway resistance (Raw) near FRC were measured by a modification (14) of a technique previously described (9, 10). Conductance (Gaw) and specific conductance (SGaw) were computed from Raw and thoracic gas volume (Vtg). The mean of five measurements of Raw and Vtg were averaged to obtain the final value. Then several forced vital capacities were carried out. FVC, FEV₁ and maximal expiratory flow rate at 50 per cent of the FVC (Vmax 50) were measured from the recordings. Finally, Raw, FRC and SGaw were measured again. The data obtained were considered as control values. After 40 min of rest, Raw and FRC measurements were repeated and the patient inhaled 400 µg salbutamol as a freon propelled aerosol. Fifteen minutes later, Raw and FRC were determined, and five repeated forced expirations were performed, followed by Raw and FRC measurements. Predicted values for lung volumes, FEV₁, Vmax 50 and airway resistance were obtained from the data of Zapletal et al. (30).

Study 2

After the previous study was completed the patient started treatment with disodium cromoglycate (DSG, Intal®) inhalations 20 mg q.i.d. Two weeks later a new set of measurements was made 30 min after inhaling 60 mg DSG.

Study 3

This study took place 9 months later after a week without treatment. An oesophageal balloon was placed in the lower third of the oesophagus (20). Static lung recoil (C_L) was measured by the interruption method during deflation from total lung capacity (TLC) to FRC (19). Expected values for static pressure (Pst (1)) and C_L were also obtained from Zapletal et al. (29). Total lung capacity was determined by adding FRC to inspiratory capacity (IC). After measuring FRC and Raw, repeated FVCs, followed by static lung recoil curves, were performed. The patient rested for 4 hours, after which atropine sulphate 1.5 mg was given intravenously. When signs of vagal block were evident (heart rate increase and dry mouth), static lung recoil curves, FRC and Raw, were measured and forced expirations were repeated.

Maximal flows were compared taking into account displacements of the static recoil curve (12). Maximal flows were plotted against static recoil pressures, and from the curve's upstream segment resistance (Rus) was calculated from the following equation:

$$Rus = \frac{Pst (1)}{Vmax} (19).$$

A few days later, Raw and FRC were measured before the patient exercised maximally on a bicycle ergometer. The load was increased 100 kg each minute, reaching 1100 kg/min at the breaking point. Once the exercise ended, measurements were repeated at regular intervals through a 40-min period.

Finally, we studied the influence of deep inspirations or expirations upon oesophageal pressure swing and Raw. The patient sat in the body-box and breathed ambient air through a mouth-piece.

RESULTS

In the first study the patient had no symptoms, but initial measurements showed hyperinflation, decreased $\dot{V}_{\max 50}$ and increased airway resistance (Tables 1 and 2). Decrease of FEV_1 and $\dot{V}_{\max 50}$ in successive expirations were observed during the control run and after salbutamol (Study 1) or DSG (Study 2) (Table 2). The log transformations of both sets of data showed a significant negative linear regression with the order of testing (Fig. 1). After inhalation of the bronchodilator, SGaw became normal, and maximal flows increased. The slope of $\dot{V}_{\max 50}$ decay was significantly less steep after the drugs than in the control run (Fig. 1, Table 2). Repeated FVC induced a fall in SGaw, even after salbutamol or DSG. Though the level attained was higher than that obtained before the treatment, the fall was quite similar (Fig. 2).

Study 3

Lung static recoil pressure and compliance were normal (Table 1). A leftward parallel displacement of the pressure-volume curve (about 3 cm H_2O at high lung volumes) and increased TLC were seen after bronchoconstriction induced by forced expirations. A similar displacement of the pressure volume curve without change in TLC was observed after atropine administration. When lung volume was expressed as a percentage of actual TLC, control and bronchoconstriction pressure-volume curves coincided. This means that the leftward deviation was secondary to the increase in TLC. On the other hand, the atropine affect was not modified by expressing volume as a percentage of actual TLC. Static lung com-

TABLE
Physical Characteristics

Sex	Age years	Weight kg	Height cm		TLC L	FRC L	FVC L
M	17	56	167	Predicted	5.49	2.30	3.70
				Found 12/70	—	3.50	4.61
				9/71	6.68	3.59	4.56

Abbreviations according to text. Predicted values for lung volumes, FEV₁, Vmax 50, Raw, Gaw, and SGaw from Zapletal et al. (30), Pst (1) and C₁ from Zapletal et al. (29).

pliance was similar during control measurements and after bronchoconstriction or atropine. The control slope (C₂, Fig. 1) of Vmax 50 was less steep than in the first study (Fig. 1). The maximal expired flow-volume slope was 1.85 sec⁻¹. At the seventh repeated forced expiration a slope of 0.93 sec⁻¹ was attained over a comparable volume range (Fig. 3). After atropine there was no significant fall in Vmax 50 during successive FVCs (Fig. 1). The flow-volume slope was not noticeably different during successive tests from the initial atropine value of 1.40 sec⁻¹ (Fig. 3). Judging from the flow/volume plot (Fig. 3), atropine flows are lower than control at iso-volume conditions. The purpose of comparing flows at iso-volume conditions is to avoid the influence upon bronchial calibre of static pressure changes. If the pressure-volume curve changes during the procedure, flows should be compared at equal recoil pressures. When comparison was made at isobaric conditions, flows were preserved (Fig. 3). The decrease in specific conductance, observed after expiratory efforts in control runs, was not modified after atropine (Table 3). The control value of Rus was 2.50 cm H₂O/l⁻¹s⁻¹, and it increased to 5.04 cm H₂O/l⁻¹s⁻¹ at the seventh expiration at the same lung volume range. After atropine, Rus was 3.09 cm H₂O and remained unchanged after the fifth expiration (Table 3, Fig. 4).

FEV ₁ L	Vmax 50 LPS	Pst (1) 90% TLC cm H ₂ O	Raw cm H ₂ O LPS	Gaw LPS cm H ₂ O	SGaw sec ⁻¹ cm H ₂ O	C ₁ L cm H ₂ O
3.05	4.60	20	2.50	0.40	0.17	0.240
2.96	2.80	—	3.39	0.307	0.087	—
3.32	2.66	16.8	3.98	0.25	0.053	0.212

 TABLE 2
 Repeated Forced Expirations.

Date	Test No.	Raw cm H ₂ O LPS	SGaw sec ⁻¹ cm H ₂ O	FRC L	FVC L	FEV ₁ L	Vmax 50 LPS
<i>Study 1</i>							
Dec. 15, 1970	Control ₁	3.39	0.087	3.50	4.61	2.96	2.8
	2	—	—	—	2.87	1.84	1.5
	3	—	—	—	2.60	1.75	1.6
	4	—	—	—	2.92	1.46	1.0
	5	14.86	0.016	4.00	3.16	1.57	1.1
	Rest	7.02	0.037	3.80	—	—	—
	Salbutamol	2.06	0.142	3.40	—	—	—
	2	—	—	—	4.70	3.25	2.5
	3	—	—	—	4.48	2.82	2.2
	4	—	—	—	4.43	2.68	2.0
	5	—	—	—	4.26	2.60	1.8
	6	—	—	—	4.17	2.51	1.6
		3.89	0.065	3.80			
<i>Study 2</i>							
Dec. 27, 1970	DSG	2.07	0.157	3.20	4.88	3.49	3.9
	2	—	—	—	4.84	3.06	2.6
	3	—	—	—	4.65	3.02	2.6
	4	—	—	—	4.84	2.78	2.2
	5	—	—	—	4.74	2.73	2.0
	6	—	—	—	4.93	2.75	2.1
	7	—	—	—	4.65	2.63	2.2
		5.86	0.048	3.50			

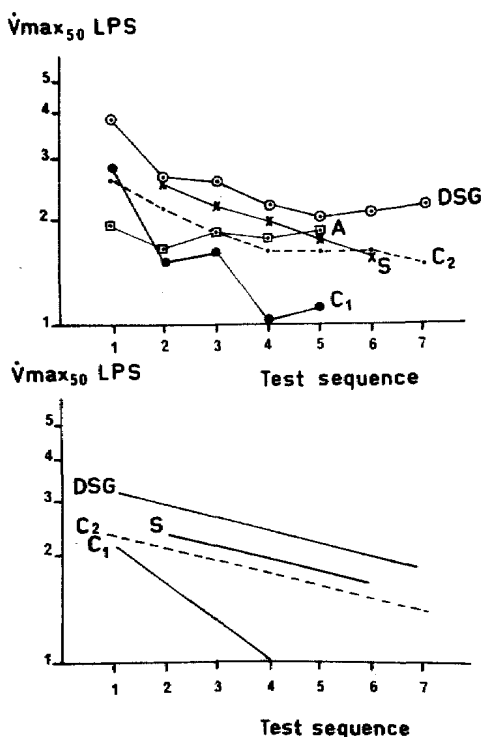


Fig. 1.

Top: semilog plot of $\dot{V}_{max 50}$ vs test sequence. C₁: control of study 1; S: post-salbutamol; DSG: disodium cromoglycate; C₂: control of study 3; A: atropine. Bottom: regression lines of data shown above.

Exercise produced a marked drop in SGaw to 50 per cent of initial level. Recovery to control values was seen 40 min later (Fig. 5). Small increases in thoracic pressure swing were observed in the last study after several deep inspirations. At the same time Raw changed from a control value of $2.41 \text{ cm H}_2\text{O/l}^{-1}\text{s}^{-1}$ to $3.15 \text{ cm H}_2\text{O/l}^{-1}\text{s}^{-1}$ ($P < 0.01$). Several deep, slow expirations produced a similar effect, with an increase in

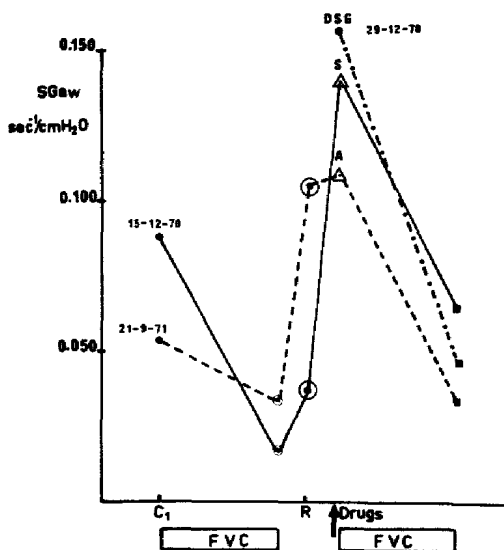


Fig. 2.

Changes in SGaw following FVC manoeuvres before and after drugs. S: salbutamol; DSG: disodium cromoglycate and A: atropine. First study —; Second study — — —; Third study - - - - -.

Raw to $3.78 \text{ cm H}_2\text{O/l}^{-1}\text{s}^{-1}$ ($P < 0.05$). Finally, after a series of 6 FVC, Raw reached $6.24 \text{ cm H}_2\text{O/l}^{-1}\text{s}^{-1}$ ($P < 0.01$).

DISCUSSION

Bronchial hyperreactivity is shown by immediate asthmatic reactions after inhalation tests in extrinsic atopic asthma. Bronchoconstriction is also seen in asthmatics after exercise, laughing, sobbing or spirometric tests. These reactions are taken to represent hyperreactivity to various stimuli. After exercise many patients show a temporary, marked decrease in FEV_1 , associated with an increase in airways resistance (18). In some cases these effects may be severe (24), and asthma attacks may follow exertion. This effect has been attributed

TABLE 3
Repeated Forced Expirations (Study 3).

Date	Test No.	Raw cm H ₂ O LPS	SGaw sec ⁻¹ cm H ₂ O	TLC		IC		FRC		Vmax 10cm H ₂ O Pst (1)		Vmax 50 cm H ₂ O LPS		Rus cm H ₂ O LPS
				L		L		L		LPS		LPS		
Sept. 1971	Control ₁	3.98	0.053	6.68		3.09		3.59		3.52		2.66		2.50
	2	-	-	-		-		-		2.40		2.16		4.04
	3	-	-	-		-		-		2.13		1.83		4.17
	4	-	-	-		-		-		2.06		1.66		4.50
	5	-	-	-		-		-		1.77		1.66		5.38
	6	-	-	-		-		-		1.77		1.66		5.38
	7	-	-	-		-		-		1.70		1.49		5.38
Rest Atropine		6.22	0.033	7.20		2.77		4.43						
		2.49	0.105	6.56		3.16		3.40						
		2.36	0.109	6.79		3.26		3.53						
	2	-	-	-		-		-		3.40		1.91		3.09
	3	-	-	-		-		-		2.81		1.66		3.80
	4	-	-	-		-		-		3.22		1.83		2.64
		-	-	-		-		-		2.43		1.74		4.00
	5	-	-	-		-		-		3.18		1.83		3.01
		5.95	0.034					4.80						

Vmax 10cm H₂O Pst (1) from Vmax/Pst (1) curve (Fig. 4).

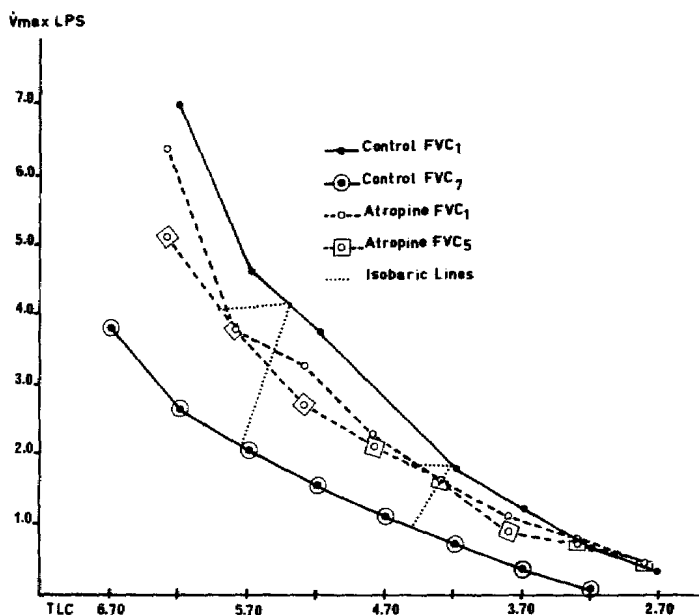


Fig. 3.
Flow-volume curves.

to spasmogenic metabolites released from the exercising muscles (15, 18). However, when bronchoconstriction develops in the same patients after voluntary hyperventilation (4, 25) or repeated expiratory manoeuvres (24), the muscle mass involved seems to be too small for this to be the cause. Hypocapnia (18) and metabolic acidosis (2) have also been suggested as possible causes. Mechanical pressure or tension may induce a release of chemical mediators from unduly fragile mast cells sensitized by reaginic antibodies. Finally, irritant lung receptors may be mechanically stimulated by exaggerated movements of the bronchial walls causing reflex bronchoconstriction, which may, in part, be vagally mediated (21). This factor is probably the most important when repeated

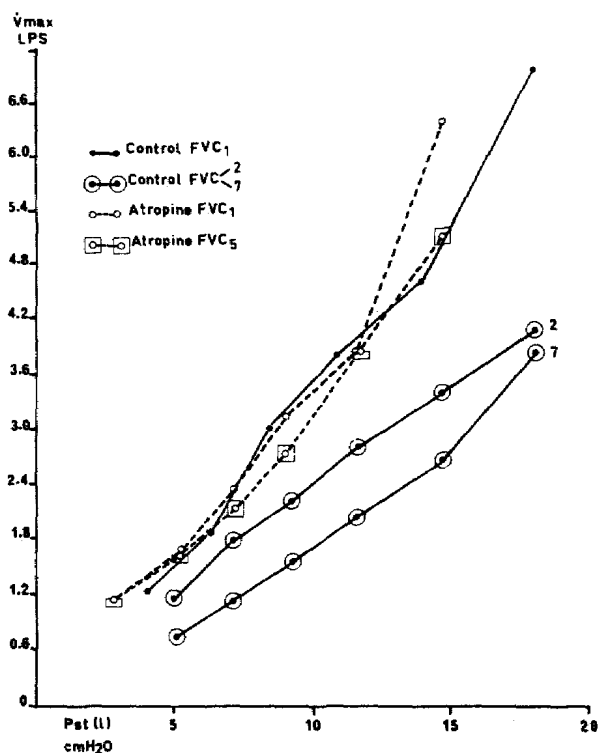


Fig. 4.
Maximal flow-static recoil pressure curves.

TABLE 4
Statistical Analysis. In $V_{max 50}$ vs Test Sequence.

Situation	Equations	r	P
Control	$1.083-0.2275 \times$	-0.889	<0.05
Bronchodilator	$1.054-0.0824 \times$	-0.988	<0.01
DSG	$1.242-0.0840 \times$	-0.814	<0.05
C ₂ atropine	$0.945-0.0842 \times$	-0.915	<0.01

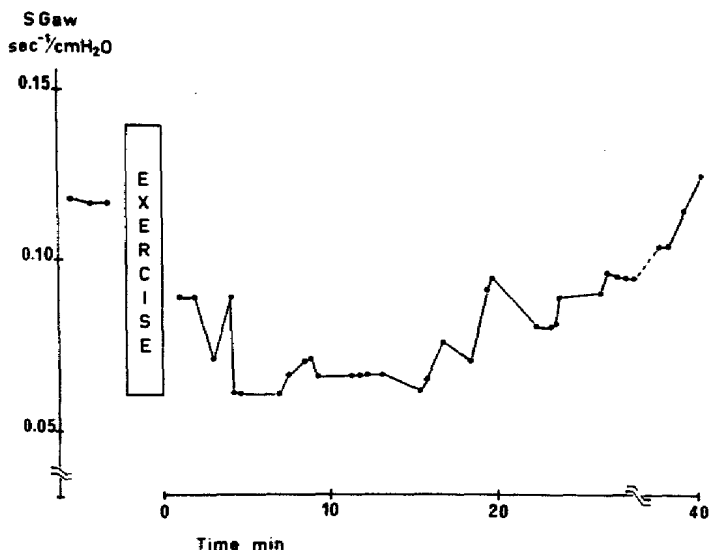


Fig. 5.

Effects of exercise on specific airway conductance (SGaw).

forced expirations are made. In fact, near to residual volume, bronchial calibre is enormously decreased in some zones (8)—probably to the point of complete closure (24). The blocking effect of atropine, observed in some studies (15), reinforces the possibility of a reflex mechanism.

Recently, evidence has been adduced to show (11) that deep inspiration is the relevant component of FVC that induces bronchoconstriction. Either slow, deep inspiration or expiration produced some bronchoconstriction in our patient; but the effect of repeated FVC was much more marked. It seems that the same conclusion may be drawn from the records published by Gimeno et al. (11). Oesophageal tidal pressure swing is much more increased after vital capacity manoeuvres than after isolated deep inspirations (11).

It is well known that it is easier to elicit exercise asthma

with disorderly effort (1) like running upstairs than with standard bicycle exercise. The effects of FVC as compared with slow VC manoeuvres and those of laughing or sobbing suggest that forced, irregular or shaking thoracic movements are particularly liable to produce bronchoconstriction. Adrenergic bronchodilators, inhaled before exercise or repeated expiration, can block this response (15, 18).

In the patient presented here, bronchoconstriction developed after exercise and during forced expirations. Bronchoconstriction caused by FVC manoeuvres could be partially blocked by previous inhalation of an adrenergic bronchodilator by DSG and by atropine injection. The first two drugs produced a similar effect upon the slope of $V_{\max 50}$. DSG has no bronchodilating properties, but only inhibitory effects upon reactions where reagin-like antibodies are involved and mast cells are mediators (5). Exercise bronchoconstriction may be partially prevented by DSG inhalation, according to Davies (7) and Raimondi et al. (23). Judging from figures of R_{aw} , FRC and $V_{\max 50}$, basal conditions at the first and third study were not too different. Nevertheless, $V_{\max 50}$ and SG_{aw} decreases were lower in the third study. The slope of $V_{\max 50}$ was about the same as that observed after DSG or bronchodilator. Bronchoconstriction was associated with a fall in lung static recoil and an increase in FRC and TLC. These results are similar to those reported (17) during acute asthma. Bronchoconstriction disappeared after rest. Atropine injection in these conditions induced leftward displacement of the pressure-volume curve. A similar effect has been described (28) in normals and attributed to relaxation of resting vagal tone of small bronchi and alveolar ducts. Atropine effects during FVC were well preserved, but SG_{aw} decreased as much as before atropine. This behaviour suggests an isolated inhibitory effect upon bronchomotor tone of peripheral bronchi. It is to be emphasized that atropine in normals has a slight effect upon total resistance, but induces an increase in maximal flows (28). It may be inferred from this that there is either relatively less vagal supply to central

bronchi or predominantly adrenergic activity in peripheral bronchi. This is in keeping with the hypothesis proposed (3) to explain peripheral or central bronchial reactivity to hemp dust, and with the suggestion of unequal distribution of cholinergic activity in dogs (16).

In summary, although the effect of DSG appeared to be less marked than that of atropine, both drugs exerted a partially protective action. It is possible then to assign bronchoconstriction to mast cell disruption and to vagal stimulation. It is tempting to speculate that the release of mediators provokes generalised effects, but vagally mediated bronchoconstriction may be localised only in the peripheral bronchi in this particular subject.

SUMMARY

An asthmatic atopic patient who developed bronchoconstriction during repeated forced vital capacity manoeuvres and after exercise is reported. Since increases in total airway and upper segment resistances and drop in FEV_1 and V_{max} 50 were induced, it is considered that bronchoconstriction involved most of the airways. Partial prevention of this effect could be demonstrated after inhalation of an adrenergic bronchodilator or disodium cromoglycate. Atropine completely prevented the flow response but did not alter the total airway resistance increase. Bronchoconstriction is interpreted as partially related to mast cell disruption and cholinergically mediated stimuli.

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