

# Effects of Smoked Marijuana in Experimentally Induced Asthma<sup>1,2</sup>

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## SUMMARY

After experimental induction of acute bronchospasm in 8 subjects with clinically stable bronchial asthma, effects of 500 mg of smoked marijuana (2.0 per cent  $\Delta^9$ -tetrahydrocannabinol) on specific airway conductance and thoracic gas volume were compared with those of 500 mg of smoked placebo marijuana (0.0 per cent  $\Delta^9$ -tetrahydrocannabinol), 0.25 ml of aerosolized saline, and 0.25 ml of aerosolized isoproterenol (1,250  $\mu$ g). Bronchospasm was induced on 4 separate occasions, by inhalation of methacholine and, on four other occasions, by exercise on a bicycle ergometer or treadmill. Methacholine and exercise caused average decreases in specific airway conductance of 40 to 55 per cent and 30 to 39 per cent, respectively, and average increases in thoracic gas volume of 35 to 43 per cent and 25 to 35 per cent, respectively. After methacholine-induced bronchospasm, placebo marijuana and saline inhalation produced minimal changes in specific airway conductance and thoracic gas volume, whereas 2.0 per cent marijuana and isoproterenol each caused a prompt correction of the bronchospasm and associated hyperinflation. After exercise-induced bronchospasm, placebo marijuana and saline were followed by gradual recovery during 30 to 60 min, whereas 2.0 per cent marijuana and isoproterenol caused an immediate reversal of exercise-induced asthma and hyperinflation.

## Introduction

Recent studies have demonstrated significant, acute bronchodilatation in healthy young men after both smoked marijuana (1, 2) and oral  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), the principal psychoactive ingredient in marijuana (2). More recently, the smoking of marijuana and ingestion of  $\Delta^9$ -THC by subjects with chronic, clinically stable, bronchial asthma of minimal to moderate severity has been shown to produce airway dilatation of a magnitude similar to that previously noted in healthy subjects (3). Although these findings appear to support the benefit ascribed to the use of cannabis in the last century

for the treatment of bronchial asthma (4), they do not provide any direct evidence for a bronchodilator effect of marijuana during an acute asthmatic attack. In the present study, the effects of smoked marijuana on bronchomotor tone were evaluated in asthmatic subjects after acute bronchospasm was induced either by inhalation of methacholine or by exercise.

## Materials and Methods

Eight patients with bronchial asthma characterized by typical attacks of wheezing, breathlessness, and cough at least partially relieved by bronchodilator medication and without other significant medical illness were selected for study. All subjects were clinically stable at the time of the study. Three subjects had participated in previous studies to evaluate the acute bronchial effects of smoked marijuana and oral  $\Delta^9$ -THC in stable asthma (3). Five subjects had smoked marijuana previously. Of these 5 subjects, one had smoked marijuana only in connection with the previous study (3), 3 had smoked infrequently (less than 1 joint per month), and one had smoked regularly, but mildly (1 joint per week).

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TABLE 1  
SCHEDULE OF SCREENING, PRELIMINARY, AND EXPERIMENTAL STUDIES

Day	Studies Performed
1	Screening pulmonary function studies; spirometry, and plethysmography before and after isoproterenol inhalation.
2	Preliminary studies A.M. Graded exercise P.M. Graded doses of methacholine
3, 4*	Methacholine-induced bronchospasm A.M. Isoproterenol and saline ↓ ↓ P.M. Marijuana or placebo marijuana
5, 6*	Exercise-induced bronchospasm A.M. Isoproterenol or saline ↓ ↓ P.M. Marijuana or placebo marijuana

\*Order of days in which bronchospasm was induced by methacholine (days 3 and 4) or exercise (days 5 and 6) was randomized.

No subject had used marijuana within 7 days of the study. No subject was a tobacco cigarette smoker.

The schedule of screening, preliminary, and experimental studies is indicated in table 1. Days on which studies were performed were generally separated by 1 week or less. All oral bronchodilator drugs were withheld for at least 8 hours; inhaled bronchodilator drugs were withheld for at least 4 hours before the beginning of each morning or afternoon study session. Screening studies were performed on day 1 and consisted of spirometry using a 13.5-liter, water-seal spirometer (Warren E. Collins, Inc.), and measurement of single-breath diffusing capacity for CO (DLCO) (5), airway resistance (Raw), and thoracic gas volume (Vtg) using a 900-liter, variable-pressure, body plethysmograph (6, 7). The Vtg and Raw were measured at or near the volume of resting end-expiration. The average slope of the inspiratory and expiratory pressure-flow loops at flows of  $\pm 0.5$  liter per sec was used in the calculation of Raw. Plethysmographic and spirometric measurements were performed before and 5 to 10 min after inhalation of 1,250 mg of isoproterenol hydrochloride as previously described (3) to establish the presence of reversible bronchospasm.

Preliminary studies were performed in the morning (9 A.M.) and afternoon (1:30 P.M.) of day 2 to determine the type, duration, and severity of exercise and the dose of methacholine required to produce the required degree of bronchospasm (see below). During the morning session, two sets of control measurements of Raw and Vtg were obtained 15 min apart, after which bronchospasm was induced by exercise either on a bicycle ergometer (3 subjects) or on a treadmill (4 subjects). Treadmill exercise was used if a subject felt uncomfortable riding a bicycle or if previous exhaustive exercise on a bi-

cycle ergometer failed to produce the requisite degree of bronchoconstriction. Each subject performed steady exercise for 6 to 10 min using incremental work loads of 200 to 650 kilopond-m (bicycle ergometer) or 1 to 3.5 mph at a 0 to 10 per cent grade (treadmill) until specific airway conductance (SGaw,  $= 1/\text{Raw}/\text{Vtg}$ ) determined within 10 min of completion of the exercise decreased by at least 20 per cent from the mean of that subject's control values. When this degree of bronchoconstriction was not achieved, exercise was repeated at the next higher work load after a rest of at least 15 min and after plethysmographic measurements had returned to initial control values. In one subject (JB), bronchospasm could not be provoked despite exhaustive treadmill exercise. During the afternoon session, after plethysmographic measurements of Raw and Vtg had returned to values similar to those obtained during the control period of the morning session, each subject inhaled graded doses of methacholine (62.5 to 625  $\mu\text{g}$  in 0.25 to 0.5 ml of saline) until SGaw determined within 5 min of methacholine inhalation decreased by at least 25 per cent from that subject's control value. The methacholine solutions were nebulized via a DeVilbiss nebulizer connected to a positive-pressure breathing device powered by compressed air. Subjects inhaled the aerosol using slow, deep inspirations followed by several seconds of end-expiratory breath-holding. When the requisite degree of bronchospasm did not develop within 5 min after one dose of methacholine, the next higher dose was not administered until at least 15 min after the previous dose and after SGaw had returned to initial values.

In the morning and afternoon of days 3 and 4 (a total of 4 experimental sessions), 2 sets of control measurements of Raw and Vtg were obtained. Bronchospasm was then induced in each subject by inhalation of the same dose of methacholine that

had been shown in the preliminary studies to reduce SGaw in that subject by at least 25 per cent. During the morning sessions, approximately 8 to 9 min after induction of bronchospasm, subjects inhaled 0.25 ml of either saline or 0.5 per cent isoproterenol (Iso) in a randomly ordered, single blind fashion using the same nebulization and inhalation techniques that had been used to administer the methacholine solution. Serial plethysmographic measurements were performed within 1 to 2 min ("zero" time), and at 5, 10, 15, 30, and 60 min after saline or Iso inhalation. During the afternoon sessions, experimental bronchospasm was induced only after plethysmographic measurements had returned to the baseline values recorded at the beginning of the morning session of the same day. Immediately after the development of bronchospasm, subjects smoked a joint containing 500 mg of marijuana assayed at either 2.0 per cent  $\Delta^9$ -THC or 0.0 per cent  $\Delta^9$ -THC (placebo) according to a randomly ordered, single blind protocol. Joints were smoked during a 10-min period using a standard deep-inhalation technique (2). Marijuana and placebo marijuana preparations were obtained from the National Institute on Drug Abuse, under whose direction extraction, assay, and blending procedures were performed. Immediately after completion of smoking, serial plethysmographic measurements were repeated at the same intervals described previously.

In the morning and afternoon of days 5 and 6 (4 experimental sessions), after control measurements were made, bronchospasm was induced in each subject by the type, duration, and degree of exercise that had been demonstrated during preliminary studies to reduce SGaw in that subject by at least 20 per cent. Afternoon exercise was begun only after measurements had returned to the control values determined during the same morning. Using a randomly ordered, single blind protocol, in morning sessions, subjects inhaled Iso or saline 8 to 9 min after the development of bronchospasm, and in afternoon sessions, subjects smoked 2.0 per cent marijuana or placebo during a period of 10 min immediately after the induction of bronchospasm. Serial measurements of Raw and Vtg were performed at the same intervals after inhalation or smoking of the test preparations, as indicated for the methacholine experiments.

The order of the experiments in which bronchospasm was induced by either methacholine inhalation or exercise was randomized among the subject population.

**Calculations.** The SGaw was calculated from each set of measurements of Raw and Vtg to correct for changes in Raw secondary to changes in lung volume (8). For each subject at each time interval during each experimental protocol, per cent changes in SGaw and Vtg were calculated from the average of the 2 pre-methacholine or pre-exercise control

TABLE 2  
ANTHROPOMETRIC AND BASELINE PULMONARY FUNCTION DATA

Subject	Sex	Height (cm)	Weight (kg)	Age (years)	FEV <sub>1</sub> /FVC (% pred.)*	FEV <sub>1</sub> (% pred.)*		SGaw† (sec <sup>-1</sup> · cm H <sub>2</sub> O <sup>-1</sup> )		Vtg (liter)		DLCO (% pred.)*
						BB	AB	BB	AB	BB	AB	
HG	F	158	66	59	68.3	57	77	0.075	0.107	3.22	2.79	100
MW	F	163	59	27	74.0	46	76	0.053	0.098	4.11	2.83	104
JB	F	168	66	28	70.1	75	78	0.124	0.234	3.09	2.80	97
BG	M	172	64	24	79.1	64	73	0.076	0.106	5.21	4.23	98
ES	F	166	61	56	48.6	75	132	0.127	0.203	3.35	3.04	106
NG	M	170	61	19	75.3	85	97	0.143	0.208	3.64	3.57	110
RD	F	182	54	40	77.3	77	85	0.132	0.170	3.20	3.00	138
MC	M	185	107	32	75.6	60	78	0.110	0.178	4.31	3.90	83
Mean		168	66.9	35.6	71.0	67.4	87.0	0.105	0.163	3.78	3.27	104
±SD		8.2	16.7	14.8	9.7	12.8	19.7	0.033	0.053	0.72	0.56	15.7

**Definition of abbreviations:** FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 sec; SGaw = specific airway conductance; Vtg = thoracic gas volume; DLCO = diffusing capacity of the lung for CO; BB = before bronchodilator; AB = after bronchodilator (SGaw and FEV<sub>1</sub> were measured 5 and 10 min, respectively, after bronchodilator).  
\*Predicted values for FEV<sub>1</sub>/FVC, FEV<sub>1</sub>, and DLCO were based on the regression equations of Berglund and associates (9), Kory and associates (10), Ferris and co-workers (11), and Hammer and Meade, as reported by Cotes (12).  
†Predicted value for our laboratory is 0.250 ± 0.043.

TABLE 3  
MEAN  $\pm$  SE INITIAL PLETHYSMOGRAPHIC VALUES

	Methacholine-Induced Bronchospasm (n = 8)		Exercise-Induced Bronchospasm (n = 7)	
	SGaw ( $\text{sec}^{-1} \cdot \text{cm H}_2\text{O}^{-1}$ )	Vtg (liter)	SGaw ( $\text{sec}^{-1} \cdot \text{cm H}_2\text{O}^{-1}$ )	Vtg (liter)
Smoked placebo marijuana	0.076 $\pm$ 0.010	3.67 $\pm$ 0.16	0.092 $\pm$ 0.015	3.88 $\pm$ 0.34
Smoked 2% marijuana	0.060 $\pm$ 0.006	4.12 $\pm$ 0.30	0.090 $\pm$ 0.010	3.97 $\pm$ 0.19
Inhaled saline	0.074 $\pm$ 0.012	3.83 $\pm$ 0.32	0.087 $\pm$ 0.014	4.16 $\pm$ 0.27
Inhaled 0.5% isoproterenol	0.081 $\pm$ 0.018	4.09 $\pm$ 0.37	0.085 $\pm$ 0.014	4.25 $\pm$ 0.40

values. At each time interval for each type of experiment, the individual per cent changes in SGaw and Vtg were averaged for all subjects, thereby minimizing the factor of intersubject variability of control values. The significance of the average per cent changes in SGaw and Vtg from initial control values, of the per cent changes that followed marijuana, compared with placebo or saline, and that followed isoproterenol, compared with saline or marijuana, was determined using "Student's" *t* test (paired observations). In addition, the average individual differences in control values among the various types of experiments were tested for significance using the *t* test (paired observations) to ascertain whether all experiments were performed under comparable conditions.

### Results

Physical characteristics of each subject and the results of baseline pulmonary function studies are given in table 2. Three men and 5 women from 19 to 59 years of age were studied. The ratio of 1-sec forced expiratory volume (FEV<sub>1</sub>) to forced vital capacity ranged between 49 and 79 per cent of the predicted value, indicating the presence of minimal to moderately severe airway obstruction. Inhalation of Iso resulted in mild to moderate increases in FEV<sub>1</sub> and SGaw, indicating the presence of reversible bronchospasm. The DL<sub>CO</sub> was normal or greater than normal, consistent with bronchial asthma (13).

The mean initial control values of SGaw and Vtg during each experimental session before induction of bronchospasm with methacholine or exercise are shown in table 3. The average individual differences in control values for each measured variable, comparing any one session with any other, were not significantly different from zero.

The mean per cent changes in SGaw and Vtg after smoked marijuana or placebo, or inhaled Iso or saline after methacholine-induced bronchospasm are shown in figures 1 and 2. Methacholine inhalation promptly caused significant

bronchoconstriction, with average decreases in SGaw of 40 to 55 per cent, and significant hyperinflation, with mean increases in Vtg of 35 to 43 per cent. After subsequent placebo marijuana smoking or saline inhalation, SGaw increased only modestly, remaining significantly less than initial control values for 30 to 60 min, and Vtg decreased only gradually, remaining significantly increased for 15 min. On the other hand, 2 per cent marijuana and Iso each resulted in a prompt return of SGaw and Vtg to control values, which were significantly different from values after placebo and saline. Although the mean values for SGaw after Iso were greater than both initial control values and those after smoked marijuana, these differences were not significant.

The average per cent changes in SGaw and Vtg that followed each test preparation after exercise-induced bronchospasm are shown in figures 3 and 4. Exercise resulted in average decreases in SGaw of 30 to 39 per cent and average increases in Vtg of 25 to 35 per cent. There was a gradual return to control values during 30 to 60 min after placebo and saline. After marijuana, on the other hand, SGaw and Vtg returned promptly to pre-exercise values, which were significantly different from values after placebo and saline for 15 to 60 min. The Iso caused a prompt return of Vtg to baseline values and an immediate increase in SGaw to values that significantly exceeded initial control values and remained significantly greater than values after saline and marijuana for as long as 60 min.

The 4 subjects who had previously used cannabis experienced emotional changes after smoking marijuana that were generally pleasant, whereas no "high" developed after placebo marijuana. Because these subjects were able to distinguish between real and placebo marijuana, these experiments were not truly blind. The 4 subjects with essentially no previous cannabis experience either admitted to no central nervous

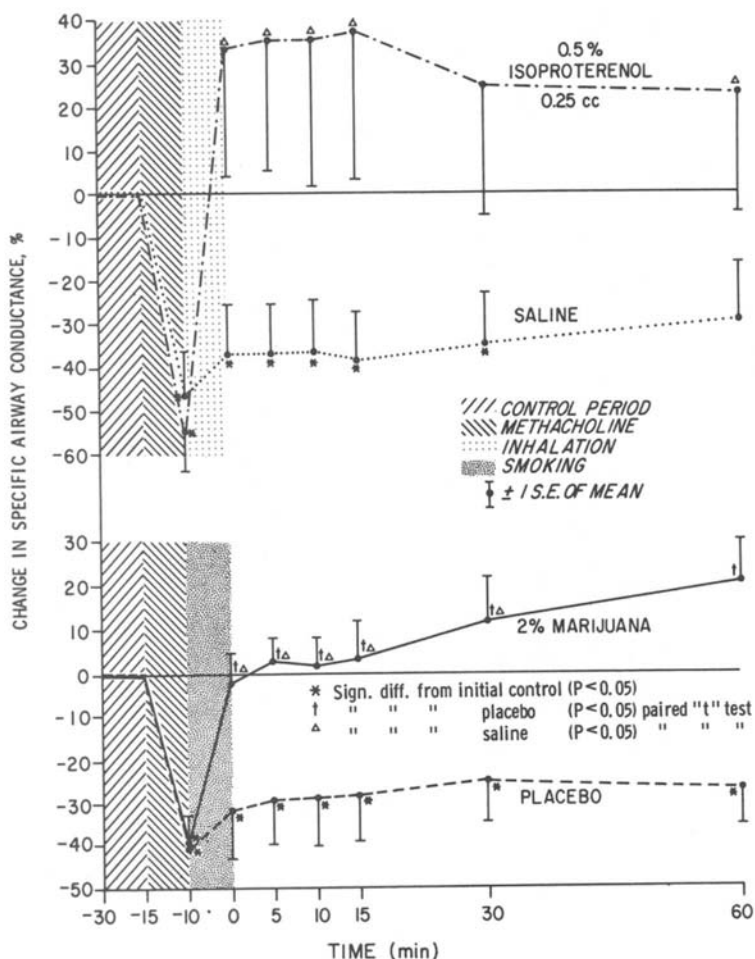


Fig. 1. Average per cent change with time in specific airway conductance (SGaw) from initial control values after smoking of 2 per cent marijuana and placebo, and inhalation of 0.25 ml of 0.5 per cent isoproterenol and saline after methacholine-induced bronchospasm ( $n = 8$ ).

system changes or experienced mild somnolence or light-headedness after marijuana.

### Discussion

The 40 to 50 per cent decrease in SGaw after inhalation of  $\leq 625 \mu\text{g}$  of methacholine noted in our subjects is consistent with the known bronchial hyper-reactivity of asthmatic subjects to muscarinic stimulation (14). In our laboratory, normal subjects require more than 5 times these doses of methacholine to develop a comparable degree of bronchoconstriction. The associated increase in Vtg observed in our asthmatic subjects was probably related to the increase in expiratory flow resistance.

There was a relatively small and nonsignificant ( $P > 0.05$ ) average individual difference in

the magnitude of the methacholine-induced decrease in SGaw when any one of the 4 experimental sessions was compared with any other, and a very small difference when the marijuana and placebo marijuana sessions were compared with each other ( $1.4 \pm 4.8$  per cent SE). These findings indicate a reasonable degree of reproducibility of airway constriction after inhalation of the same dose of methacholine by individual subjects from one session to the next, thereby permitting a reliable comparison of the effects of marijuana, placebo, Iso, and saline on methacholine-induced bronchospasm.

Comparison of placebo marijuana smoking and saline inhalation showed negligible differences in the magnitude or duration of methacholine-induced bronchoconstriction (figure 1)

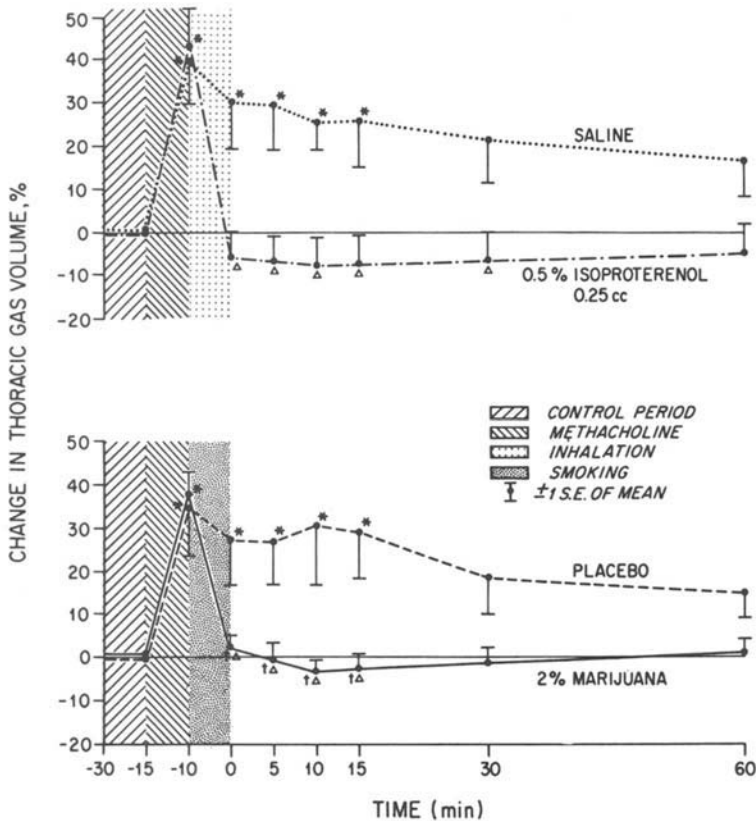


Fig. 2. Average per cent change with time in thoracic gas volume ( $V_{tg}$ ) from initial control values after smoking of 2 per cent marijuana and placebo, and inhalation of 0.25 ml of 0.5 per cent isoproterenol and saline after methacholine-induced bronchospasm ( $n = 8$ ). Symbols for statistical significance are similar to those shown in figure 1.

and hyperinflation (figure 2) after these two preparations. This suggests that any bronchial irritant effect of marijuana smoke was not sufficient to aggravate or perpetuate existing acute bronchospasm to an extent greater than that which might result from an irritant effect of inhaled saline. Comparison of the magnitude and time course of changes in SGaw and  $V_{tg}$  immediately after marijuana smoking to those after placebo marijuana and saline indicate that inhaled  $\Delta^9$ -THC causes a prompt, complete, and sustained reversal of methacholine-induced bronchospasm and correction of the associated hyperinflation. These effects were not significantly different from those observed after Iso, although there was a tendency toward a greater degree of bronchodilatation after the latter.

The 30 to 39 per cent average decrease in SGaw and 25 to 35 per cent average increase in  $V_{tg}$  after mild to heavy exercise for 6 to 10 min in 7 of the 8 asthmatic subjects tested are con-

sistent with previous reports of bronchospasm (15) and hyperinflation (16) after exercise. The average individual difference in exercise-related decrease in SGaw when any of the 4 study periods was compared with any other was small and nonsignificant ( $P > 0.2$ ), so that the effects of smoked and inhaled test preparations on exercise-induced bronchospasm could be validly compared.

The appropriateness of comparing effects of various drugs on bronchospasm provoked by exercise twice on the same day might be questioned, because McNeill and associates (17) found partial to complete loss of exercise-induced bronchoconstriction in 3 of 4 asthmatic subjects after repeated periods of exercise throughout one day. In our subjects, however, there were no consistent differences between the per cent decrease in SGaw after exercise during afternoon sessions and that observed in the same subjects during morning sessions. The mean  $\pm$  SE morning-to-

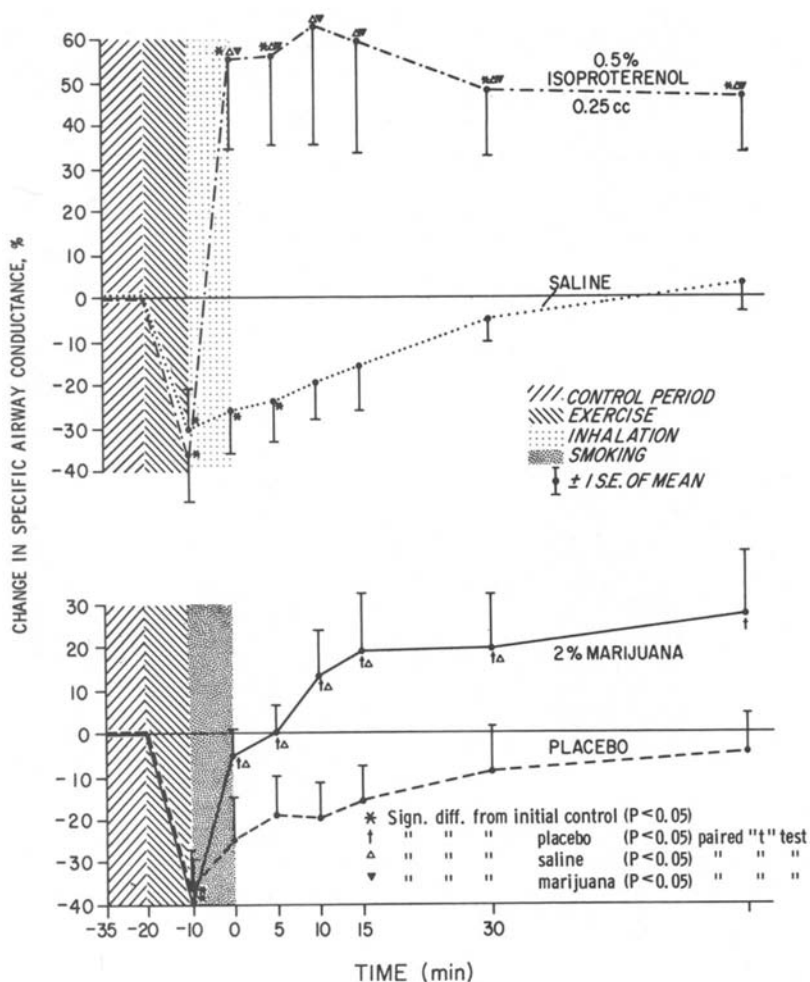


Fig. 3. Average per cent change with time in specific airway conductance (SGaw) from initial control values after smoking of 2 per cent marijuana and placebo, and after inhalation of 0.25 ml of 0.5 per cent isoproterenol and saline after exercise-induced bronchospasm ( $n = 7$ ).

afternoon individual difference was  $-1.7 \pm 3.1$  per cent ( $P > 0.5$ ). Our findings are more in agreement with those of Godfrey and co-workers (18) and Silverman and Anderson (19). They showed a reproducible magnitude of postexercise bronchospasm in individual asthmatic children after a similar type and severity of exercise when repeat tests were performed either on separate days within 1 week or 2 hours apart within the same day. These investigators found more variability after bicycle ergometer than treadmill exercise.

The occurrence of the most marked changes in SGaw and Vtg during the first 10 min after induction of bronchospasm, with a gradual return to control values during 30 to 60 min after placebo or saline is characteristic of the time course

of exercise-induced asthma (15, 16). The prompt return of SGaw and Vtg to pre-exercise values after smoked marijuana contrasts with the delayed recovery that followed placebo and saline, indicating the efficacy of inhaled  $\Delta^9$ -THC in the correction of exercise-induced asthma. Comparison of the response to 1,250  $\mu\text{g}$  of Iso with that to 2 per cent marijuana (10 mg of  $\Delta^9$ -THC), however, revealed that the former caused a significantly greater degree of bronchodilatation in the doses used.

The effects of smoked marijuana on acute, experimentally induced bronchoconstriction and hyperinflation noted in the present study extend over our previous observations of significant bronchodilatation and reduction in hyperinflation in resting patients with stable bronchial asthma (3).

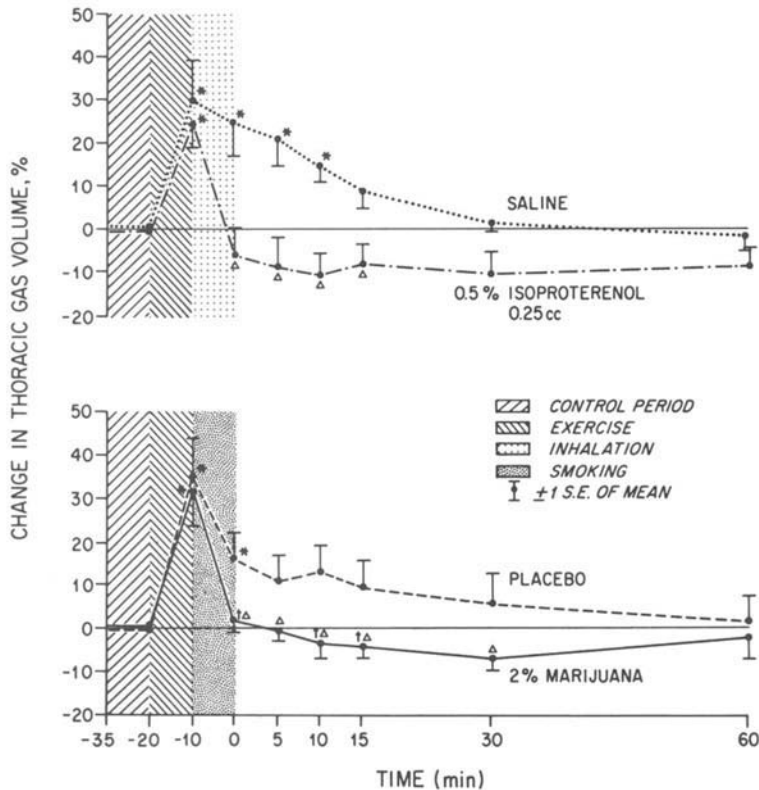


Fig. 4. Average per cent change with time in thoracic gas volume from initial control values after smoking of 2 per cent marijuana and placebo, and after inhalation of 0.25 ml of 0.5 per cent isoproterenol and saline after exercise-induced bronchospasm ( $n = 7$ ). Symbols for statistical significance are similar to those shown in figure 3.

Although suggestion and other psychological factors probably play an important role in the response of asthmatic patients to inhalants (20), the lack of response to  $\Delta 9$ -THC-extracted marijuana in the present study suggests that a placebo effect was not responsible for the reversal of experimentally induced asthma observed to follow smoking of natural marijuana. Moreover, it is unlikely that pleasant emotional sensations after marijuana contributed significantly to the bronchodilatation. Although the 4 subjects with no or negligible prior cannabis experience did not admit to a feeling of tranquility or euphoria after smoking marijuana, they did demonstrate a degree of correction of experimentally induced bronchospasm comparable to that observed in the subjects who had used cannabis previously. Although the mechanism of  $\Delta 9$ -THC-induced bronchodilatation has not been completely determined, previous studies have demonstrated that this effect is not mediated by  $\beta$ -adrenergic stimulation or inhibition of muscarinic receptors (21). A vagolytic mechanism proximal to

the muscarinic receptor site is suggested by correlative studies involving the dog salivary gland (22) and guinea pig ileum (23).

Our present findings and those previously reported (1-3) demonstrated acute airway dilatation after smoked marijuana. In contrast, mild, but significant, reductions in forced expiratory flows and SGaw after chronic, heavy marijuana smoking were recently reported (24), suggesting airway obstruction secondary to a chronic irritant effect of the smoke. An acute, deleterious effect of the gas phase of marijuana smoke on alveolar macrophages has also been demonstrated *in vitro* (25). Consequently, smoking would not appear to be an appropriate long-term method for administration of bronchodilator cannabinoid compounds for potential therapeutic purposes. Although ingestion of  $\Delta 9$ -THC in a sesame oil vehicle has produced bronchodilatation in asthmatic patients (3), less dilatation was noted than that after smaller doses of  $\Delta 9$ -THC delivered by smoking (3). In preliminary studies in our laboratory, aerosolization of an ethanol solution



of  $\Delta^9$ -THC using a Freon® propellant resulted in mean peak increase in SGaw of 88 per cent in 4 normal subjects, but unwanted psychological effects were not circumvented. Regardless of its route of administration,  $\Delta^9$ -THC does not appear to be a suitable bronchodilator for therapeutic use because of its systemic psychotropic and possible undesirable endocrine, immunologic, and cytogenetic effects (26). Related cannabinoid compounds, however, such as cannabinal and cannabidiol, do not produce the central nervous system effects or tachycardia characteristic of cannabis (27), but appear to share another and potentially useful property with  $\Delta^9$ -THC, reduction of intraocular pressure (28). These compounds should be further investigated for possible bronchodilator activity and therapeutic utility.

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