SINGLE-DOSE EFFECT OF MARIHUANA SMOKE

Bronchial Dynamics and Respiratory-Center Sensitivity in Normal Subjects

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Abstract Normal volunteers with previous marihuana smoking experience inhaled the total smoke from 3.23 mg per kilogram of marihuana, using a bag-in-box technic. Randomly, nine received marihuana containing a high (2.6 per cent), and eight a low (1.0 per cent) concentration of delta-9 tetrahydrocannabinol.

Physiologic variables were monitored before and for 20 minutes after smoking. In the high-dose group the heart rate increased 28 per cent. Concomitantly, airway resistance, measured in a body plethysmograph, fell 38 per cent; the functional residual capacity remained unchanged (± 50 ml) throughout, and specific airway conductance increased 44 per cent. Flow-volume loops showed a 45 per cent increase in flow rate at 25 per cent of vital capacity. The low-dose group showed no increase in heart rate but significant, if lesser changes, in airways dynamics. Carbon dioxide sensitivity, measured by rebreathing remained unchanged in both groups.

Marihuana smoke, unlike cigarette smoke, causes bronchodilatation rather than bronchoconstriction and, unlike opiates, does not cause central respiratory depression. (N Engl J Med 288:985-989, 1973)

THE inhalation of marihuana smoke is the most common method used to obtain its euphoric sensation. The major advantage of smoking, rather than ingestion, is that inhalation offers both very rapid absorption[1] and some control over dosage.

Despite its widespread use, its effect on respiration is not documented; clinical reports from the last century are inconclusive.[2] Therefore, we began to study the influence of marihuana on respiration in health and disease. This report concerns the acute effect of marihuana smoke on the normal tracheobronchial tree and on respiratory control.

Abbreviations Used	
delta-9 THC:	delta-9 tetrahydrocannabinol
$D_{L_{CO}}SB$:	carbon monoxide diffusing capacity (single breath)
FEV_1:	forced expiratory volume in first second
FVC:	forced vital capacity
MMEF:	maximal mid-expiratory flow
R_{AW}:	airway resistance
SG_{AW}:	specific airways conductance
TGV:	thoracic gas volume
$\dot{V}_E$:	minute ventilation

METHODS

Subjects

The volunteers were students from a local academic institution who responded to an advertisement: "Smoke for Science and Dollars." Their ages ranged from 18 to 26 years; informed consent and, for those under 21, parental consent were obtained.*

The subjects were screened by a psychiatric interview, medical-history questionnaire, physical examination, chest roentgenogram and comprehensive pulmonary-function tests. They had to meet the criteria of clinical normality. Furthermore, prior experience of marihuana smoking was required.

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Screening Pulmonary-Function Studies

These tests included conventional steady-state spirometry with determination of minute ventilation, oxygen uptake and lung volume compartments including functional residual capacity by helium rebreathing. Dynamic tests consisted of analysis of the forced vital capacity (FVC) for volume and per cent exhaled in the first second (FEV_1), the maximal mid-expiratory flow (MMEF), and peak expiratory flow rate; the carbon monoxide diffusing capacity ($D_{LCO}SB$) was determined by the single-breath method. All these measurements were made on a 13-liter spirometer system with adequate dynamic characteristics (linear within ± 1 per cent with tidal volumes from 0.5 to 3 liters, with frequencies to 120 cpm and flow rates to 11.6 liters per second); spirographic and gas analyses, as well as computations were performed by small on-line computers.[3] The best of three efforts was selected and compared to normal predicted values.[4]

Airway resistance (R_{AW}) and thoracic gas volume (TGV) were measured in a constant-volume body plethysmograph.[5] Airway conductance, the reciprocal of R_{AW}, was expressed per liter of TGV, as specific conductance (SG_{AW}). Tests were performed in triplicate before smoke administration and at two to four, six to eight and 20 minutes after smoking.

Flow-volume loops[6] permitted a second method of analysis of the airway mechanics. Volume, measured in a 10-liter waterless piston spirometer, was plotted against flow, obtained by electrical differentiation of the volume signal, on a rapidly responding X-Y recorder. The maneuvers were performed in the following sequence: after several tidal-volume loops, the subject exhaled slowly to residual volume and inspired to ½ of his previously measured FVC. A meter indi-

cated the volume of air to which he was to inspire. He then exhaled as rapidly and as completely as possible. The flow rate was measured at ½ of this volume — that is, at 25 per cent of vital capacity. Loops were recorded in triplicate before smoking and at four to six, eight to 10 and 20 minutes after smoking.

Respiratory-center sensitivity was measured by a closed-circuit rebreathing method.[7] A 9-liter water spirometer initially contained 95 per cent oxygen and 5 per cent carbon dioxide; every effort was made to continue rebreathing until the inspired carbon dioxide reached 9 per cent. A small computer continuously recorded the instantaneous respiratory rate, tidal volume, minute ventilation ($\dot{V}_E$) and end-tidal carbon dioxide tension from a nondispersion infrared spectrophotometer. Subsequently, the slope of the line, expressed in liters per minute per torr of carbon dioxide, was calculated, as well as the minute ventilation at 9 per cent end-tidal carbon dioxide (64 torr). Studies were performed twice before and once after smoking.

The heart rate was recorded continuously throughout these experiments.

Drug Administration

We used a modification of the method of Renault et al.[8] to allow control over the amount of smoke available for absorption. We substituted a box-balloon system for the spirometer (Fig. 1). The smoke from the combustion of a carefully weighed amount of marihuana was drawn into the rubber bag, itself in a box connected to a spirometer so that the volume of gas in the bag could be measured. This modification permitted a more homogeneous dilution and cooling of the smoke and prevented its contact with the water surface of the spirometer. The smoke was mixed with enough room air to fill the bag to a volume of 9 liters.

The marihuana supplied by the National Institute of Mental Health was *Cannabis sativa*, female, Mexican grown, crop of 1969. One batch had a concentration of 2.6 per cent delta-9 tetrahydrocannabinol (delta-9 THC), and the other 1.0 per cent. The subjects were assigned at random the high or the low concentration. Each then received the total smoke from the burning of 3.23 mg of marihuana per kilogram of body weight. This allowed the delivery of identical volumes of smoke with different amounts of delta-9 THC: 84 μg per kilogram for the high and 32 μg per kilogram for the low concentration. The material was analyzed before delivery and again eight months later. It was kept at 4°C until used.

One investigator (L.V.) prepared the dose and monitored the electrocardiogram. The subjects as well as the other investigators were told that the test might involve marihuana of good or of poor quality or a placebo. It was acknowledged that the subjects would recognize which material they had received, and they were asked to refrain from commenting until all measurements were completed. The fact that no placebo was used was not revealed to the subjects nor to the other investigators until the entire study had been completed.

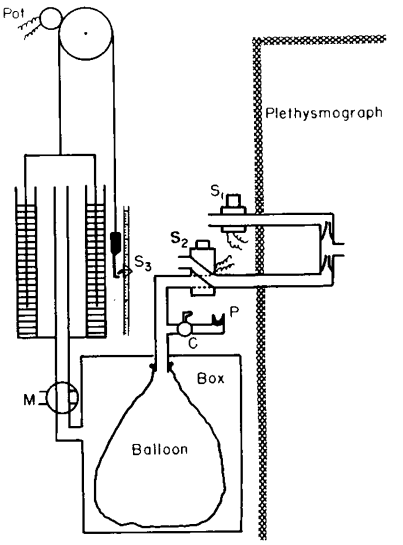

Figure 1. Apparatus Used for the Administration of Marihuana.
The 20-liter balloon is emptied as follows: the manual 3-way valve (M) is turned to connect the 6-liter spirometer to room air and it is filled; M is turned to connect the spirometer to the box, and the bell is lowered. This is repeated until the balloon is empty. A weighed amount of marihuana is then placed in the small metal pipe (P). A petcock (C) is opened, and the pipe is smoked slowly by raising the spirometer bell gently. Usually, the marihuana was burned completely in 30 seconds with about 3 liters of air. The spirometer bell is then emptied through M and raised repeatedly until exactly 9 liters of gas has entered the balloon. The petcock (C) is then closed. The subject is seated in the body plethysmograph inspiring room air through a three-way solenoid valve (S_2) and expiring through a two-way solenoid valve (S_1). This circuit is guarded by two flutter valves to provide unidirectional flow. The spirometer bell is then raised, and a microswitch (S_3) is set to permit an inspiration of 3 liters. The subject then expires to residual volume. A control circuit, including a timer, is triggered to switch S_2 to the balloon, to close S_1 and to sound a buzzer, signaling to the subject to inspire slowly. After inspiration of exactly 3 liters S_3, activated by the spirometer, closes S_2. The subject now holds his breath for 20 seconds. The end of the period is signaled by the buzzer, and S_1 and S_2 open, permitting breathing of room air for 30 seconds. This maneuver is repeated twice.

Results

There were eight male subjects and one female in the high-dose group and seven male and one female for the low-dose group. Both groups had identical mean ages, 21.8 years, and similar stature. There was one slight cigarette smoker (two package-years) in each group; the others were nonsmokers. Marihuana use ranged from heavy or 15 "high" per week-years to light or two "high" per week-years, with a similar distribution in both groups (Table 1).

Screening Lung-Function Studies

Results (Table 1) were within the normal range for each subject. There were no significant differences between group means except that the low-dose group had a slightly larger mean per cent predicted residual volume ($p<0.05$). All chest roentgenograms were normal.

Table 1. Initial Screening Data on Respiratory Function.

DATUM	HIGH DOSE		LOW DOSE	
NO. MALE/FEMALE	8/1		8/1	
	DETERMINED ± SD	MEAN % PREDICTED	DETERMINED ± SD	MEAN % PREDICTED
Age (yr)	21.8 ± 1.3		21.8 ± 1.4	
Height (cm)	175.5 ± 8.6		181.1 ± 6.3	
Weight (kg)	65.8 ± 8.2		70.6 ± 12.7	
FVC (liters)	5.18 ± 0.73	104	5.5 ± 1.04	110
FEV_1 (%)	84 ± 6		80 ± 7	
$MMEF_{25-75}$ (liters/sec)	5.4 ± 1.3	101	4.7 ± 11	92
Total lung capacity (TLC) (liters)	6.39 ± 0.83	102	6.98 ± 1.15	111
Residual volume (RV) (liters)	1.32 ± 0.15	106	1.57 ± 0.26	127
RV/TLC (%)	20.8 ± 2.5		22.8 ± 2.6	
$D_{L_{CO}}$ SB (ml/min/torr)	35.2 ± 6.5	98	33.5 ± 7.5	98

Subjective Response

The subjects who were given the high concentration readily recognized that they had received "good dope." Their comments ranged from "among the best trip ever" to "more than 7.5 on a scale of 10." Those given the low concentration were equally certain that they had received "practically nothing" or "very little" marihuana.

Heart Rate

The familiar rise[9] (Fig. 2) was apparent in the high-concentration group. The base-line value, 82 ± 6 (mean ± S.D.) rose to 105 ± 18 at 15 minutes. A two-way analysis of variance for repeated measures — that is, two drug levels with several measurements on the same subjects — showed (a) that the effect of the two drug levels were different ($p = 0.022$, 2-tailed), (b) that the drug effect changed over time ($p = 0.002$, 2-tailed), and (c) that this change over time was different in the "high" group as compared to the "low" group ($p = 0.005$, 2-tailed). This change over time was curvilinear ($p<0.001$) and significantly different from that of the "low" group ($p<0.01$).

Airway Resistance

In every subject of each group R_{AW} decreased (Fig. 2). The mean in the "high" group fell from 1.90 ± 0.067 liters per second per centimeter of water to 1.38 ± 0.42 at 20 minutes and for the "low" group from 2.06 ± 0.31 to 1.67 ± 0.32.

Specific Airway Conductance

Since all measurements were made at the same mean lung volume (Fig. 2), the changes in SG_{AW} mirrored the resistance changes. The two-way analysis of variance showed that SG_{AW} rose over time for all subjects ($p<0.001$, 2-tailed). The difference between the two drug concentration groups did not quite reach significance ($p = 0.059$, 2-tailed). This discrepancy occurred because the "low" group showed a significant rise at 20 minutes as compared to its own base line (paired comparison t test, $p<0.05$, 2-tailed), suggesting that SG_{AW}, measured by the plethysmograph, is particularly sensitive to even a low concentration of delta-9 THC.

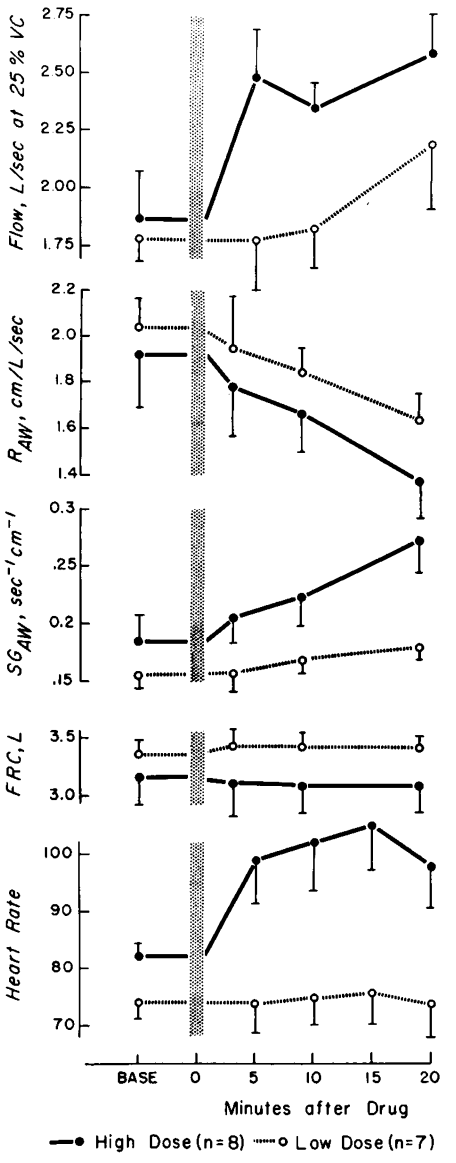

Figure 2. Physiologic Measurements at Base Line and at Intervals after Marihuana Smoking.

Mean values and the standard error of the mean are indicated for the high-dose and low-dose groups. A marked increase in the heart rate was observed only in the former. Concomitantly, there was a significant fall in the R_{AW}, and since the functional residual capacity (FRC) remained unchanged, there was a corresponding rise in SG_{AW}. These changes in airways dynamics were also reflected by a progressive increase in the airflow rate at the point when the subjects had exhaled down to 25 per cent of vital capacity. Significant, but lesser, airways changes occurred in the low-dose group.

Flow-Volume Curves

The bronchodilator effect was also observed in the flow-volume curves (Fig. 2). The mean expiratory flow rate at 25 per cent of vital capacity increased from 1.79 ± 0.24 to 2.59 ± 0.43 liters per second for the "high", and from 1.88 ± to 0.49 to 2.20 ± 0.69 liters per second for the

"low" group. Analysis of variance showed an increase in the flow rate over the successive measurements for all subjects ($p = 0.002$, 2-tailed), and the trend of this increase was different for the two treated groups ($p = 0.26$, 2-tailed). Since the "low" group showed little increase at the 20-minute period, it may be that this method is less sensitive than the plethysmograph for the effect of delta-9 THC.

Correlation between Bronchodilation and Tachycardia

Predictably, there was no meaningful correlation between the actual heart rates and SG_{AW} values at base line (Pearson's $r = 0.03$), but the correlations became significant after drug administration (at five minutes, $r = 0.50$; at 10 minutes, $r = 0.71$, $p<0.01$; and at 20 minutes, $r = 0.68$, $p<0.01$). The heart-rate change at five minutes after the drug was the best predictor of the airway change at 20 minutes after smoking ($r = 0.81$, $p<0.001$). This observation indicates that the drug effects in the two organ systems are highly correlated but with different time characteristics.

Carbon Dioxide Sensitivity Curves

The curves were measured twice before drug administration. We observed the wide variation between individual responses of normal subjects as has been reported by others.[10] In some subjects the two trials matched well, whereas in others the ventilatory response was decreased the second time, but there was no statistical difference between the two trials. For each test the calculated best-fit line had a correlation coefficient of 0.91 or more. After marihuana smoking, there was no significant change with either concentration when the response of the respiratory center was expressed in terms of the slope of the curve (Fig. 3). Similarly, there was no change of ventilation at 9 per cent carbon dioxide; this value was 52.9 ± 32.9 before and 65.3 ± 30.6 liters per minute after smoking for the "high" and 69.9 ± 31.2 and 64.5 ± 21.5 liters per minute respectively for the "low" group. The threshold also did not change.

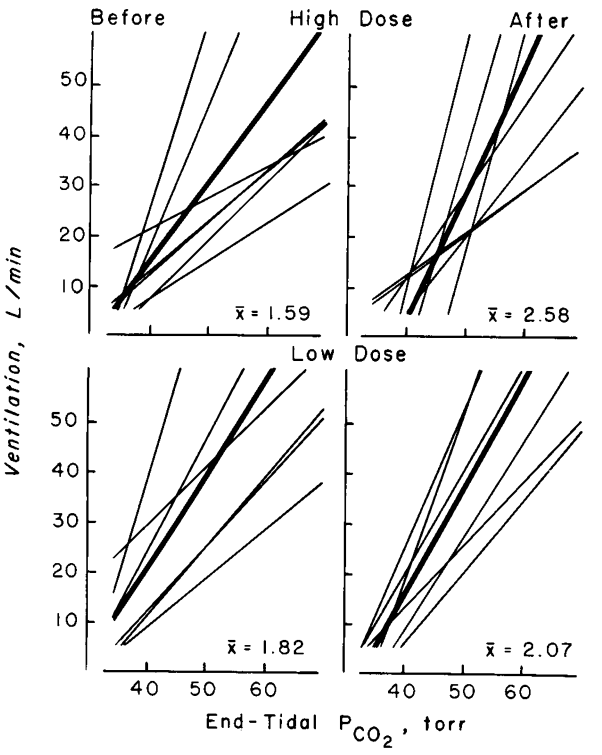

Figure 3. Ventilatory Response to Increasing Inspired Carbon Dioxide Concentrations before and after Marihuana Smoking.
Minute ventilation and end-tidal carbon dioxide tension (Pco_2) were monitored continuously during rebreathing and recorded by a small computer; a best-fit line was drawn for each individual response ($r < \geqslant 0.91$ for each test). The mean response, $\bar{x}$, in liters/torr Pco_2 is indicated. The difference after marihuana smoking was not significant in either group.

Discussion

The advantage of the mode of administration that we selected is that it permitted a certain measure of control over the amount of smoke offered for absorption: two different concentrations of delta-9 THC were presented in identical amounts of "vehicle." This method, although not unlike the water-pipe and similar technics often used to inhale marihuana smoke, is sufficiently unique to caution against generalization. It is possible that the temporary storage in the rubber bag, the dilution and the cooling of the smoke caused some loss of 9-delta THC as well as potentially irritating substances.

Body plethysmograph data indicate that marihuana smoke has a striking bronchodilator effect. The flow-volume curves support this observation. The mean decrease of 38 per cent in R_{AW} compared very well with the mean increase of 45 per cent in flow rate at ¼ of vital capacity. The effect was dose related. When the heart rate was taken as an index of delta-9 THC physiologic activity, a dose-response relation is strongly supported. Tobacco smoke, which also causes tachycardia, lead to an increase in airway resistance,[11] which is due to constriction of large airways.[12] This effect is mediated by isoproterenol and atropine.[13] Cigarette smoking has not been studied with the present box-balloon system.

These findings are congruent with those of Beaconsfield et al.[14] regarding the cardiovascular system. They observed that tachycardia and vasodilatation after marihuana smoking are still present after administration of atropine but not after pretreatment with propranolol. They suggest that cannabis may be a beta-adrenergic agent.

Our observations of lack of an effect of marihuana on the respiratory center at the doses used is not surprising in view of its usual clinical effect, but it sharply contrasts with the marked depressive effects of the opiates and related compounds.[13]

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ECHOCARDIOGRAPHIC MEASUREMENT OF THE LEFT VENTRICULAR OUTFLOW GRADIENT IN IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

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Abstract The characteristic hemodynamic abnormality in idiopathic hypertrophic subaortic stenosis is a highly variable subaortic obstruction to left ventricular ejection. Previous studies have shown that during systole, the left ventricular outflow tract is narrowed by motion of the anterior mitral leaflet toward the ventricular septum. If this were responsible for the obstruction, we believed it would be possible to predict quantitatively the gradient in the disease from echocardiograms. We computed an obstruction index by dividing the duration of outflow narrowing by the mean septal-anterior mitral-leaflet distance and compared the result with the simultaneously measured peak left ventricular outflow pressure gradient in 56 beats from 11 patients with this form of subaortic stenosis. The correlation between the obstruction index and gradient was highly significant (gradient = 1.8 obstruction index - 35; r = 0.95). Echocardiography thus confirms that the pressure gradient in the disorder is caused by narrowing of the left ventricular outflow tract between the anterior mitral leaflet and ventricular septum, and the technic may be used to quantitate the gradient. (N Engl J Med 288: 989-993, 1973)

THE characteristic hemodynamic abnormality in idiopathic hypertrophic subaortic stenosis is a highly variable subaortic obstruction to left ventricular ejection.[1] In the early 1960's the mechanism responsible for the obstruction was thought by many investigators to be obliteration of the left ventricular outflow tract by the markedly hypertrophied and vigorously contracting ventricular septum.[1-5] Others, however, questioned whether true outflow obstruction existed, and suggested that the gradient was caused by entrapment of the ventricular catheter in the obliterated left ventricular apex.[6] Subsequently, angiographic studies revealed an abnormal forward motion of the anterior mitral leaflet during ventricular systole,[7-10] a finding confirmed more recently by echocardiography.[11-16] (Fig. 1 and 2). On the basis of these observations it has been suggested that obstruction to left ventricular outflow does occur in the disease and is caused by apposition of the forward-lying anterior mitral leaflet with the hypertrophied ventricular septum.[7-18]

If the narrowing produced by the apposition of these two structures is responsible for the gradient in patients with this disorder, we surmised that the magnitude of the left ventricular outflow gradient would be inversely proportional to the septal-mitral leaflet distance (i.e., the distance between the septum and the anterior mitral leaflet during systole), and directly proportional to the duration of outflow narrowing (i.e., the time during which these structures are in close proximity). Moreover, if these two assumptions were correct and the echocardiogram reliably measured these variables, we hypothesized that the pressure gradient across the left ventricular outflow tract might be measured noninvasively by echocardiography.

The present study was undertaken to test this hypothesis by comparison of the subaortic pressure gradient with the simultaneously recorded motion of the anterior mitral leaflet and ventricular septum in patients with idiopathic hypertrophic subaortic stenosis subjected to a variety of interventions.

METHODS

Eleven consecutive patients suspected of having the disease in whom adequate echocardiograms could be obtained were studied in the cardiac catheterization laboratory after sedation with 100 mg of pentobarbital. The diagnosis was confirmed by retrograde catheterization of the left side of the heart in every patient by the usual catheterization criteria.[18] Concomitantly, asymmetric septal hypertrophy was demonstrated by

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