Cardiovascular Effects of Marihuana in Man

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Twenty-eight subjects, matched by sex and Cannabis experience, received by controlled inhalation under single- and double-blind conditions 600 mg marihuana placebo and marihuana. Forearm, venous and arterial pressures, forearm blood flow, and heart rate were recorded while supine. Derived functions such as "dp/dt", regional arterial resistance, and venous compliance were calculated from these variables. (1) Placebo produced no intoxication or consistent physiological responses. (2) Marihuana produced intoxication in all Cannabis-experienced and half the non-experienced subjects. (3) Cardiovascular responses occurred in response to marihuana in the absence of intoxication, indicating that they were not psychogenically mediated. (4) Inhibition of vagal tone may contribute to the tachycardia seen with marihuana. (5) Reflexly mediated sympathetic responses may be muted in the presence of marihuana.

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Vingt-huit sujets sains, groupés en fonction de leur sexe et de leur familiarité avec le Cannabis, ont reçu dans des conditions controlées à simple et double insu une inhalation de 600 mg de marihuana ou de placébo de marihuana. La pression veineuse et artérielle et le débit sanguin du bras ainsi que la fréquence cardiaque sont enrégistrés en position couchée. A partir de ces données, nous calculons d'autres paramètres dont la dp/dt, la résistance artérielle régionale et la compliance veineuse. (1) Le placébo ne produit ni intoxication ni effets physiologiques. (2) La marihuana produit une intoxication chez tous les sujets familiers et chez la moitié des sujets naifs. (3) Les effets cardiovasculaires surviennent même en l'absence d'intoxication suggérant ainsi qu'ils ne seraient pas d'origine psychogénique. (4) L'inhibition du tonus vagal contribuerait à la tachycardie observée avec la marihuana. (5) Les réponses reflexes médiées par le système sympathique seraient diminuées en présence de marihuana.

[Traduit par le journal]

Introduction

Conjunctival injection and dose-dependent tachycardia are well-recognized physiological responses to acute administration of marihuana in man. Other effects on the cardiovascular system are less well-established. Arterial blood pressure is usually unchanged or increased slightly in the supine subject, but generally is decreased in the upright individual (Isbell *et al.* 1967; Woskow *et al.* 1970; Weiss *et al.* 1972). This observation suggests the possibility of a dilator effect on capacitance vessels with secondary effects on venous return, cardiac output, and arterial pressure. Two groups of investigators have also reported that Cannabis increases forearm blood flow and interferes with the integrity of peripheral vascular reflex responses in man (Weiss *et al.* 1972; Beaconsfield *et al.* 1972). In addition, considerable evidence has accumulated to indicate effects in man on both the sympathetic (Beaconsfield *et al.* 1972; Kiplinger and Manno 1971; Drew *et al.* 1972; Martz *et al.* 1972) and parasympathetic (Johnson and Domino 1971) divisions of the autonomic nervous system. It is clear, then, that, in man, marihuana has significant cardiovascular effects, both on the heart and peripheral circulation. Unfortunately, differing experimental protocols, frequently employing oral administration of drug, make it difficult to assess the dimensions of these changes and to establish mechanisms of action. The present study employs an experimental design that overcomes many of the limitations of earlier studies.

The Interim Report of the Canadian Com-

mission of Inquiry into the Non-Medical Use of Drugs (Le Dain 1970) notes: "... Subjects must be similar to the general population ... Variables such as age, sex and social class ... must be taken into careful consideration ... The dose, mode of administration and general circumstances of the study must be relevant to the pattern of use in the general population." The Commission also discusses the need for the use of a placebo, single-blind, and, when possible, double-blind techniques. In the subsequent Cannabis report (Le Dain 1972) the Commission also presents arguments for employing female as well as male subjects in studies on Cannabis derivatives. These factors in experimental design have been discussed by Weil *et al.* (1968) and by Kionoff (1973).

In the design of the present study, considerable emphasis was placed on such factors as: subject selection representative of the general population, a socially relevant psychological set, physical setting, and delivered dosage, as well as on consideration of possible sex differences and differences related to prior Cannabis use.

Methods

This study was part of a general study concerned not only with cardiovascular, but also with sensory and perceptual effects of marihuana. Volunteers were obtained through newspaper articles which indicated that Cannabis-experienced and Cannabis-naive adult subjects (21 years or older) of both sexes from all sectors of the community were sought. A form which requested only a minimum of information was completed and returned; no attempt was made to elicit a drug history at this time. The average age of the 1600 volunteers was 30 (range, 21–85); average education was 12.7 years (range, "no education" to 3 years postdoctoral). No one occupational or socioeconomic group had disproportionately large representation; students, for example, comprised only 20% of the volunteers. The percentage of males was 51%. Over 1½ years, 25% of the volunteer pool was interviewed after random selection.

At interview, after assurance of confidentiality, volunteers were asked about personal usage of Cannabis derivatives; about 50% had previous experience. Details of experimentation were described and subjects were told that they could volunteer for either psychological or physiological studies.

All prospective subjects next completed a detailed medical history, part of which was an extensive drug history, and had a detailed physical examination. Volunteers were excluded who had the following: diabetes, chronic ulcer, urinary tract infections, renal failure, recent liver disease, confirmed cardiovascular or pulmonary disease, "hard" drug abuse, alcohol abuse, or who were pregnant. (In the case of women of childbearing age, pregnancy tests were done the day of experimentation.) Finally, all subjects were interviewed by a psychiatrist.

Volunteers were considered "non-experienced" with respect to Cannabis products if they had never used them in any form; "experienced" volunteers were defined as those who had used Cannabis derivatives on one or more occasions in the past 2 years and who had experienced an unequivocal "high". Volunteers who had tried marihuana or hashish but who had experienced no characteristic symptomatic effects were excluded.

Volunteers interested in participating in physiological experiments were taken to the room where the experiments were done and the methodology was described in detail with no attempt to minimize the procedure. Subjects were self-selecting insofar as each had the option of not volunteering for this particular experiment. Each subject was paid $40.00 for participation.

Experimental requirements were for 28 subjects between the ages of 21 and 55 years, equally divided between males and females. The exclusion of those under 21 was based on medical–legal considerations and of those over 55 on the basis of possible increased risk of complications. Single-blind studies required 16 subjects, with equal representation from "experienced" and "non-experienced" groups; double-blind studies required 12 "experienced" subjects.

Our "physiological subjects" were therefore selected both by themselves and by us. In spite of this, their general characteristics were very similar to the total volunteer pool (average age 29.7 *vs.* 30.0; average education 13.2 years *vs.* 12.7 years).

The protocols and informed consent forms used were approved by two separate university ethics committees. The informed consent form employed described in detail the methodology and possible complications; it also indicated that subjects would receive "an inert substance and/or marihuana", and constituted an agreement that for 7 days before experimentation, the subject would not take illicit drugs or other drugs, such as patent medicines, which might influence the central nervous system or cardiovascular system. Subjects were allowed to take coffee, tea, and tobacco but were instructed not to take alcoholic beverages for 24 h before testing. There was no guarantee that these proscriptions would be followed; accordingly, both to ensure adaptation to the environment, and to be reasonably confident that the subjects were drug-free, experiments were not done for 6–12 h after arrival.

All experiments were done in an apartment setting which was informal and non-threatening. The experimental room was equipped with a modified La-Z-Boy chair (Fig. 1). Colored posters were hung on the walls; investigators were dressed informally. The room was not a constant temperature room but the temperature was consistently about 22 °C.

All procedures were done by at least two physicians with emergency equipment present. While objective

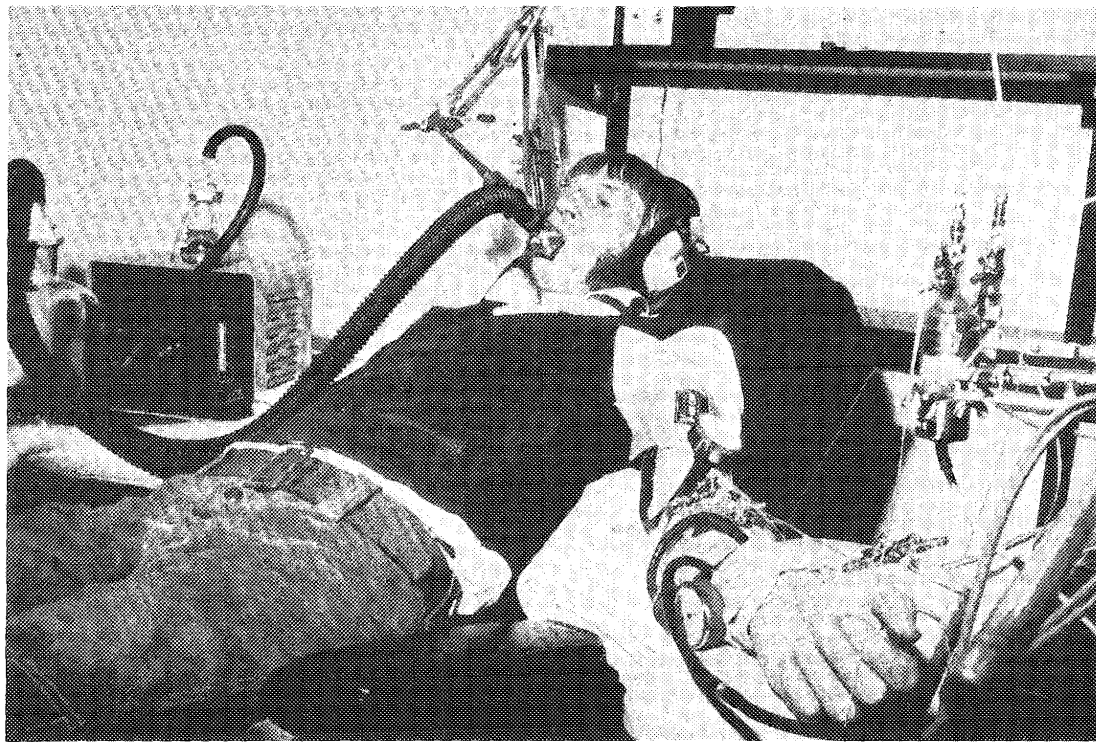

FIG. 1. Illustration of procedure for drug administration and physiological recording. The ignition chamber and dilution apparatus are shown at the left. Under experimental conditions, the subject was more supine than is shown in the photograph.

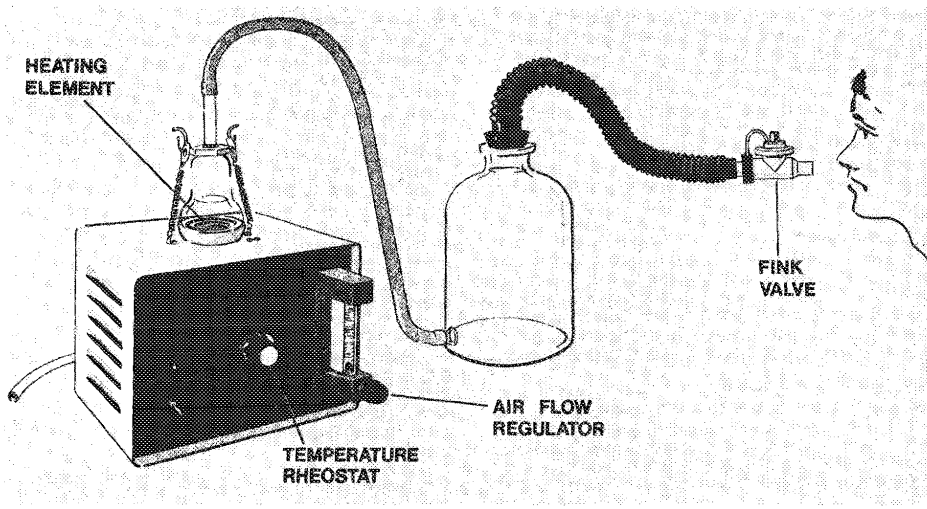

FIG. 2. Details of system used for administration of marihuana and placebo.

intoxication had usually disappeared within 2–3 h, subjects were detained a minimum of an additional 9 h. They were never left without an attendant and were driven home at the end of the observation period. All subjects had repeat medical examinations approximately 2 weeks after participation.

The possibility of administering drug by cigarette was considered and rejected since the tightness of packing in cigarette manufacture, the subject's breathing characteristics, and the variable loss of smoke (particularly in a non-cigarette smoker) might modify the response. Accordingly, we sought a sys-

tem (*a*) which could be used by smoker and nonsmoker, (*b*) which incinerated a known quantity of substance under standardized conditions, and (*c*) in which quantification of the amount of smoke received was possible.

Fig. 2 shows the administration apparatus. The smoking device consisted of a small forced air electric grill combustion chamber connected by tubing to a 4 liter glass reservoir bottle connected in turn through tubing to an anesthetic valve. The subject was instructed to breathe normally and not to try to prolong retention of the smoke. The heating element and a forced air system permitted the material to be combusted under constant conditions. The "reservoir" provided sufficient dilution of the smoke with air so that it was tolerable to the nonsmoker. The one-way valve provided a system whereby all expired air was vented.

The "active" (batch 2 PF-126) and the "placebo" (solvent extracted) marihuana were manicured on receipt to remove twigs, but to retain seeds. The placebo was confirmed by local assay to contain less than 0.01% Δ-9-tetrahydrocannabinol (Δ^9THC). The active substance was stated to contain 1.5% Δ^9THC. This was also confirmed by local assay using solvent extraction and gas–liquid chromatography, assaying against a NIMH Δ^9THC standard stored under nitrogen. (There is some reason to believe, however, that the standard may be in error by 33%, and that the active marihuana may contain only 1.0% Δ^9THC.)

The breathing apparatus and the expired air (passed through cigarette filters) were assayed for Δ^9THC. Regardless of absolute amounts, under the conditions of our experiments, 60–70% of the Δ^9THC contained in the marihuana was lost in the breathing apparatus and expired air. There was no deterioration with time of Δ^9THC content of stored marihuana.

Detailed Protocols

The subject, who was fasted at least 3 h, lay supine in the reclining chair and a 6 in. (15.2 cm) blood pressure cuff attached around the upper arm was connected to a reservoir which inflated it at 40 mm Hg pressure and at a cycle length of 12 s (6 s "on", 6 s "off"). A 2 in. wrist cuff could be inflated by a handbulb (to 240 mm Hg).

A Whitney mercury-in-rubber strain gauge was attached to the forearm and calibrated. In the cubital fossa, a catheter (19 gauge Intercath®) was then inserted retrograde into a vein draining forearm muscle, and advanced until it wedged against a valve. It was then pulled back slightly and taped in place. An arterial catheter (B-D Longdwel® 18 gauge) was inserted antegrade into the brachial artery at the same site. Both venous and arterial punctures were done using minimal amounts of 1% lidocaine (Xylocaine®). The arm was adjusted to heart level and venous and arterial catheters were attached to Statham pressure transducers (P23 BB and P23 Db, respectively) calibrated at heart level. Standard electrocardiogram (EKG) limb leads were attached.

The EKG and strain gauge inputs were led by coaxial cable to Beckman preamplifiers and amplifiers. Outputs were fed simultaneously into a Beckman RM recorder, into a four-channel oscilloscope, and into a Precision Instrument 6200 FM tape recorder. The recorder, run at slow speed, permitted identification of events occurring over many minutes; the oscilloscope permitted observation of rapid events, such as the shape of the pulse wave; finally, recording on tape permitted a subsequent time base compression or expansion, as well as computer analysis. All variables were recorded continuously.

Throughout, the subject was permitted to listen to music of his or her choice through stereo earphones. This occupied the subjects and prevented them from overhearing and possibly misinterpreting conversations. The experimenters replied to any comments but made no attempt to initiate discussion or question the subject once the experiment started. In addition, the room was semidarkness with only sufficient illumination for experimental procedures.

Pilot Studies

The objects of pilot experiments were (*a*) to determine the practicability of making physiological measurements with intervention techniques in intoxicated subjects, (*b*) to determine in a crude way whether body mass, sex, or previous drug experience modified the dose necessary, and (*c*) to establish whether changes in protocol would be necessary. These pilot experiments were done using staff members as subjects. Administration of drugs (varying doses) was "single-blind".

Single-Blind Studies

The initial preparation of the subject was the same as that described previously. Each subject was told that he or she would receive "half of the material now and the other half after a pause". No subject correctly appraised that he or she would receive placebo then marihuana.

During an initial control period of approximately 15 min, basal measurements were made and the following procedures were done sequentially: inflation of wrist cuff to 240 mm Hg (2 min), Valsalva maneuver (20 s), and cold pressor test (opposite hand in water at 1 °C for 1 min). Sufficient time was allowed between procedures for recorded parameters to return to base line.

The subject breathed through the mouthpiece for at least 2 min before the material was ignited and smoke was delivered. Six hundred milligrams of marihuana placebo was administered by inhalation over a period of 15 min (200 mg every 5 min). At the end of this time, the wrist cuff inflation, Valsalva maneuver, and cold pressor test were repeated and calibration of instruments was checked.

Twenty minutes after cessation of placebo administration, marihuana in a dose of 600 mg was administered over 15 min (200 mg every 5 min) and the above tests were repeated. The experiment was continued at least 30 min after the termination of smoking marihuana. Subjects were told they could request termination of the experiment at any point; none requested premature termination, although most experienced some discomfort by the end of the procedure.

Double-Blind Studies

The protocol for these studies was identical with those of the single-blind studies with the exception that (*a*) only "experienced" individuals were used as subjects and (*b*) the cold pressor test and the Valsalva maneuver were omitted.

An investigator not associated with the study coded subjects as follows: (*a*) marihuana followed by placebo, four subjects (two male, two female); (*b*) placebo followed by placebo, four subjects (two male, two female); (*c*) placebo followed by marihuana, four subjects (two male, two female). The code was not broken until the entire series of 12 subjects was completed.

Following analogue to digital conversion, records were analyzed off-line with a PDP 11 computer, using a program which gave the following functions over any preset interval of time: heart rate, mean venous pressure, systolic, diastolic, and true mean arterial blood pressures, "dp/dt", calculated forearm blood flows, arterial resistance, and venous compliance.

Mean arterial pressure was calculated from the area under the pulse contour curve.

Determination of true dp/dt, *i.e.*, the rate of rise of pressure per unit time, would involve pressure recording from the left ventricle. The value of "dp/dt" calculated here was derived from the slope of the brachial artery pulse wave. The value must be considered only an approximation of the true dp/dt.

Forearm blood flows were calculated from the formula (Eq. 1):

$$[1]\quad \text{Flow} = 2 \times 60 \times 100 \times (\text{Slope of strain gauge tracing/Circumference}) = (\text{ml}/100\ \text{ml tissue/min})$$

Arterial resistance (A.R.) was calculated from the formula (Eq. 2):

$$[2]\quad \text{A.R.} = ((\text{Mean arterial pressure} - \text{venous pressure}) \times 60 \times 1332)/\text{Flow} = (\text{dynes} - \text{s/cm}^5)$$

Since cardiac output was not measured, this value is a regional (forearm) resistance and does not necessarily correlate with total peripheral resistance (T.P.R.).

Venous compliance (V.C.) was calculated from the formula (Eq. 3):

$$[3]\quad \text{V.C.} = \text{Flow}/(\Delta\ \text{Venous pressure} \times 1332 \times 60) = (\text{cm}^5/\text{dyne} - \text{s})$$

The paired "*t*" test was employed in statistical analysis of data.

Results

Data obtained from our previous studies indicated that solvent-extracted marihuana was an effective placebo and that a fixed dose of 600 mg marihuana would produce intoxication in about 65% of non-experienced subjects and 95% of experienced subjects. (Subjects were considered intoxicated if they exhibited giggling, euphoria, and difficulty with speech.) In pilot experiments, the first two subjects, experienced males closely associated with protocol development, received only marihuana in a dose of 600 mg, and both experienced unpleasant intoxication, characterized by anxiety or pain. A similar response was seen in a third subject, a non-experienced female who also exhibited considerable anxiety before commencement of the procedure. The next two pilot subjects, both of whom had previous experience with Cannabis, fortuitously had participated previously in a study which involved similar intervention techniques, but no marihuana administration. Both of these subjects became pleasantly intoxicated with marihuana. Similar responses were noted in a sixth subject, a non-experienced male.

These experiments emphasized the importance of "set," and, in subsequent experimentation, additional measures were taken to relieve anxiety (*e.g.* demonstration of equipment prior to volunteering and exposure and adaptation to the apartment setting 6–12 h before the experiment).

In spite of these measures, we felt that the difficulties that might be encountered could not be anticipated fully and, in the interests of subject safety, the first series of experiments was done single-blind.

Single-Blind Experiments

The characteristics of the subject population are given in Table 1. All of the subjects used alcohol in moderation (less than six bottles of beer per week or less than 6 oz of spirits). Only two subjects had previous experience with other "street drugs" (amphetamines on one occasion, only, in each subject; numerous occasions of use of hallucinogens, chiefly lysergic acid diethylamide (LSD) in both). Experienced subjects varied considerably in their use of Cannabis but all had used marihuana or hashish at least once a month for at least 3 years.

Pilot experiments demonstrated an "anticipation" effect in that heart rate frequently changed before smoke was presented. In all studies, therefore, we accepted as control values those taken just before the subject accepted

TABLE 1. Characteristics of subject population

Drug order	Group	Age (years)	Weight (kg)	Education (years of schooling)	Occupation
			Single-blind		
P–M	Non-experienced males	51	83.0	9	Insurance
		29	80.0	9	Railroad worker
		49	97.0	15	Manager
		32	70.5	19	Graduate student
P–M	Experienced males	23	63.5	9	Jeweller
		23	70.0	15	Student
		24	71.5	10	Laborer
		32	81.5	15	Computer programmer
P–M	Non-experienced females	25	52.8	16	Practical nurse
		28	66.5	12	Receptionist
		25	58.0	18	University instructor
		37	96.4	9	Housewife
P–M	Experienced females	30	58.1	17	Housewife
		25	53.5	12	Keypunch operator
		25	55.7	12	Caretaker
		25	51.0	16	Housewife
			Double-blind		
P–P	Experienced males	22	60.5	13	Warehouse manager
		27	64.5	12	Office clerk
P–P	Experienced females	29	58.2	15	Nurse/Housewife
		41	61.4	15	Nurse/Housewife
M–P	Experienced males	29	88.5	14	Mechanic
		31	80.0	12	Manager
M–P	Experienced females	25	51.0	12	Nurse/Housewife
		21	66.8	12	Secretary
P–M	Experienced males	24	82.0	11	Plumber
		23	79.5	13	Autopaint mixer
P–M	Experienced females	23	44.3	12	Housewife
		23	63.4	16	Teacher

NOTE: P = placebo; M = marihuana.

the mouthpiece, which was routinely presented 2 min before the substance was ignited. Continuous recording also established that there was considerable variability in physiological measurements during the period of smoking either placebo or marihuana, and that this appeared to be related to the concentration of smoke. Accordingly all data collected during smoke inhalation were rejected. "Test" values were taken as those recorded 3 and 20 min, respectively, after termination of smoking. (These times were selected since during the intervening 17 min, wrist cuff occlusion, Valsalva maneuver, and cold pressor test were done.) The greater of these test values was taken as representing the maximal change produced.

As was the case with the pilot experiments, no subject became intoxicated in response to placebo. Moreover, subjects showed no consistent changes in heart rate, arterial blood pressure, or venous pressure following administration of placebo. In general, "dp/dt" tended to increase (not statistically significant), but there were no consistent changes in blood flow, vascular resistance, or venous compliance. The placebo responses to the Valsalva maneuver and cold pressor test were unchanged from control.

Marihuana produced slight intoxication, as judged subjectively, or as judged by the experimenters, in three out of eight non-experienced subjects. Slight intoxication was present in one experienced subject, heavy intoxication in another, and moderate intoxication in the remainder. Even though five non-experienced subjects exhibited no intoxication, they nevertheless all exhibited an increase in heart rate. A representative example is presented in Fig. 3.

Differences in the response to marihuana relative to placebo were examined by comparing pre–post smoking differences (marihuana)

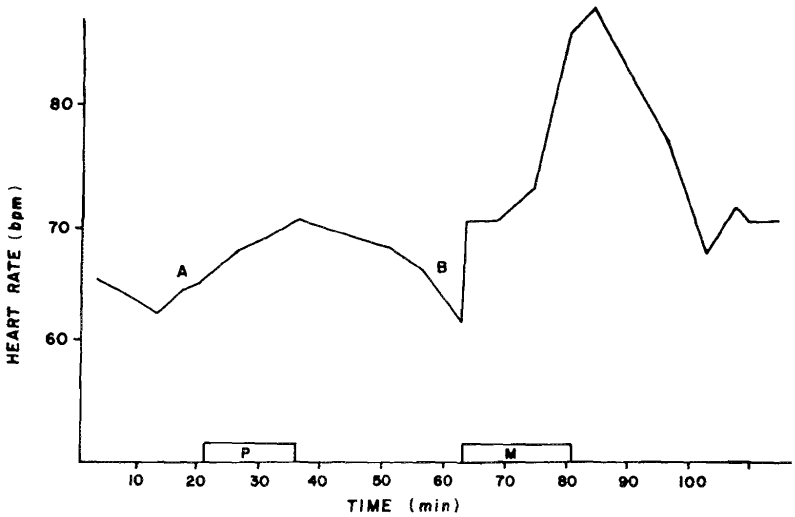

FIG. 3. Heart rate response (beats/min) in non-experienced subject that did not become intoxicated (no subjective or objective response) following placebo (P) and marihuana (M). A and B respectively indicate the points at which the Fink valve was presented to the subject.

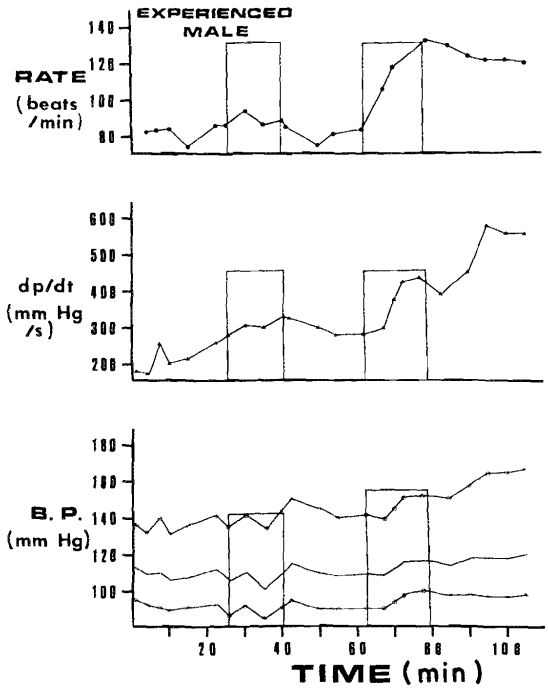

FIG. 4. Response to placebo (first block) and marihuana (second block) in an experienced male subject (single-blind). Data obtained during the actual period of administration may be unreliable due to the irritant effect of the smoke. The blood pressure (B.P.) data are those for systolic, mean, and diastolic pressures, respectively. Note that "dp/dt" is still increasing after marihuana at a time when heart rate is stable or decreasing.

with pre–post smoking differences (placebo). Using this comparison, non-experienced subjects showed statistically significant increases in heart rate ($P < 0.01$) and venous pressure ($P < 0.02$). Experienced subjects showed statistically significant increases in heart rate only ($P < 0.001$); the increase in venous pressure was not significant ($P < 0.1$). When all subjects, experienced and non-experienced, were grouped together, there were statistically significant increases in heart rate ($P < 0.001$) and venous pressure ($P < 0.02$). Changes in other variables were not statistically significant.

The magnitude of responses to marihuana in experienced subjects tended to be greater than in non-experienced subjects, but a statistically significant "experience" difference was noted only in the case of heart rate ($P < 0.02$) and "dp/dt" ($P < 0.01$). Fig. 4 shows responses in an experienced male subject to placebo and to marihuana. In this subject, as in all subjects who showed an increase in heart rate and "dp/dt", "dp/dt" was still increasing after heart rate had plateaued (or in some cases was decreasing).

There were no statistically significant "sex" differences in any variable. However, three of four experienced males exhibited a decrease in limb flow associated with an increase in resistance. The remaining experienced male, and three of four experienced females showed an

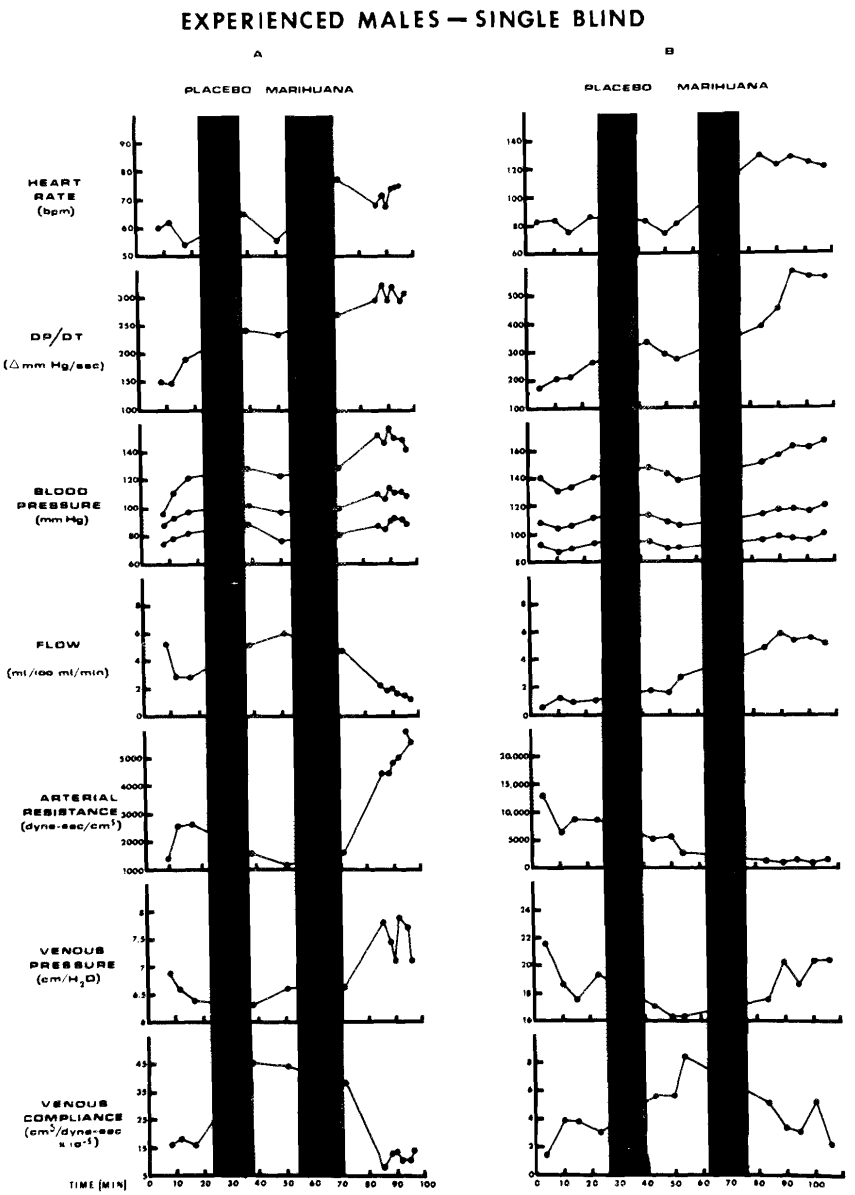

FIG. 5. Comparison of response to placebo (first block) and to marihuana (second block) in each of two experienced males (A and B) under single-blind conditions. Note that in response to marihuana one subject shows decrease in forearm blood flow while the other subject exhibits an increase.

increase in limb flow associated with a decrease in resistance. (Data were lost on the remaining female as a result of technical difficulties.)

Fig. 5 shows responses in two experienced male subjects to marihuana and to placebo. In response to marihuana, both subjects exhibited similar changes in heart rate, "dp/dt", and blood pressure. However, the first subject (A) exhibited a decrease in forearm flow associated with an increase in calculated resistance, while the second subject (B) exhibited increased flow and decreased peripheral resistance in parallel with intoxication. Neither type of response was associated with the presence of pain. It is possible that an initial high level

of sympathetic tone in this subject (as indexed by high venous pressure, low blood flow, and elevated regional vascular resistance) may have modified the peripheral vascular effects of marihuana.

Double-Blind Experiments

The previous experiments convinced us that double-blind experiments could be done safely and indicated that the greatest amount of information would be obtained with experienced subjects.

The ages and weights of these 12 subjects are given in Table 1. All of the subjects used alcohol in moderation with the exception of one of the males who averaged 18 bottles of beer and 40 oz of spirits per week. All subjects used marihuana or hashish at least once a month. One male and four females had used hallucinogens.

Neither administration of placebo produced intoxication in the four subjects who received placebo on both occasions, nor was there a difference in physiological response between the two placebo administrations. This served to establish that the effects noted in the single-blind experiments were indeed attributable to marihuana.

All eight subjects who received marihuana became intoxicated.

Four subjects received marihuana and placebo in that order. Although the marihuana response was clearly different from placebo, these "marihuana" data could be compared only to the control period and not to the placebo period since there was a possibility that the response to placebo was contaminated by the previous marihuana.

Although the experimenters did not question the subjects during the procedure, using the physiological data, they were able to identify with 90% accuracy which substance was received on which occasion. This observation indicates that a double-blind cannot be maintained when physiological records are available to the investigator. As a consequence, the data for the four subjects who received placebo and marihuana in that order (same order as single-blind experiments) were grouped with the data from the single-blind experiments.

Figure 6 shows the average percentage change in the various parameters of each subgroup (single-blind plus double-blind) in response to placebo and marihuana.

The pattern of response to marihuana is one of increases in heart rate, dp/dt, arterial blood pressure, and venous blood pressure, which are more marked in experienced males. In the experienced male subjects the trend was toward an increase in peripheral resistance which was not significant ($P < 0.1$). In contrast, experienced females tended to show a decrease in peripheral resistance, and an increase in flow. These changes were statistically significant ($P < 0.05$). There were no specific effects on "skin" or "muscle" blood flow or reactive hyperemia as indexed by wrist cuff occlusion.

Induced Changes in Autonomic Tone

The apparent temporal dissociation of positive chronotropic effects and positive inotropic effects (as judged by "dp/dt") suggests a vagal inhibitory effect. Two tests were done at a point in time when this vagal inhibitory effect might have been expected to be present: the Valsalva maneuver and the cold pressor test.

Fig. 7 shows a representative response to the Valsalva maneuver under placebo and marihuana conditions. When marihuana has been presented, the initial heart rate and blood pressure are slightly elevated, but the fall in blood pressure is greater, and the "overshoot" less, both suggesting some lessening of sympathetic tone. Moreover, the final vagal slowing is less marked, and although this may be a function of the greater initial heart rate, it may also reflect some vagal inhibition. The statistical values given are those derived from the 12 subjects in whom this procedure was done.

Fig. 8 shows the response to a cold pressor test. After marihuana, the initial heart rate and arterial pressures are slightly elevated. Immersion of the hand in ice water produced less of an increase than under placebo conditions. The quantitatively smaller response of the blood pressure (but not heart rate) was statistically significant ($P < 0.005$) in the 12 subjects in whom this maneuver was done. The decrease in forearm blood flow during cold pressor was also significantly less after marihuana. Likewise, the post-cold pressor bradycardia was significantly reduced.

Discussion

The present study on the cardiovascular effects of marihuana differs from previous studies

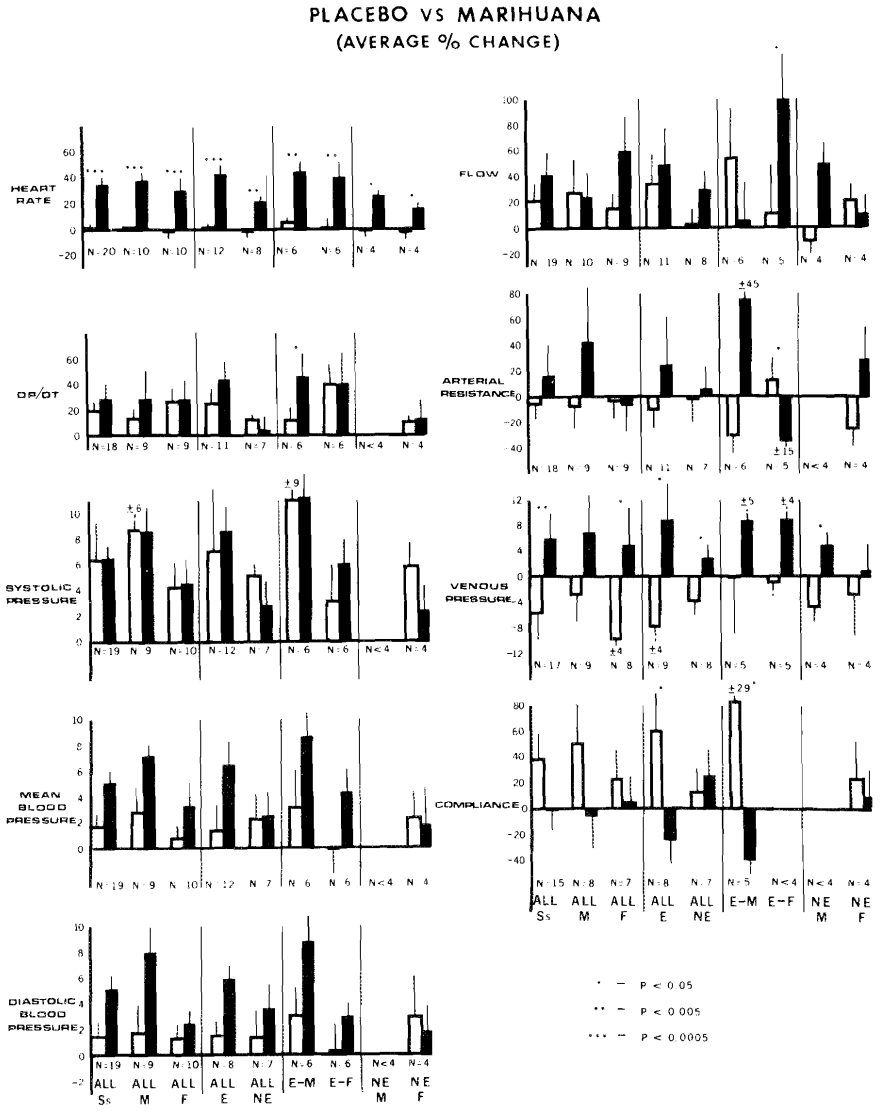

FIG. 6. Comparison of response (± percentage change from control (0)) to placebo (open bars) and to marihuana (closed bars) for all subjects (single-blind plus double-blind). Lines indicate standard deviation of mean. Only four non-experienced males and four non-experienced females were used as subjects. Some data from one subject in each group were lost due to technical difficulties. In such cases the notation $N < 4$ is used to indicate statistical analysis was not possible. Ss = subjects; M = males; F = females; E = experienced; NE = non-experienced.

in comparing responses not only in experienced and non-experienced individuals but also in both females and males. It extends previous observations by comparing data obtained under single-blind conditions with those obtained under double-blind conditions. In general, this study, with its added measure of control of set, setting, and protocol, augments previous, less controlled studies, and lends support to the conclusions reached in such studies.

The cardiovascular responses observed are consistent enough that the investigators were able to "break" a double-blind code simply by inspecting the physiological data. At the same time, the magnitude of the cardiovascular response to intoxicating doses, while statistically significant, is not marked.

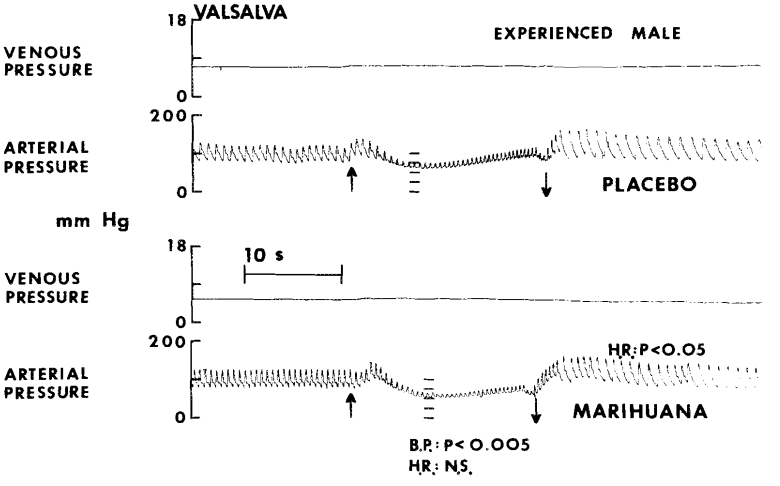

FIG. 7. Representative Valsalva response in experienced male following placebo (upper panel) and following marihuana (lower panel). Arrows indicate beginning and end of maneuver. Pooled data from all subjects were used to obtain the statistical values shown. The values presented below the depressor response and above the period of bradycardia are with reference to maximal changes observed. Reference lines are superimposed on the blood pressure tracings for ease of comparison. H.R., heart rate; N.S., not significant.

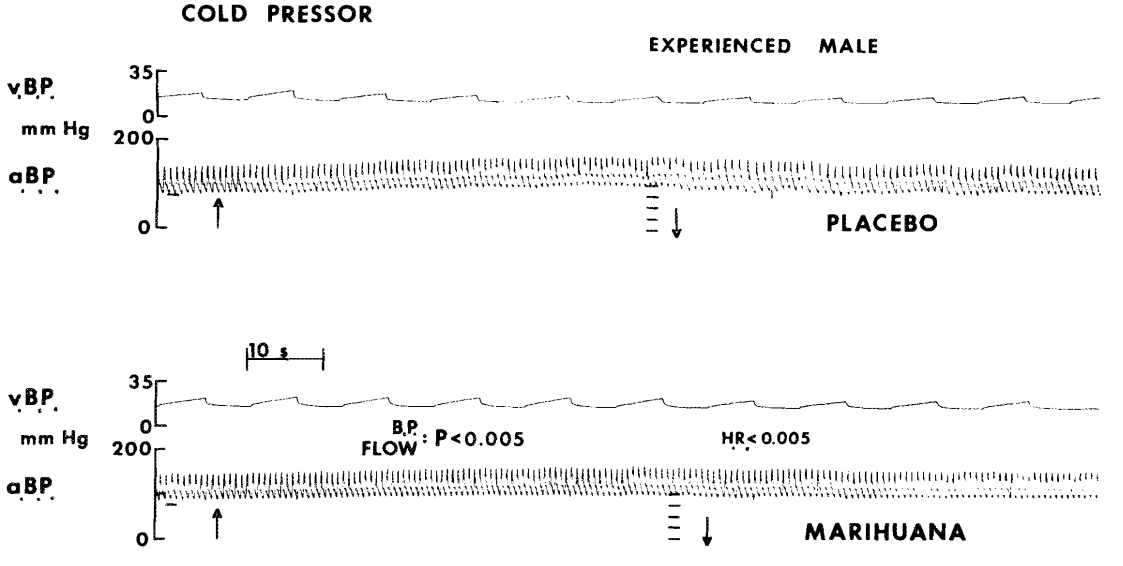

FIG. 8. Representative cold pressor response in experienced male following placebo (upper panel) and following marihuana (lower panel). Arrows indicate beginning and end of immersion of opposite hand in water at 1 °C. Abbreviations: v.B.P., venous pressure; a.B.P., arterial pressure. Pooled data from all subjects were used to obtain the statistical values shown. See legend to Fig. 7.

The difference in subjective intoxication between experienced subjects (all of whom became intoxicated) and inexperienced subjects (37% of whom became intoxicated) support anecdotal comments that experienced individuals more easily become "high".

Other investigators have reported tolerance to behavioral effects of Cannabis in animals in response to large doses given on a repetitive basis (McMillan *et al.* 1971); however, firm data, which would extend such observations to man, are lacking. If pharmacological

tolerance to the cardiovascular effects of marihuana were present, the responses would be expected to be less in the case of the experienced person. In general, however, the cardiovascular responses quantitatively were greater, at a fixed dose of marihuana, in experienced individuals than in non-experienced individuals. However, this difference was statistically significant only in the case of heart rate and "dp/dt". Weil *et al.* (1968) also found a greater increase in the heart rates of chronic users than those of naive subjects. While Renault *et al.* (1971) found no such difference, their particular study was characterized by small numbers of subjects, inadequately defined according to drug experience.

It is of interest that non-experienced subjects who do not become intoxicated (see Fig. 3) may, nevertheless, exhibit characteristic cardiovascular responses. This clearly demonstrates that at least some of the physiological effects of marihuana are not secondary to excitement associated with intoxication.

We are unable to document a sex difference in the cardiovascular response to marihuana. Males, in general, tended to exhibit more marked cardiovascular responses than females. However, these quantitative differences were not statistically significant. The data relating to effects on peripheral blood flow might be taken to indicate possible qualitative differences between the sexes, but the variability is such that inter-subject differences independent of sex may be more likely.

Tachycardia was the most consistent cardiovascular response to marihuana. The increased heart rate could be due to direct or indirect sympathetic stimulation, vagal inhibition, or a combination of both. The fact that it occurs in subjects who do not become intoxicated casts some doubt on psychogenically mediated increases in sympathetic tone as a mechanism.

The temporal dissociation, early in the intoxication, between "dp/dt" and tachycardia is similar to that which one sees with atropine and suggests vagal inhibition. This suggestion is supported by data obtained with the Valsalva and cold pressor tests. The Valsalva maneuvers done in our experiments were less controlled than ideal. However, although the subjects did not expire against a known resistance, the duration of the maneuver was standardized and all subjects had preliminary practice runs to ensure consistency. An analysis of the response to the Valsalva maneuver after marihuana shows that the bradycardia which occurs after release of breath holding is less marked than under placebo conditions. (The bradycardia can be blocked by anticholinergic agents such as propantheline and is thus believed to occur by a vagal mechanism (Cudkowicz 1968).) Whereas this observation can be taken to support a thesis of vagal inhibition, it must also be noted that the basal heart rate, at the beginning of the Valsalva maneuver, was greater after marihuana than after placebo. The bradycardia which occurs in the cold pressor test on removal of the cold stimulus was also less under marihuana conditions than under placebo conditions.

Taken collectively, these data suggest that the early tachycardia in response to marihuana may be due in part to vagal inhibition. Additional evidence for an atropine-like action of Cannabis in man is supplied by Renault *et al.* (1971). They report a suppression of sinus arrhythmia by Cannabis. Since this arrhythmia is mediated by the vagus, they suggest marihuana may alter normal vagal tone. In retrospect, in attempting to dissociate sympathetic and vagal factors, it is unfortunate that the Valsalva maneuver was not done repetitively in our experiments at a later time when there was no temporal dissociation between increases in heart rate and increases in "dp/dt".

While there are indices of increased sympathetic tone during this stable tachycardia associated with intoxication (for example, increased "dp/dt", increased venous pressure, and increased peripheral resistance (particularly in male subjects)), there are also indications of decreased reflex sympathetic responses. In our experiments, the hypotensive phase of the Valsalva maneuver was more marked after marihuana than after placebo. This type of response is similar to that seen following surgical (Wilkins *et al.* 1948) and chemical (Cudkowicz 1968; Wilkins *et al.* 1948; Mason and Braunwald 1964) interference with efferent sympathetics and to that observed in certain pathological conditions such as tabes dorsalis (Cudkowicz 1968) or familial dysautonomia (Mason *et al.* 1966), where interference is believed to occur on the afferent side of the baroreceptor reflex arc. The blood pressure

"overshoot" which occurs after the Valsalva maneuver was also less marked after marihuana than after placebo. (It has generally been accepted that this overshoot is a result of restored cardiac output forced into a blood reservoir still constricted from the hypotensive period (Cudkowicz 1968; Earnest *et al.* 1968; Sarnoff *et al.* 1948).) Again, this diminution in response after marihuana suggests some disturbance in homeostatic mechanisms. Similar inferences could be drawn from the observation that the rise in pressure and decrease in flow occurring with the cold pressor test is less marked after marihuana than after placebo. (However, the base-line blood pressure at initiation of the cold pressor test was also greater.)

These latter data are consistent with those in a recent paper by Beaconsfield *et al.* (1972) and support their suggestion of impaired reflex responses following Cannabis intake. Similarly, in studies on anesthetized dogs, Dewey *et al.* (1970) have shown that the pressor response to bilateral carotid occlusion is blocked by Δ^9THC, 1.0 mg/kg.

Although it is not emphasized in the literature, other authors have noted an increase in blood pressure in supine subjects in response to marihuana (Isbell *et al.* 1967). The small rise in blood pressure which we observed in our experiments was most likely due to an increase in cardiac output. Certainly increased vasoconstriction did not play a significant role since the increase in blood pressure occurred even in those subjects who showed a decrease in regional vascular resistance.

Beaconsfield *et al.* (1972) found significant increases in peripheral blood flow in non-experienced males in response to marihuana; Weiss *et al.* (1972) studied only experienced males and reported significant increases in forearm flow in the supine but not the upright position. In contrast, in our study there was a statistically significant increase only in the case of experienced females ($P < 0.05$). When wrist cuff occlusion was used as an index of partitioning between skin and muscle blood flow, we were unable to document consistent marihuana effects. Similarly reactive hyperemia was not influenced.

Further experimentation is necessary to establish precisely the effects of marihuana on the peripheral circulation. The general pattern, however, is one of peripheral cardiovascular effects being even less marked than effects on the heart itself.

In summary, this study has examined under well-controlled circumstances the cardiovascular responses to marihuana in man. Although subjects with existing heart disease have not been studied, no data have emerged which would indicate that acute administration of this substance presents a significant hazard to the cardiovascular system. If the data which suggest a muting of reflex cardiovascular responses can be corroborated, however, one might have some apprehension that, in an emergency, an intoxicated individual's reflex vascular responses may be reduced to a clinically significant degree.

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