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Human Cigarette Smoking: Effects of Puff and Inhalation Parameters on Smoke Exposure[1]

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ABSTRACT

This study determined effects of three smoking behavior components: puff volume, inhalation volume and lung exposure duration on biological measures of smoke exposure. A microcomputer-based auditory feedback system allowed subjects (N = 9 or 10 per experiment) to control puff and inhalation parameters as they smoked usual brand cigarettes. In each of four experiments, one smoking parameter was manipulated across sessions while two other parameters were held constant. Biological samples were obtained before and after each 8-puff smoking session conducted under a given set of behavioral parameters for analysis of plasma nicotine and expired air carbon monoxide (CO) levels. In Experiment I, both nicotine and CO levels were influenced systematically as puff volume was varied from 15 to 60 ml (inhalation volume = 50% of vital capacity, lung exposure time = about 9 sec). Nicotine boost (post- minus presession levels) increased 4-fold and CO boost increased 9-fold over this range of puff volume values. In Experiment II, nicotine levels were unaffected when average lung exposure times varied from 5 to 21 sec (puff volume = 50 ml, inhalation volume = 50% of vital capacity), suggesting that all the nicotine available may be absorbed during a normal smoking inhalation cycle with no breathholding. CO levels increased systematically with longer breathholds. In Experiments III and IV, inhalation volumes from 10% and 20% to 60% of vital capacity had no effect on either nicotine or CO levels, and this was true whether lung exposure time was about 8 sec (Experiment III) or about 4 sec (Experiment IV). This series of studies has shown that puff volume is an important determinant of tobacco smoke exposure, but that inhalation components of smoking behavior, at least within the range of parameters tested, have no effect on nicotine exposure levels.

Biological exposure to smoke constituents, such as nicotine and CO, is determined by a combination of physiological factors, cigarette characteristics, amount smoked and smoking topography. Physiological factors that influence smoke constituent exposure include absorption and metabolism rates (Benowitz *et al.*, 1982), lung size (Darby *et al.*, 1984) and presence of disease (McMorrow and Foxx, 1985). Cigarette characteristics include tobacco weight and blend, degree of filtration, filter ventilation and paper porosity (Robinson and Forbes, 1975; United States Public Health Service, 1981). Systematic variations in number of cigarettes smoked (Henningfield *et al.*, 1980) or number of puffs taken from cigarettes (Chait *et al.*, 1985) affect smoke exposure. In addition, measures of daily cigarette use (*e.g.*, reported cigarettes per day) are correlated moderately with biological exposure levels (Benowitz *et al.*, 1983; Biglan *et al.*, 1985; Hill *et al.*, 1983; Jaffe *et al.*, 1981; Rickert and Robinson, 1981; Russell *et al.*, 1980). The relationship between smoke exposure and more detailed smoking topography parameters such as puff volume, inhalation volume and lung exposure duration is not as well understood. There are several lines of evidence, though, which suggest that these puff and inhalation parameters play a role in determining smoke exposure.

The first line of evidence comes from studies that have examined the relationship between cigarette yields of commercially available cigarettes, as determined by a standard smoking machine methodology, and smoke exposure levels, as determined by blood or alveolar CO, or by plasma nicotine, cotinine or thiocyanate levels. Although one recent study (Gori and Lynch, 1985) has documented a moderate correlation (r = 0.37) between package label cigarette yields and actual plasma nicotine levels in human smokers, a majority of studies have found no relationship between cigarette yields and smoke exposure levels (Battig *et al.*, 1982; Benowitz *et al.*, 1983; Ebert *et al.*, 1983; Feyerabend *et al.*, 1982; Folsom *et al.*, 1984; Rickert and Robinson, 1981; Russell *et al.*, 1980; Sutton *et al.*, 1982). The lack of a high correlation could result from smokers consuming

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ABBREVIATIONS: CO, carbon monoxide; VC, vital capacity; ANOVA, analysis of variance.

relatively more low yield and fewer high yield cigarettes, but this does not appear to happen (Battig *et al.*, 1982; Ebert *et al.*, 1983; Folsom *et al.*, 1984; Garfinkel, 1979; Gori and Lynch, 1985; Russell *et al.*, 1980). Alternatively, the lack of a high correlation between cigarette yields and smoke exposure could result from between-yield differences in the number of puffs, volume of puffs or extent of smoke inhalation.

A second and related line of evidence comes from brand switching studies in which smokers change from their accustomed brand to a lower or higher yield cigarette while their biological exposure levels are monitored. A general finding in yield switching studies is that some degree of compensation occurs: after the switch, decreases or increases in smoke exposure levels are not proportional to the decreases or increases in cigarette yields. Because a number of these studies demonstrate the compensation effect without changes in number of cigarettes smoked (Ashton *et al.*, 1979; Jaffe *et al.*, 1982; Kanzler *et al.*, 1983; Ossip-Klein *et al.*, 1983; Russell *et al.*, 1982; Sepkovic *et al.*, 1984), it is plausible that puff and/or inhalation parameters may be responsible for regulation of smoke exposure.

A third, and related, line of evidence comes from studies which have found that puff parameters, *i.e.*, puff number and/or puff volume, are sensitive to manipulations of cigarette yield (Adams, 1978; Ashton and Watson, 1970; Creighton and Lewis, 1978; Gust and Pickens, 1982; Herning *et al.*, 1981; Rawbone *et al.*, 1978; Tobin and Sackner, 1982). For example, puff volume increased as the cigarette nicotine yield decreased (Gust and Pickens, 1982; Herning *et al.*, 1981). This observation is consistent with the notion that smokers adjust smoke exposure *via* puffing and inhalation parameters.

The final line of evidence for the importance of these smoking behaviors comes from studies in which puff and/or inhalation parameters have been found to covary with smoke exposure (Gust and Pickens, 1982; Herning *et al.*, 1981; Herning *et al.*, 1983; Zacny and Stitzer, 1986). In one study, for example, systematic manipulations of puff volume produced orderly changes in CO exposure (Zacny and Stitzer, 1986). In another study, which used multiple regression analysis, puffing and inhalation parameters contributed significantly to the prediction of plasma nicotine rise from smoking a single cigarette (Herning *et al.*, 1983).

Although the above evidence suggests that puff and/or inhalation parameters may influence smoke constituent exposure, further studies are needed to establish and to examine the independent effects of different smoking behaviors. For the present study, a methodology was developed whereby puff and inhalation parameters could be manipulated and controlled. In a series of three experiments, one of three smoking parameters (puff volume, inhalation volume or breathhold duration) was manipulated systematically while holding the other two constant. This strategy permitted investigation of the independent influence of each smoking parameter on nicotine and CO exposure. In a fourth experiment, the inhalation volume manipulation was repeated using a breathhold duration that corresponded more closely to natural cigarette smoking. Nicotine and CO were chosen as biological markers of acute smoke exposure because they are the most readily measured representatives of the particulate (nicotine) and gaseous (CO) smoke phases. These markers of smoke intake are biologically important because they are thought to be risk factors for cardiovascular disease (Hill *et al.*, 1983).

Methods

Subjects

Subjects were 17 cigarette smokers (13 males, 4 females): mean age, 28.8 years (range 19–38); mean years smoking, 12.8 (range 4–25); mean number of cigarettes smoked per day, 31.8 (range 20–50). The subjects all inhaled cigarette smoke, as evidenced by elevated breath CO levels (Jarvis *et al.*, 1980; Rawbone *et al.*, 1976). Their usual brand cigarettes delivered medium to high levels of nicotine, tar and CO (Federal Trade Commission levels: mean nicotine, 1.0 mg/cigarette; mean tar, 16.0 mg/cigarette; mean CO, 14.7 mg/cigarette). Six subjects smoked regular size (80 mm) cigarettes, 10 subjects smoked king size (84 mm) cigarettes and 1 subject smoked 100-mm cigarettes. Ten subjects (JW, BE, VL, BC, KM, CW, DW, MS, SB, DD) served in Experiment I, 9 subjects (JW, BE, VL, BC, KM, CW, DW, SB, MM) served in Experiment II, 10 subjects (JW, BE, VL, BC, KM, CW, DW, MS, MM, MD) served in Experiment III and 10 subjects (CC, DW, JW, JB, BE, MM, MDM, FU, JS, SB) served in Experiment IV.

Experimental Procedures

Base-line smoking topography. In order to establish a range of puff and inhalation parameters generated from relatively unconstrained smoking, 15 of the 17 subjects were studied individually during a single session, before the experimental manipulations, under conditions that allowed the size and duration (but not number) of puffs and inhalations to vary.

Session procedure. Subjects were instructed to arrive at the laboratory in the morning after having abstained from smoking for at least 12 hr. An abstinence criterion was imposed to ensure uniformly low base-line exposure levels. To verify smoking abstinence, a CO criterion of 20 ppm was used: if subjects exceeded this criterion, they were considered nonabstinent and the smoking session scheduled for that day was cancelled.

During sessions, subjects were seated in a room housing the smoking measurement equipment. The experimenter was present in the room to light cigarettes and place them in a cigarette holder, and to carry out other experimental procedures. During each session, subjects took a single puff from each of 8 freshly lit full-length cigarettes of their usual brand, with puffs spaced at 60-sec intervals.

Experimental manipulations. In each of the four experiments, one of three parameters (puff volume, inhalation volume, breathhold duration) was manipulated experimentally across sessions while the other two were held constant throughout the experiment. The specific targeted levels of puff volume, inhalation volume and breathhold duration for each of the four experiments are listed in table 1. With the exception of the 0% of VC condition in Experiments III and IV, smoke was inhaled into the lungs after each puff. In the 0% of VC condition, subjects, after taking a puff, immediately expelled the smoke from their mouths without inhaling.

In each experiment, a repeated-measures design was used. Subjects participated in four or five daily 1.5-hr sessions. During each session, subjects took 8 puffs spaced at 60-sec intervals under one set of controlled smoking topography conditions shown in table 1. The value of the smoking parameters being manipulated changed across sessions. Order of conditions was determined by a randomized block.

Puffing and inhalation control. In order to standardize puffing

TABLE 1

Smoking topography parameter values

	Puff Volume	Inhalation Volume	Breathhold Duration
	ml	*% of VC*[a]	*sec*
Experiment I	15, 30, 45, 60	50	4
Experiment II	50	50	0, 4, 8, 16
Experiment III	50	0, 20, 40, 60	4[b]
Experiment IV	50	0, 10, 20, 40, 60	0

[a] VC = vital capacity.
[b] Under the 0% of VC condition, there was no breathhold duration.

and inhalation patterns, subjects were trained, before the study, to puff at the end of an exhalation and to inhale immediately after puff offset. Puff volume, inhalation volume and breathhold duration were controlled through the use of microcomputer-based feedback delivered to the subjects. The computer measured topography in real time. That is, while the subject was puffing, inhaling, breathholding and exhaling, the computer was continually updating puff volume, inhalation/exhalation volume and lung exposure duration values. The computer was programmed to generate an auditory stimulus (a 0.75-sec tone) when reference values fed previously into memory for puff volume, inhalation volume or breathhold duration had been reached. The beginning of each puff/inhalation cycle after the 60-sec interpuff interval was initiated with a verbal signal from the experimenter. After this signal, the first tone cued the subject to stop puffing and start inhaling (puff volume control); the second tone was a cue to stop inhaling and start breathholding (inhalation volume control) and the third tone was a cue to stop breathholding and start exhaling (breathhold duration control). Before each puff, the experimenter could change the values at which the auditory stimuli were generated. In this way, transient undershooting or overshooting of the three variables within each 8-puff experimental condition could be counteracted. Criteria were established for average puff volume (±5 ml), inhalation volume (±100 ml) and breathhold duration (±1 sec) appropriate to the condition being studied. If average values during an 8-puff session did not fall within the prescribed range, the experimental condition was repeated on another day. Few conditions had to be repeated inasmuch as subjects practiced the smoking feedback procedure with lit cigarettes before the experiment, and also practiced before each experimental session, using unlit cigarettes and parametric values that were to be used in that particular session.

Measurement Procedures

Puffing topography. Four puffing parameters were assessed in the four experiments: 1) puff volume (the amount of smoky air drawn from the cigarette rod into the mouth), 2) peak flow (highest flow rate during a puff), 3) puff duration (temporal period from puff onset to offset) and 4) interpuff interval (temporal period from the offset of one puff to the onset of a subsequent puff).

The system used to measure the puff parameters has been described in detail elsewhere (Gust *et al.*, 1983; Nemeth-Coslett and Griffiths, 1985). Briefly, a pneumotachograph situated distal to the cigarette rod was used to measure pressure changes created by puffing. These pressure changes were processed by a microcomputer, which integrated flow rates over the duration of the puff to provide the puff volume measure. The puff volume measurement system was calibrated on a daily basis by drawing 50 ml of air from an unlit cigarette *via* a syringe. If the puff volumes registered by the system deviated from 50 ml more than 6%, the system was adjusted accordingly. The highest flow rate measured during a puff was selected by the microcomputer for the peak flow measure. Puff duration and interpuff interval were meaured by a pressure-sensitive switch proximal to the cigarette rod, which signalled onset and offset of puffing.

Respiration topography. Four postpuff respiration topography variables were measured in these studies: 1) inhalation volume (amount of air inhaled after a puff), 2) exhalation volume (amount of air exhaled after a postpuff inhalation), 3) breathhold duration (temporal period from peak inhalation to exhalation onset) and 4) lung exposure duration (temporal period between inhalation onset and end of exhalation).

The respiration parameters were measured with a respiratory inductive plethysmograph (Respitrace; Non-Invasive Monitoring Systems, Inc., Ardsley, NY). Elastic cloth bands containing induction coils were placed around the thoracic and abdominal areas of the subject. Abdominal and chest wall movement changed the electrical signal from the coils. Both inhalation and exhalation volumes were calculated directly by the Respitrace software by comparing signal changes with those obtained during a calibration procedure. Respitrace calibration was conducted before each experimental session using a 800-ml volume of air. After completing this calibration procedure, Respitrace values for the inhalation volume to be used in the subsequent session were validated with known volumes of air determined by spirometry (Collins Vitalometer, Braintree, MA). Across the four experiments, the inhalation volumes measured by the Respitrace during this validation procedure deviated from the spirometer volumes by an average of 5.5% with range of volumes tested being 250 to 3500 ml.

In order to control for the different lung sizes of subjects, inhalation and exhalation volumes were expressed as percentages of VC. VC, a measure of lung size, was obtained for each subject at the start of the experiment by having them exhale as much air as possible into the water spirometer (mean VC: 4259 ml; range 2825–5800 ml).

Lung exposure duration as measured by the microcomputer was the timed interval between offset of the puff signal to the trough of the electrical signal generated by the end of an exhalation. The computer did not measure breathhold duration directly inasmuch as it started timing at the onset of inhalation. Rather, breathhold duration was measured in a *post hoc* fashion using computer printouts of real time respiration profiles obtained in a session. The chart distance from inhalation peak to exhalation onset was measured and then transformed into a proportional time-based measure, *i.e.*, breathhold duration.

Plasma nicotine. An angiocatheter was inserted into a forearm vein before each session so that multiple blood samples could be drawn. Seven milliliters of blood was drawn immediately before, and at 1 min, 10 min and 30 min after the completion of each 8-puff smoking session. Nicotine levels in the plasma were determined by gas chromatography (Jacob *et al.*, 1981). The increase in plasma nicotine from immediately before to 1 min after the smoking session constituted the measure of nicotine boost.

CO. Expired air samples were obtained immediately before, and at 2 min, 11 min and 31 min after each smoking session. Subjects exhaled residual air from their lungs, then took a deep breath and held it for 20 sec. They then exhaled successively into two 1-l polyvinyl bags; the second bag, containing alveolar air, was analyzed for CO content using an Ecolyzer 2000 (Energetics Science, Elmsford, NY). The increase in CO levels from immediately before to 2 min after the smoking session constituted the measure of CO boost. Expired air CO levels obtained *via* the above procedure are highly correlated with carboxyhemoglobin levels ($r = +0.98$) (Jarvis *et al.*, 1980).

Subjective reports. After completion of each 8-puff smoking session, subjects were asked to make several subjective ratings concerning their feedback-controlled smoking behavior and characteristics of the smoke puffs. Subjects made each of their ratings by placing a vertical hatch mark somewhere along a 100-mm bipolar scale. Subjects were asked to estimate their puff sizes (small/large), inhalation depths (no inhalation/very deep) and breathhold times (no breathhold/very long). Subjects rated the strength (very weak/very strong), harshness (very mild/very harsh), heat (no heat/very hot) and acceptability (very unsatisfying/very satisfying) of the puffs. Also, subjects were asked to rate their current craving (no craving/extreme craving) for a cigarette.

Data Analysis

The primary data analytic technique was a one-way repeated measures ANOVA, which examined data across levels of the experimentally manipulated smoking parameter. ANOVAs were conducted in each experiment for four puff parameters (puff volume, puff duration, peak flow, interpuff interval), four respiratory parameters (breathhold duration, lung exposure duration, inhalation volume and exhalation volume), two biological exposure measures (CO and nicotine boost) and eight subjective report measures. Tukey *post hoc* comparison tests were done, when appropriate. To test the effects of postsmoking interval on nicotine and CO levels, ANOVAs with orthogonal decomposition (Cohen and Cohen, 1983) were conducted for each experiment, using the postsmoking temporal periods and experimental conditions as factors.

Results

Base-line Smoking Topography

Subjects, when taking 8 puffs from full-length cigarettes without constraints on puff volume, inhalation volume or breathhold duration, took mean puffs of 60.5 ml (S.E.: 4.7, range: 30.6–101.8 ml) and mean inhalations of 979.7 ml (S.E.: 111.8, range: 465.9–1831 ml) or 23.8% of VC (S.E.: 2.6, range: 12.6–44.9% of VC). Mean breathhold time was 1.4 sec (S.E.: 0.2, range: 0–2.9 sec) and mean lung exposure duration was 5.6 sec (S.E.: 0.4, range: 3.7–7.6 sec). Mean CO boost was 8.1 ppm (S.E.: 0.7, range: 4–12 ppm).

Experiment I. Effects of Puff Volume on Smoke Exposure

Smoking topography. Mean values of the smoking parameters measured in this experiment are shown in table 2. Puff volume varied systematically across conditions, and average puff volume in each experimental condition varied less than 1 ml from the targeted puff volume. Puff duration and peak flow, two puff parameters that were not controlled in this experiment, increased in a systematic fashion across conditions. Interpuff interval and the four respiratory parameters (breathhold duration, lung exposure duration, inhalation volume, exhalation volume) did not vary across conditions.

Nicotine and CO boost. Figure 1 (top) shows that nicotine boost increased as a function of puff volume, $F(3,27) = 23.3$, $P < .001$. Nicotine boost was 4.6, 7.5, 11.8 and 16.2 ng/ml, respectively, after 8 controlled inhalations of 15-, 30-, 45- and 60-ml puffs. Figure 1 (bottom) shows that CO boost also increased in an orderly fashion as a function of puff volume, $F(3,27) = 90.3$, $P < .001$. CO boost was 1.0, 4.2, 6.3 and 8.7 ppm, respectively, after 8 controlled inhalations of 15-, 30-, 45- and 60-ml puffs. *Post hoc* tests revealed that for both CO boost and nicotine boost, values from each of the four puff volume conditions differed significantly from each other.

Time course of postsmoking nicotine and CO levels. Figure 2 shows plasma nicotine levels (top) and expired air CO levels (bottom) as a function of time since the last puff of the smoking session for each of the puff volume conditions. Mean plasma nicotine levels differed as a function of both condition, $F(3,27) = 18.3$, $P < .001$, and time, $F(2,18) = 21.6$, $P < .001$. The decreasing trend in plasma nicotine levels across time was both linear $F(1,9) = 24.6$, $P < .001$, and quadratic, $F(1,9) = 9.1$, $P < .01$, in nature. Mean CO levels also differed as a function of both condition, $F(3,27) = 18.5$, $P < .001$, and time, $F(2,18) = 81.4$, $P < .001$. The decreasing trend in CO levels across time was linear in nature, $F(1,9) = 152.0$, $P < .001$.

TABLE 2
Experiment I topography measures[a]

	Puff Volume				Main Effects
	15	30	45	60	
	ml				
Puff parameters					
Puff volume (ml)	15.8*	29.6*	44.9*	60.4	$P < .01$
	0.5	0.2	0.2	0.6	
Puff duration (sec)	0.94*	1.40*	1.88	2.08	$P < .001$
	0.10	0.10	0.20	0.14	
Peak flow (ml/sec)	26.9	31.2*	42.1	50.2	$P < .001$
	3.6	2.7	5.3	6.0	
Interpuff interval (sec)	65.7	63.0	64.2	62.1	N.S.[b]
	3.1	2.1	1.5	1.5	
Respiration parameters					
Inhalation volume (% of VC)	49.5	49.7	49.5	49.6	N.S.
	0.5	0.5	0.4	0.7	
Exhalation volume (% of VC)	51.3	50.9	51.5	50.6	N.S.
	1.5	1.4	1.2	1.0	
Breathhold duration (sec)	3.86	3.77	3.89	3.84	N.S.
	0.07	0.03	0.10	0.03	
Lung exposure duration (sec)	9.56	9.71	9.59	9.09	N.S.
	0.61	0.54	0.66	0.28	

[a] Mean ± S.E.
[b] N.S. indicates main effect was not significant.
* Significantly different from next highest puff volume condition using Tukey *post hoc* comparison test.

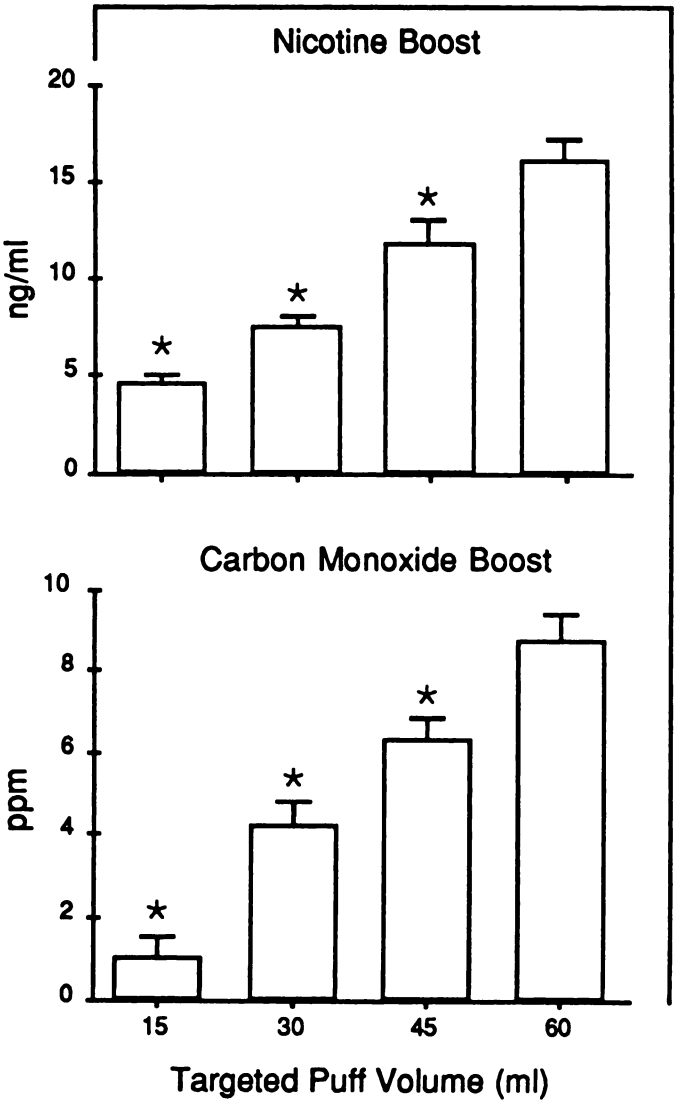

Fig. 1. Mean nicotine boost (nanograms per milliliter) and CO boost (parts per million) for 10 subjects are shown as a function of cigarette puff volume (milliliters). Plasma nicotine and breath CO were measured before and 1 to 2 min after 8 puffs of a specific volume (15–60 ml) were inhaled to 50% of VC, and held in the lungs for 4 sec. Boost refers to post- minus presmoking levels. Brackets indicate 1 S.E. An asterisk above a bar indicates that the condition is significantly different from the next highest puff volume condition.

Subjective effects. Puff size ratings increased as puff volume increased, $F(3,27) = 27.2$, $P < .001$. Mean subject-rated puff sizes (in millimeters along a 100-mm scale; S.E. in parentheses) were 9.3 (2.6), 25.1 (4.4), 38.8 (4.4) and 65.7 (5.6), respectively, in the 15-, 30-, 45- and 60-ml conditions (0 mm = small and 100 mm = large puffs). *Post hoc* tests revealed that puff size estimates from each of the four puff volume conditions

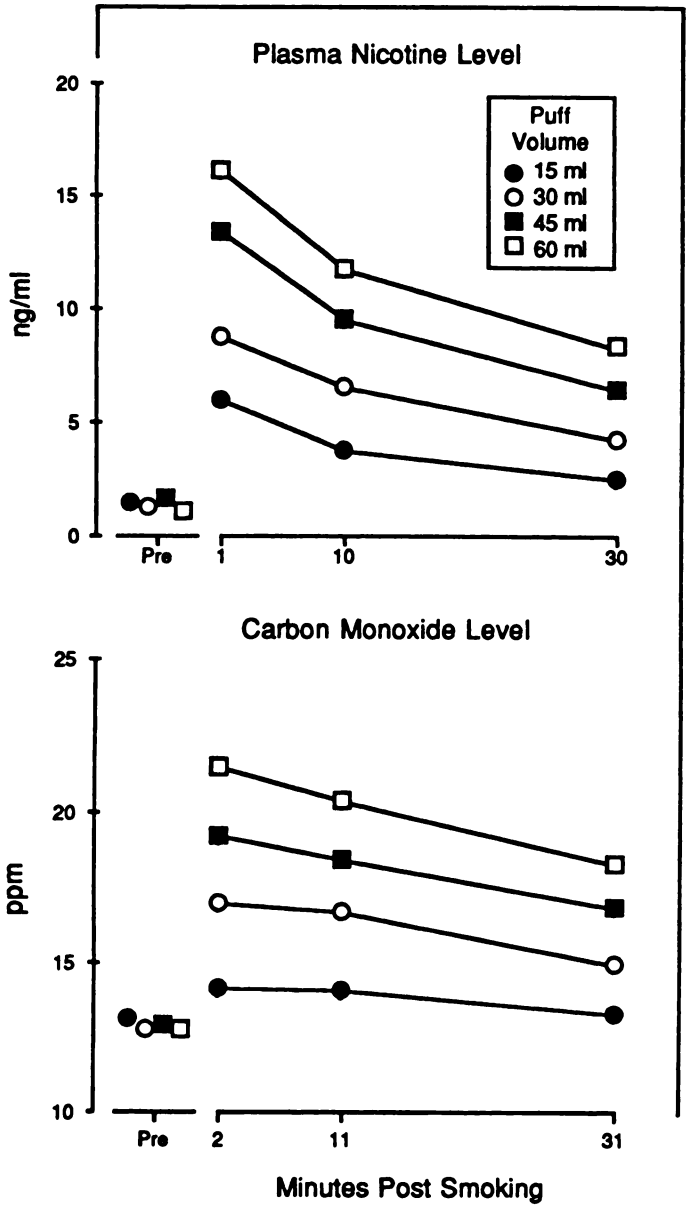

Fig. 2. Mean (N = 10) pre- and postsmoking plasma nicotine levels (nanograms per milliliter) and CO levels (parts per million) are shown separately for four puff volume conditions. Blood samples for nicotine analysis were drawn immediately before and 1, 10 and 30 min after 8 puffs were smoked under a specified set of parameters. Breath samples for CO analysis were collected immediately before and 2, 11 and 31 min after smoking.

differed significantly from each other. Puff volume also affected strength, $F(3,27) = 9.8$, $P < .001$, and satisfaction ratings, $F(3,27) = 6.0$, $P < .01$. Subjects rated both 45- and 60-ml puffs as being significantly stronger and more satisfying than 15-ml puffs.

Experiment II. Effects of Breathhold Duration on Smoke Exposure

Smoking topography. Mean values of the smoking parameters measured in this experiment are shown in table 3. Breathhold duration and lung exposure duration, of which breathhold duration is a component, varied systematically across conditions. The average breathhold duration for each experimental condition was within 0.4 sec of the targeted breathhold duration. The other two respiratory parameters (inhalation and exhalation volumes) did not vary across conditions. One of the four puff parameters, interpuff interval, was significantly longer in the 16-sec condition than in the other three conditions, but absolute differences in interpuff interval across the four conditions were small. The other three puff parameters (puff volume, puff duration, peak flow) did not vary across conditions.

TABLE 3
Experiment II topography measures[a]

	Breathhold Duration				Main Effects
	0	4	8	16	
	sec				
Puff parameters					
Puff volume (ml)	49.7	49.8	49.7	48.9	N.S.[b]
	0.4	0.4	0.4	0.4	
Puff duration (sec)	1.91	2.06	1.91	1.87	N.S.
	0.10	0.15	0.16	0.12	
Peak flow (ml/sec)	42.9	41.5	43.0	42.6	N.S.
	3.3	2.8	3.6	3.9	
Interpuff interval	59.9	61.5	61.3*	65.4	P < .01
(sec)	0.9	0.8	0.5	0.5	
Respiration parameters					
Inhalation volume	50.4	50.0	50.7	50.3	N.S.
(% of VC)	0.2	0.3	0.2	0.3	
Exhalation volume	53.3	49.4	52.9	51.9	N.S.
(% of VC)	2.4	3.3	2.2	2.6	
Breathhold duration	0.08*	3.87*	7.61*	15.83	P < .001
(sec)	0.04	0.10	0.11	0.23	
Lung exposure duration (sec)	4.85*	8.84*	12.82*	20.91	P < .001
	0.49	0.42	0.35	0.51	

[a] Mean ± S.E.
[b] N.S. indicates main effect was not significant.
* Significantly different from next highest breathhold duration condition using Tukey *post hoc* comparison test.

Nicotine and CO boost. Figure 3 (top) shows that nicotine boost increased from 10.9 ng/ml at 0-sec breathhold to 14.9 ng/ml at 16-sec breathhold, but the differences across conditions were not significant. Figure 3 (bottom) shows that CO boost increased in an orderly fashion as breathhold duration increased $F(3,24) = 54.8$, $P < .001$. CO boost was 4.4, 5.4, 7.3 and 9.3 ppm, respectively, after 0, 4, 8 and 16 sec of breathholding. *Post hoc* tests revealed that, except for the difference between the 0- and 4-sec conditions, which was not significant, all other comparisons between conditions were statistically significant.

Time course of postsmoking nicotine and CO levels. Mean plasma nicotine levels differed as a function of time, $F(2,16) = 34.2$, $P < .001$, but not condition, $F(3,24) = 2.04$, $P < .14$. The decreasing trend in plasma nicotine across time was both linear, $F(1,8) = 42.6$, $P < .001$, and quadratic, $F(1,8) = 12.3$, $P < .01$, in nature. Mean CO levels differed as a function of both condition, $F(3,24) = 13.1$, $P < .001$, and time $F(2,16) = 65.6$, $P < .001$. The decreasing trend in CO levels across time was linear in nature, $F(1,8) = 143.6$, $P < .001$.

Subjective effects. The only subjective report measure that differed significantly across the breathhold conditions was the estimate of breathhold duration, $F(3,24) = 8.3$, $P < .001$. Mean subject-rated breathhold durations (in millimeters along a 100-mm scale; S.E. in parentheses) were 2.3 (0.9), 50.4 (6.2), 75.2 (6.9) and 84.8 (5.7), respectively, in the 0-, 4-, 8- and 16-sec conditions (0 mm = no breathhold and 100 mm = very long breathhold). *Post hoc* tests revealed that with the exception of breathhold duration estimates in the 8- and 16-sec conditions,

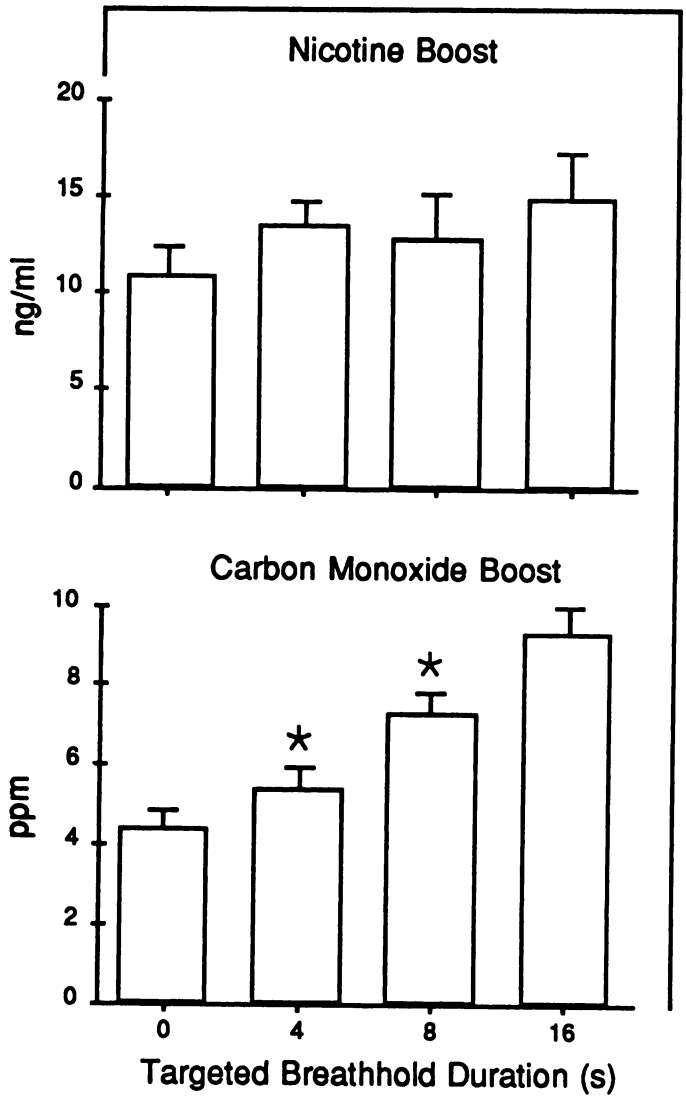

Fig. 3. Mean nicotine boost (nanograms per milliliter) and CO boost (parts per million) for 9 subjects are shown as a function of breathhold duration (sec). Plasma nicotine and breath CO were measured before and 1 to 2 min after eight 50-ml puffs were inhaled to 50% of VC and held in the lungs for a specified duration (0–16 sec). Boost refers to post- minus presmoking levels. Brackets indicate 1 S.E. An asterisk above a bar indicates that the condition is significantly different from the next highest breathhold duration condition.

which did not differ from each other, all other comparisons were significant.

Experiment III. Effects of Inhalation Volume (with 4-sec Breathhold) on Smoke Exposure

Smoking topography. Mean values of the smoking parameters measured in this experiment are shown in table 4. Inhalation volume varied systematically across conditions, and the average inhalation volume in each experimental condition varied less than 1% from the targeted volume. Exhalation volume also varied systematically across conditions, and differed only slightly in magnitude from inhalation volume. Significant effects on the breathhold and lung exposure duration measures were due primarily to differences between the inhalation and no-inhalation (0% of VC) conditions, although lung exposure duration was also significantly shorter in the 20% of VC condition than in the 40 and 60% of VC conditions. Puff volume

TABLE 4
Experiment III topography measures[a]

	Inhalation Volume				Main Effects
	0	20	40	60	
	% of VC				
Puff parameters					
Puff volume (ml)	49.6	49.1	50.2	49.6	N.S.[b]
	0.3	0.4	0.3	0.3	
Puff duration (sec)	1.88	2.24*	1.67	1.62	P < .001
	0.13	0.24	0.11	0.11	
Peak flow (ml/sec)	44.1	39.3	45.6	50.3	P < .01
	3.9	4.3	3.4	4.1	
Interpuff interval	59.8	62.1	60.8	62.7	P < .05
(sec)	0.3	0.8	0.8	0.7	
Respiration parameters					
Inhalation volume (%	0*	20.2*	39.6*	60.1	P < .001
of VC)	0	0.4	0.3	0.2	
Exhalation volume	0*	23.0*	41.6*	62.6	P < .001
(% of VC)	0	1.3	1.1	1.9	
Breathhold duration	0*	3.84	3.86	3.87	P < .001
(sec)	0	0.07	0.07	0.07	
Lung exposure du-	0*	7.34*	8.31	8.77	P < .001
ration (sec)	0	0.30	0.41	0.36	

[a] Mean ± S.E.
[b] N.S. indicates main effect was not significant.
* Significantly different from next highest inhalation volume condition using Tukey *post hoc* comparison test

did not vary across conditions. Significant effects were obtained on puff duration, peak flow and interpuff interval measures. Puff duration tended to be longer and peak flow lower under the small (20% of VC) inhalation volume condition than under the larger inhalation volume conditions.

Nicotine and CO boost. Figure 4 (top) shows that there was a negligible nicotine boost in the 0% of VC condition, but substantial boosts when smoke was inhaled and then breathheld, $F(3,27) = 36.6$, $P < .001$. *Post hoc* tests revealed that nicotine boost did not differ significantly across the three smoke inhalation conditions. The same type of exposure pattern was evident for CO. Figure 4 (bottom) shows that CO exposure was negligible under the 0% of VC condition, and much greater when smoke was inhaled, $F(3.27) = 66.5$, $P < .001$. *Post hoc* tests revealed that CO boost did not differ significantly across the three smoke inhalation conditions.

Time course of postsmoking nicotine and CO levels. Mean plasma nicotine levels measured after the last puff of the smoking session differed as a function of both condition, $F(3,27) = 37.3$, $P < .001$, and time, $F(2,18) = 41.0$, $P < .001$, with inhalation/no-inhalation differences accounting for condition effects. Plasma nicotine levels changed across time in the three inhalation conditions but not in the no-inhalation condition. The decreasing trend in plasma nicotine levels across time in the smoke inhalation conditions was both linear, $F(1,9) = 55.7$, $P < .001$, and quadratic, $F(1,9) = 13.1$, $P < .006$, in nature. Mean CO levels also differed as a function of both condition, $F(3,27) = 19.3$, $P < .001$, and time, $F(2,18) = 68.2$, $P < .001$, with inhalation/no-inhalation differences accounting for condition effects. CO levels changed across time in the three inhalation conditions but not in the no-inhalation condition. The decreasing trend in CO levels across time in the smoke inhalation conditions was linear in nature $F(1,9) = 97.0$, $P < .001$.

Subjective effects. Inhalation depth estimates increased as a function of inhalation volume, $F(3,27) = 52.2$, $P < .001$. Mean subject-rated inhalation depths (in millimeters along a 100-mm

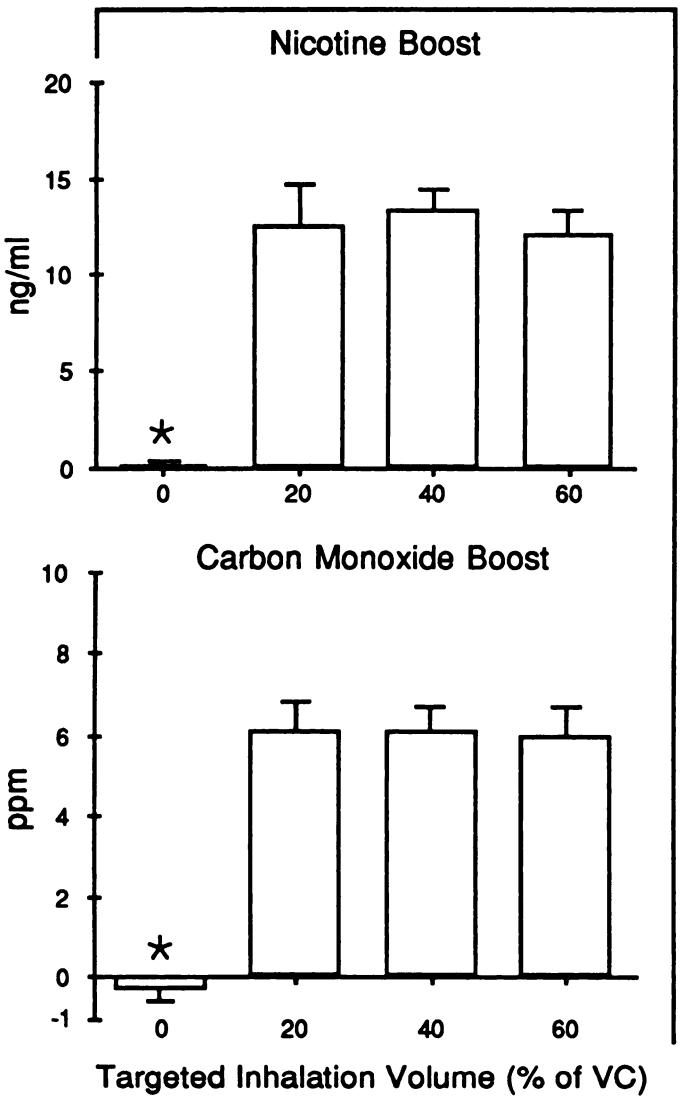

Fig. 4. Mean nicotine boost (nanograms per milliliter) and CO boost (parts per million) for 10 subjects are shown as a function of inhalation volume, which was measured as percentage of VC to standardize for individual differences in lung volume. Plasma nicotine and breath CO were measured before and 1 to 2 min after eight 50-ml puffs were inhaled to a specified lung volume (0–60% of VC) and held in the lungs for 4 sec. Under the 0% of VC condition, puffs were not inhaled. Boost refers to post- minus presmoking levels. Brackets indicate 1 S.E. An asterisk above a bar indicates that the condition is significantly different from the next highest inhalation volume condition.

scale; S.E. in parentheses) were 0.8 (0.4), 24.6 (3.2), 56.7 (7.1) and 74.4 (7.7), respectively, in the 0, 20, 40 and 60% of VC conditions (0 mm = no inhalation and 100 mm = very deep). *Post hoc* tests revealed that all comparisons between conditions were statistically significant. There were significant differences in strength ratings, $F(3,27) = 5.7$, $P < .01$, satisfaction ratings, $F(3,27) = 30.7$, $P < .001$ and craving ratings, $F(3,27) = 11.3$, $P < .001$, across the experimental conditions; *post hoc* tests revealed that these differences were between the no-inhalation condition and the three smoke inhalation conditions. Subjects rated noninhaled puffs as significantly weaker and less satisfying than inhaled puffs, and rated cigarette craving higher after noninhaled puffs.

Experiment IV. Effects of Inhalation Volume (with No Breathhold) on Smoke Exposure

Smoking topography. Mean values of the smoking parameters measured in this experiment are shown in table 5. Inhalation volume varied systematically across conditions, and the average inhalation volume in each experimental condition varied less than 2% from the targeted volume. Exhalation volume also varied systematically across conditions, and was slightly higher in magnitude than inhalation volume. Breathhold durations were less than 0.1 sec in all conditions. Lung exposure duration increased across the inhalation volume conditions; *post hoc* tests revealed that lung exposure durations were significantly shorter at the 10 and 20% of VC conditions than at the 40 and 60% of VC conditions. Puff volume and interpuff interval did not vary across conditions. Puff duration and peak flow differed significantly across conditions, with shorter puffs and larger peak flows under the 60% of VC condition than under the other conditions.

TABLE 5
Experiment IV topography measures[a]

	Inhalation Volume					Main Effects
	0	10	20	40	60	
	% of VC					
Puff parameters						
Puff volume (ml)	50.8 0.5	49.5 0.3	49.6 0.5	50.1 0.7	50.4 0.3	N.S.[b]
Puff duration (sec)	1.67 0.09	1.87 0.10	1.81 0.08	1.69* 0.09	1.40 0.07	P < .001
Peak flow (ml/sec)	49.8 3.6	43.3 2.9	44.1 1.9	45.7* 2.3	55.1 3.0	P < .01
Interpuff interval (sec)	61.9 1.0	62.5 1.7	61.3 0.6	61.9 1.4	61.4 1.6	N.S.
Respiration parameters						
Inhalation volume (% of VC)	0* 0	11.7* 0.6	21.2* 0.6	40.3* 0.3	60.2 0.8	P < .001
Exhalation volume (% of VC)	0* 0	16.6* 1.7	25.6* 1.6	44.3* 1.5	65.7 2.4	P < .001
Breathhold duration (sec)	0 0	0.02 0.01	0.05 0.05	0.04 0.04	0.05 0.03	N.S.
Lung exposure duration (sec)	0 0	3.39 0.36	3.91* 0.27	4.82 0.43	5.42 0.32	P < .001

[a] Mean ± S.E.
[b] N.S. indicates main effect was not significant.
* Significantly different from next highest inhalation volume condition using Tukey *post hoc* comparison test.

Nicotine and CO boost. Figure 5 (top) shows that there was a negligible nicotine boost in the 0% of VC condition, but substantial boosts when smoke was inhaled, $F(4,36) = 16.5$, $P < .001$. Although nicotine boost was slightly lower in the 10% of VC condition compared to the other smoke inhalation conditions, *post hoc* tests revealed no significant differences between the boosts in the four smoke inhalation conditions. The lower average nicotine boost at the 10% of VC condition is due in part to 2 of the 10 subjects who showed no detectable nicotine boosts in this condition. Figure 5 (bottom) shows that there was a negligible CO boost in the 0% of VC condition, but substantial boosts when smoke was inhaled, $F(4,36) = 33.5$, $P < .001$. *Post hoc* tests revealed that CO boost did not differ across the four smoke inhalation conditions. One of the two subjects who showed no nicotine boost in the 10% of VC condition also showed no CO boost in this condition.

Time course of postsmoking nicotine and CO levels. Mean plasma nicotine levels differed as a function of both condition, $F(4,36) = 19.1$, $P < .001$, and time since the last puff in the smoking session, $F(2,18) = 51.1$, $P < .001$, with inhalation/no-inhalation differences accounting for condition effects.

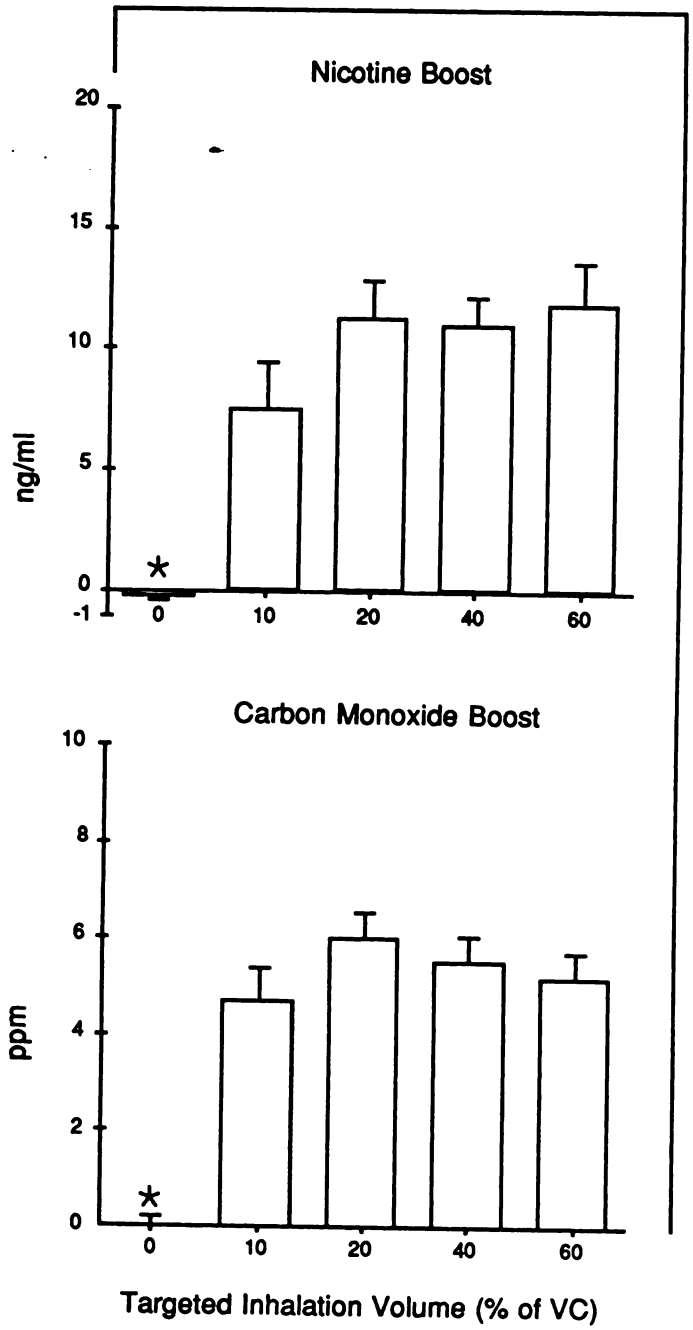

Fig. 5. Mean nicotine boost (nanograms per milliliter) and CO boost (parts per million) for 10 subjects are shown as a function of inhalation volume, which was measured as a percentage of VC. Plasma nicotine and breath CO were measured before and 1 to 2 min after eight 50-ml puffs were inhaled to a specified lung volume (0–60% of VC) and then exhaled immediately. Under the 0% of VC condition, puffs were not inhaled. Boost refers to post- minus presmoking levels. Brackets indicate 1 S.E. An asterisk above a bar indicates that the condition is significantly different from the next highest inhalation volume condition.

Plasma nicotine levels changed across time in the three inhalation conditions but not in the no-inhalation condition. The decreasing trend in plasma nicotine levels across time in the smoke inhalation conditions was both linear, $F(1,9) = 59.1$, $P < .001$, and quadratic, $F(1,9) = 27.8$, $P < .001$, in nature. Mean CO levels also differed as a function of both condition, $F(4,36) = 4.6$, $P < .004$, and time, $F(2,18) = 44.4$, $P < .001$, with inhalation/no-inhalation differences accounting for condition effects. CO levels changed across time in the three smoke inhalation conditions but not in the no-inhalation condition. The decreasing trend in CO levels across time in the smoke inhalation conditions was both linear, $F(1,9) = 51.0$, $P < .001$, and quadratic, $F(1,9) = 7.2$, $P < .03$, in nature.

Subjective effects. Inhalation depth estimates varied as a function of inhalation volume, $F(4,36) = 37.6$, $P < .001$. Mean subject-rated inhalation depths (in millimeters along a 100-mm scale; S.E. in parentheses) were 1.1 (0.6), 18.9 (6.5), 35.0 (6.6), 55.2 (6.3) and 76.1 (7.2), respectively, in the 0, 10, 20, 40 and 60% of VC conditions (0 mm = no inhalation and 100 mm = very deep). *Post hoc* tests revealed that except for the differences between the 0 and 10% of VC conditions, and the 10 and 20% of VC conditions, all other comparisons between conditions were statistically significant. Inhalation volume affected harshness ratings, $F(4,36) = 3.07$, $P < .05$, satisfaction ratings, $F(4,36) = 10.1$, $P < .001$ and craving ratings, $F(4,36) = 7.24$, $P < .001$. Noninhaled puffs were rated as significantly less harsh than inhaled puffs. Subjects rated puffs from the 0 and 10% of VC conditions as significantly less satisfying than puffs from the other smoke inhalation conditions, and had significantly higher cigarette craving ratings after puffs from the 0 and 10% of VC conditions.

Discussion

Both nicotine and CO boost increased in a systematic fashion when puff volume was manipulated across a 4-fold range of values (15–60 ml) while respiratory parameters were held constant. Nicotine boost increased 4-fold and CO boost increased 9-fold. These results are consistent with other studies that have documented covariations between puff volume and smoke exposure in humans (Gust and Pickens, 1982; Herning *et al.*, 1981; Zacny and Stitzer, 1986). The results confirm that puff volume is a fundamental determinant of smoke dose as reflected in biological exposure to nicotine and CO. The present demonstration is compelling particularly because it is unconfounded by cigarette length, cigarette brand or respiratory parameter variations, and also because two different measures of smoke exposure were used. However, puff volume alterations were accompanied by changes in puff duration and peak flow rate. Previous smoking machine studies have shown that flow rate, *per se*, can independently affect CO delivery (Rickert *et al.*, 1980; Robinson and Forbes, 1975). Thus, the effects of puff volume on CO boost (and perhaps nicotine boost) may have been confounded by the systematic changes in flow rate across puff volume conditions.

The results from Experiment I are relevant to the understanding of normal smoking. First, the tested puff volumes were within the range of volumes measured during the base-line smoking phase in this study, and during *ad libitum* smoking in other studies (Adams *et al.*, 1983; Battig *et al.*, 1982; Guillerm and Radziszewski, 1978; Herning *et al.*, 1983; Hinds *et al.*, 1983; McBride *et al.*, 1984; Rawbone *et al.*, 1978; Schulz and Seehofer, 1978). Secondly, the confound between puff volume and flow rate also exists in *ad libitum* smoking situations: smokers who take larger puffs also tend to have high peak flows (Gritz *et al.*, 1983). Finally, it is probable that the effects of puff volume observed for nicotine and CO measures of exposure would also be seen in measures that reflect exposure to other smoke constituents as well (*cf.* Schlotzhauer and Chortyk, 1983). Thus, the effects of puff volume observed here would appear applicable to natural smoking. However, it is possible that larger puff volumes would result in fewer puffs per cigarette during natural smoking, due to a faster burn time. This could tend to

counteract the increased exposure predicted for larger puff volumes.

Experiment II showed that variations in lung exposure duration between 5 and 21 sec influenced CO, but not nicotine absorption. CO boost doubled over this range of lung exposure durations, whereas nicotine boost was not related systematically to lung exposure duration. The effect of lung exposure duration on CO uptake can be explained by the fact that CO diffusion from the alveoli into the bloodstream is time-dependent (Davies, 1982). Results obtained in our study are consistent with those from a recent CO absorption study in which 65% of an inhaled CO bolus was absorbed after 0 sec of breathholding, whereas 20 sec of breathholding resulted in almost complete CO absorption (*cf.* McBride *et al.*, 1984).

Only the lung exposure durations obtained in Experiment II under the 0-sec breathhold condition (mean of 4.85 sec) were consistent with lung exposure durations obtained in the baseline smoking phase (mean ± SD; 5.6 ± 1.3 sec) and in other studies that have assessed *ad libitum* smoking (Adams *et al.*, 1983: 4.3 ± 2.3 sec; Herning *et al.*, 1983: 4.7 ± 1.7 sec; Tobin *et al.*, 1982: 4.5 ± 1.3 sec). Because lung exposure durations during *ad libitum* smoking are relatively short, increased CO exposure at 4-, 8- and 16-sec breathholds, corresponding to lung exposure durations of 8.8, 12.8 and 20.8 sec, respectively, would appear to have little relevance to natural smoking. It would be interesting to examine CO absorption after a series of shorter lung exposure times that were all within the range of normal smoking to determine whether CO exposure is regulated by lung exposure time during natural smoking.

In contrast to CO, lengthening the amount of time that smoke was breathheld in the lungs did not increase the amount of nicotine absorbed from the particulate smoke phase during smoking. A lung residence time of 5 sec was apparently sufficient for maximal nicotine deposition and absorption. Although there are studies which provide support for the notion that nicotine deposition is completed during relatively short lung exposure durations (Mitchell, 1962; Isaac and Rand, 1972), results from other studies suggest that deposition of particles similar in size to those found in tobacco smoke increases in a graded fashion with longer lung exposure durations (Palmes *et al.*, 1967; Palmes *et al.*, 1973). Our results, which support a rapid nicotine deposition process, are an important addition to the literature inasmuch as surprisingly little is known about the dynamics of nicotine deposition in, and absorption from, the lungs (Darby *et al.*, 1984). It is, of course, possible that nicotine absorption levels would vary over a range of shorter lung exposure times (*e.g.*, 2–5 sec) that are within the range seen during normal smoking.

Experiment III showed that the quantity of air mixed with the smoke as it was inhaled into the lungs had no influence on CO or nicotine exposure. The same results were obtained when the experiment was repeated using a breathhold duration that approximated more closely natural smoking (Experiment IV). The results are relevant to natural smoking where inhalation volumes vary from about 15 to 30% of VC (Adams *et al.*, 1983; Rawbone *et al.*, 1978; Tobin *et al.*, 1982). The failure of inhalation volume to affect CO and nicotine uptake may be due to the effects of lung volume on two proposed controlling mechanisms of smoke uptake: membrane surface area and alveolar concentration of smoke constituents (Adams *et al.*, 1983). According to Adams *et al.* (1983), increasing lung volume 1) increases membrane surface area, which should increase smoke uptake, but 2) decreases alveolar concentration of smoke constituents, which should decrease smoke uptake. Because these two proposed determinants of CO and nicotine uptake act in opposite directions when inhalation volume is altered, it is plausible that inhalation volume variations would have no effect on CO and nicotine boost.

These results are consistent with a recent study in which inhalation volumes from *ad libitum* smoking did not predict CO boost (Adams *et al.*, 1983). The results from Experiments III and IV are also consistent with a recent study by Herning *et al.* (1983), in which a combination of puffing and inhalation parameters increased substantially the amount of explained variance of nicotine uptake in a multiple regression analysis. However, β weights reported for the multiple regression analysis suggest that inhalation volume and duration, in particular, contributed relatively little to the prediction. The results from Experiments III and IV are important because they contradict previous speculation that smokers may use inhalation volume to regulate their smoke exposure (*e.g.*, Ebert *et al.*, 1983; Herning *et al.*, 1983; Robinson *et al.*, 1982; Wald *et al.*, 1980, 1983). Overall, these data suggest that recent recommendations calling for the measurement of respiration parameters in studies that attempt to relate smoking topography to nicotine exposure appear to be unwarranted (Herning *et al.*, 1983).

In Experiments III and IV, when smoke was taken into the mouth but not inhaled, no CO or nicotine absorption could be detected. This is consistent with a number of other studies which have found that nicotine and CO from smoke are not absorbed in the mouth (Armitage, 1978; Dalhamn *et al.*, 1968; Guyatt *et al.*, 1981; Higgenbottam *et al.*, 1980; Rawbone *et al.*, 1976; Schoenfish *et al.*, 1980). The surface area for nicotine and CO absorption in the lungs is literally thousands of times greater than the surface area in the mouth (West, 1985). In addition, nicotine from cigarette smoke is absorbed more readily in the acidic environment of the lung than in the alkaline environment of the mouth (Armitage *et al.*, 1975; Schievelbein, 1982).

Multiple sampling of nicotine plasma levels after completion of the smoking bout revealed that the rate of plasma nicotine decline was faster in the initial part of the postsmoking period (from 1-min–10-min postsmoking) than in the middle and latter part of the period (from 10-min–30-min postsmoking). This finding is consistent with a number of other studies that have established a biphasic time course for the decline of plasma nicotine concentration after smoking (*e.g.*, Benowitz, 1983; Hopkins *et al.*, 1984; Isaac and Rand, 1972). In the initial phase, nicotine is eliminated rapidly from the bloodstream and distributed into various body tissues. In the second and much longer phase, nicotine is eliminated more slowly from the bloodstream by metabolism, excretion and tissue distribution. Rate of CO decline in alveolar air was linear across the postsmoking period. These results are consistent with other studies that have measured expired air CO levels after smoking (Henningfield *et al.*, 1980; Hopkins *et al.*, 1984).

Subjects in all four experiments were able to track manipulated parameters in their subjective reports: relative estimates of puff size, inhalation depth and length of breathhold varied in an orderly fashion with experimental alterations in puff volume, inhalation volume and breathhold durations. In contrast, other studies have found no relationship between self-reported estimates of inhalation depth and actual measured inhalation volumes (Adams *et al.*, 1983; Tobin *et al.*, 1982;

Tobin and Sackner, 1982). Our results may be due to the practice that subjects received with manipulated smoking parameters before and during the experiment, which provided them with reference points that could be used when estimating inhalation magnitude.

Across the four experiments, ratings of puff strength and satisfaction varied only when changes in plasma nicotine levels were observed. In Experiment I, larger puffs were rated as stronger and more satisfying than smaller puffs. In Experiment II, strength and satisfaction ratings covaried with nicotine levels, which remained unchanged across conditions, and not with CO levels, which increased across conditions. These findings are consistent with the widely held hypothesis that nicotine, and not CO, is responsible for the reinforcing effects of cigarette smoking (*cf.* Gritz, 1980; Henningfield, 1984).

In conclusion, the present experimental analyses of smoking topography have shown that puff volume is an important determinant of tobacco smoke exposure as measured by plasma nicotine and expired air CO boosts. In contrast, the volume and duration of the postpuff inhalation had no influence on nicotine or CO exposure levels within a range of inhalational parameters observed in normal smoking. Because health risks of smoking are dose-related, especially with regard to cardiovascular disease (Petitti and Friedman, 1985), these results suggest that smokers who draw and inhale large puffs will have greater health risks than smokers who draw and inhale a similar number of small puffs. However, smokers who take large inhalations of air with their puffs would not be expected to have increased health risks, at least in regard to cardiovascular disease. These results also suggest that smokers who attempt to reduce the health risks of smoking by reducing the number or yield of cigarettes smoked per day should be aware that increases in puff volume could at least partially counteract their risk reduction efforts.

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