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Immediate response to cigarette smoke

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ABSTRACT Using an automated method of calculating airways resistance in the body plethysmograph, we have investigated changes occurring immediately after inhalation of cigarette smoke. Decreases in specific conductance occurred by the time of the first measurement seven or eight seconds after exposure to single inhalations of cigarette smoke in 12 smokers and 12 non-smokers. Less than half of the initial change was present 40 seconds after the inhalation. Initial responses were greater in the non-smokers. Responses recurred with repeated inhalations in smokers and non-smokers. Prior administration of salbutamol and ipratropium bromide significantly inhibited the response and this inhibition appeared to be greater in non-smokers. Sodium cromoglycate inhaled as a dry powder had no effect on the response.

Narrowing of the airways in response to the inhalation of irritant substances such as cigarette smoke is usually regarded as a defensive lung reflex[1] or at least as a remnant of a phylogenetically earlier reflex. To be an effective defence against further exposure to the irritant substances the onset of airway narrowing should occur as soon after the onset of the stimulus as possible. Most studies of such responses in man have examined changes some minutes after the stimulus. Simonsson *et al*[2] performed measurements immediately after the end of a stimulus and found changes within five seconds of a single inhalation of citric acid in asthmatic patients. Empey *et al*[3] used five inhalations of citric acid and found a similar time course of decay of the response. A rapid decay of the changes induced by cigarette smoke might explain the variable results in previous studies of airway responses in man. The changes within the first 30 seconds of inhalation of cigarette smoke do not appear to have been investigated previously. This study was designed to look for changes occurring during this period immediately after inhalation of cigarette smoke and to study the characteristics of such changes.

Those reports with a consistent response to cigarette smoke have usually put constraints on the manner of smoking, frequent inhalations of smoke being used rather than the normal pattern.[4–9] Nadel and Comroe[10] found changes in specific conductance (sGaw) within one minute of beginning to smoke. Their measurements were made in a body plethysmograph, however, and it is not clear whether subjects smoked while in the plethysmograph and what was the precise relation between measurements of sGaw and the beginning of cigarette smoke inhalation.

In addition to the time delay in shutting subjects in the body plethysmograph and allowing temperature equilibration to minimise drift in the box pressure signal, a drawback of the body plethysmograph has been the variability of the measurements. Because of this variability most workers make several measurements and use the mean value to assess changes. This process makes it difficult to follow short-term changes such as those to be described in the first 30 seconds after inhalation of cigarette smoke.

We have used an automated measurement of airways resistance measured in the body plethysmograph.[11] With this method measurements can be obtained every 6–10 seconds with a significantly smaller degree of variation than the conventional manual method (coefficient of variation of sGaw less than 10%). Computer calculation removes the possibility of observer bias and interobserver variation, which is usually considerable.[12] The method takes account of information obtained over the whole of the respiratory cycle to produce a value that is an average of resistance in both inspiratory and expiratory phases. With this technique we have been able to investigate the immediate response to inhalation of acute irritants in man.

Methods

Twenty-four hospital workers aged 21–30 years

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were studied in the initial assessment and subjects from this same group were used in the other studies described. Non-smokers had never smoked regularly, while smokers had consumed 10–25 cigarettes a day for at least a year. None of the subjects had a history of asthma or other chronic respiratory illness. All subjects were asked to refrain from smoking for at least one hour before coming to the laboratory.

Airways resistance measurements were made in a constant-volume body plethysmograph with subjects panting at approximately 2 Hz.[13] The computer-assisted determination of airways resistance uses the first harmonics of flow and box pressure signals and calculates resistance over the whole respiratory cycle after allowing for factors producing a phase difference between the signals.[11] Resistance was converted to sGaw by taking the reciprocal of resistance and dividing by the lung volume at which the measurement was made. Changes in sGaw are shown for the first studies. For the statistical analysis a logarithmic transformation of sGaw was used (log sGaw). The distribution of log sGaw is close to a normal distribution and is therefore preferable for statistical analysis using parametric tests.[14]

Nine baseline measurements of airways resistance were made before the subjects smoked. Still sitting in the plethysmograph they then took a puff from a middle-tar, filtered cigarette (Embassy Filter). The cigarette burned outside the plethysmograph and was smoked by way of a short polythene tube with a dead space of less than 5 ml and the same external diameter as the cigarette. The action of smoking usually consists of taking a volume of smoke into the mouth (the puff) and then inhaling this to a variable depth diluted with inspired air. Because of the artificial manner of smoking in this study, subjects were asked to make some effort to inhale the cigarette smoke after taking the puff. Only the middle half of the cigarette was used.

The next airways resistance measurement was made as soon as possible after inhalation of cigarette smoke, generally 6–10 seconds later. It was then possible to make further measurements at 6–10-second intervals. The first three measurements were therefore completed within 30 seconds of exposure to cigarette smoke. Panting was required only for 3–4 seconds for each measurement, leaving several seconds during which subjects could remove their lips from the mouthpiece and take a breath if they so desired.

In 24 subjects (12 smokers and 12 non-smokers) changes in sGaw produced by single inhalations of cigarette smoke from a prelit cigarette were assessed. After nine baseline measurements one puff was taken from a cigarette and an attempt made to inhale the smoke. Five further measurements were made at intervals of 6–10 seconds.

Eight subjects (four smokers and four non-smokers) took five inhalations of cigarette smoke in a similar manner at 45–60-second intervals. Five measurements of airways resistance were made between each inhalation. After the fifth inhalation measurements were made for a further two minutes.

In three smokers and three non-smokers the response to inhalation of cigarette smoke was compared with the effect of performing the same manoeuvre with an unlit cigarette. Each subject took six inhalations—three from an unlit and three from a lit cigarette. The order of the six inhalations was randomised. Six baseline measurements were made before each inhalation and five measurements as soon as possible afterwards.

In four smokers and four non-smokers a randomised, single-blind controlled study was performed comparing the effect of 800 μg salbutamol with 40 mg sodium cromoglycate on the immediate response to inhalation of cigarette smoke. After nine baseline measurements of resistance, three inhalations of cigarette smoke were taken from a filter cigarette, with five resistance measurements after each inhalation. The first three measurements were made within 30 seconds of the inhalation of smoke and the response was assessed as the sum of change in log sGaw from the baseline value for these first three measurements. This value covers the maximum response, which is almost invariably found on one of these three recordings.

Salbutamol and sodium cromoglycate were given in random order on two days at the same time on each day. After the initial assessment of response, subjects took either 800 μg salbutamol or 40 mg sodium cromoglycate as a dry powder by spinhaler. The response to cigarette smoke was assessed 20 minutes after the drug inhalation in a similar manner.

In three smokers and three non-smokers, responses to cigarette smoke were assessed before and 40 minutes after three doses of ipratropium bromide—0·072 mg, 0·18 mg, and 0·54 mg—taken from a metered-dose inhaler providing 0·018 mg per inhalation. The three doses were given in random order at the same time on three days. Response was assessed as before on three cigarette inhalations from the sum of the change from baseline log sGaw for the first three measurements after inhalation. Nine further measurements were made two to three minutes after smoking. The effect of each dose of ipratropium was compared with the changes observed before the drug inhalation on that day by a paired t test.

The similarity of degree of smoke exposure before

and after ipratropium was assessed by measuring pulse rate and level of alveolar carbon monoxide immediately before the first inhalation and within five minutes after the third inhalation. Alveolar carbon monoxide was calculated from the level in mixed expired air with an infrared carbon monoxide analyser (Analytical Development Company).[15 16]

Results

SINGLE AND REPEATED INHALATIONS OF CIGARETTE SMOKE

Twenty-two of the 24 subjects (11 smokers and 11 non-smokers) had a significant decrease ($p < 0.05$) from the baseline log sGaw at the first or second measurement after a single inhalation of cigarette smoke. The greatest change occurred at the first measurement after inhalation of cigarette smoke in smokers and non-smokers, although in some individuals it occurred slightly later. The change at the first measurement was greater in non-smokers ($p < 0.03$). The overall pattern of response is the same in both groups, with an immediate response and return more than half way towards the baseline value by 40 seconds (table, fig 1). There was no significant difference between the mean baseline sGaw for smokers and that for non-smokers.

Changes in log sGaw produced by five inhalations at 45-second intervals are shown in figure 2. Smokers and non-smokers showed a decrease in conductance with each inhalation of cigarette smoke. There is an increasing trend with repeated exposure to fail to return to baseline values before the next inhalation and this trend was more evident in smokers than non-smokers. The level of log sGaw reached was about the same after each inhalation in smokers but non-smokers showed their greatest response to the first inhalation.

With an unlit cigarette there was sometimes a small decrease in sGaw on the first reading after inhalation. Figure 3, however, shows that changes after an unlit cigarette were very small compared with those seen after inhalation of smoke from a lit cigarette.

EFFECTS OF SALBUTAMOL, SODIUM CROMOGLYCATE, AND IPRATROPIUM BROMIDE

Mean changes in log sGaw produced by three inhalations from a cigarette before and after taking salbutamol and sodium cromoglycate are shown in figure 4. In smokers and non-smokers salbutamol significantly decreased the change in log sGaw produced by cigarette smoke (paired *t* test: smokers—$p < 0.01$; non-smokers—$p < 0.001$). Before salbutamol was given all 12 cigarette smoke challenges in each group produced a response significant at the

Immediate changes in specific conductance after a single inhalation of cigarette smoke in 12 non-smokers and 12 smokers (the values at 8–40 seconds are the first five measurements after the cigarette smoke inhalation)

Subject	*Specific conductance ($s^{-1}kPa^{-1}$)*					
	Baseline ± SD	*8 s*	*16 s*	*24 s*	*32 s*	*40 s*
			A Non-smokers			
1	1·22 ± 0·19	0·57	0·68	1·12	1·40	1·23
2	2·28 ± 0·17	1·10	1·24	1·64	1·63	1·58
3	1·36 ± 0·16	1·02	0·99	1·21	0·97	1·15
4	1·40 ± 0·05	0·52	0·47	0·81	0·89	1·02
5	1·99 ± 0·21	0·73	1·47	1·70	1·49	1·70
6	1·33 ± 0·06	1·12	1·04	1·09	1·22	1·12
7	1·70 ± 0·28	1·13	1·27	1·24	1·63	1·50
8	1·19 ± 0·11	0·95	1·16	1·15	1·08	1·18
9	1·22 ± 0·09	0·66	0·99	1·12	1·12	1·15
10	0·94 ± 0·16	0·52	0·61	0·77	0·67	0·88
11	1·37 ± 0·21	0·79	0·91	1·03	1·10	1·08
12	2·22 ± 0·25	1·39	1·30	1·89	2·02	1·73
			B Smokers			
1	2·08 ± 0·24	1·71	1·37	1·48	1·21	1·47
2	1·06 ± 0·08	0·83	0·87	0·85	0·86	0·89
3	1·62 ± 0·23	1·06	1·23	1·16	1·34	1·40
4	1·93 ± 0·15	1·48	1·71	1·78	1·79	1·74
5	1·59 ± 0·19	1·27	1·30	1·40	1·38	1·48
6	1·42 ± 0·10	1·26	1·15	1·09	1·20	1·24
7	1·07 ± 0·03	1·00	1·00	0·99	1·03	1·07
8	1·11 ± 0·09	0·76	0·99	1·07	1·10	1·10
9	1·64 ± 0·11	1·24	1·28	1·27	1·34	1·42
10	1·37 ± 0·16	1·04	1·11	1·15	1·48	1·32
11	2·01 ± 0·09	1·37	1·57	1·55	1·68	1·72
12	1·12 ± 0·21	0·68	0·73	0·68	0·87	1·00

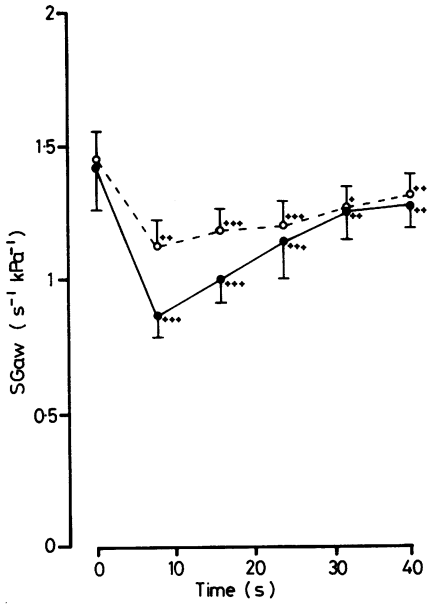

Fig 1 *Changes in specific conductance in 12 smokers (open circles) and 12 non-smokers (closed circles) after one inhalation of cigarette smoke at time 0. All values are significantly decreased from baseline levels; + = $p < 0{\cdot}01$, ++ = $p < 0{\cdot}005$, +++ = $p < 0{\cdot}001$. Vertical bars represent one standard error of the mean. At the time of the first measurement after cigarette smoke inhalation at 8 seconds non-smokers show a significantly greater change than smokers ($t = 2{\cdot}62$, $p < 0{\cdot}05$).*

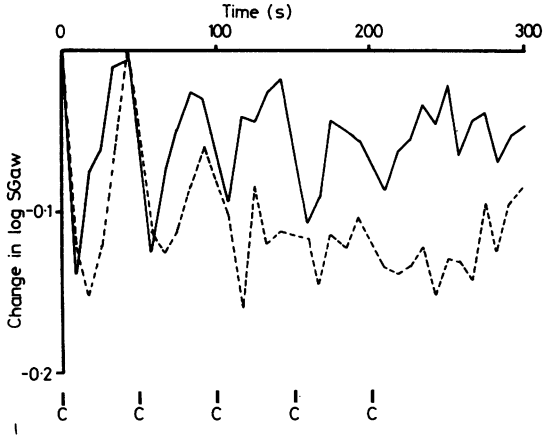

Fig 2 *Changes in log sGaw with five inhalations of cigarette smoke in four smokers (broken line) and four non-smokers (solid line). The times of the five cigarette smoke inhalations are shown by the vertical lines labelled C.*

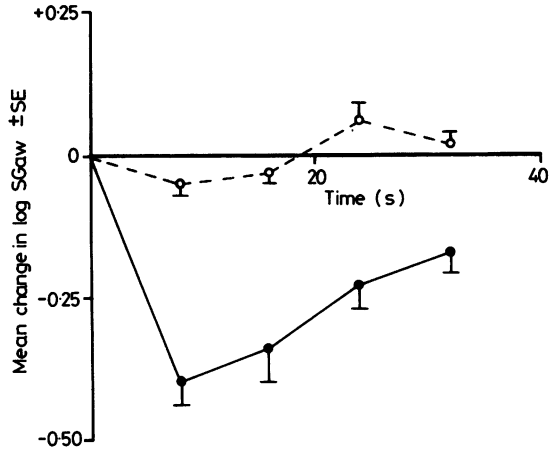

Fig 3 *Changes in log sGaw for four measurements at approximately 8-second intervals in three smokers and three non-smokers after inhalations from a lit cigarette (solid line) and an unlit cigarette (broken line).*

5% level. After salbutamol administration there were significant decreases in log sGaw in seven of 12 inhalations in smokers and in five out of 12 in non-smokers. Baseline sGaw increased by a mean of 21% after salbutamol was given ($p < 0{\cdot}01$).

Sodium cromoglycate had no effect on the response to cigarette smoke. Before and after sodium cromoglycate 23 of the 24 inhalations produced a response significant at the 5% level.

Baseline levels of alveolar carbon monoxide were higher in smokers than non-smokers (2·03 and 1·6 Pa respectively, $p < 0{\cdot}001$). Increases after three inhalations of cigarette smoke were significant only in smokers, in whom the mean level rose from 2·03 to 2·18 Pa ($p < 0{\cdot}03$). There was no significant difference between the increases in carbon monoxide with smoking before and after ipratropium bromide was given. Cigarette smoke inhalation before and after administration of ipratropium produced increases in heart rate that were not significantly different.

Immediate responses to cigarette smoke are shown in figure 5. All three doses of ipratropium significantly decreased the response in non-smokers, while in smokers this was achieved only with a dose of 0·54 mg. The baseline sGaw was increased by all three doses—a mean increase of 29% after 0·072 mg, 34% after 0·18 mg and 46% after 0·54 mg.

Significant decreases in log sGaw two to three minutes after three inhalations of cigarette smoke were found on five out of nine occasions in non-smokers and three out of nine occasions in smokers. After ipratropium was given log sGaw was not

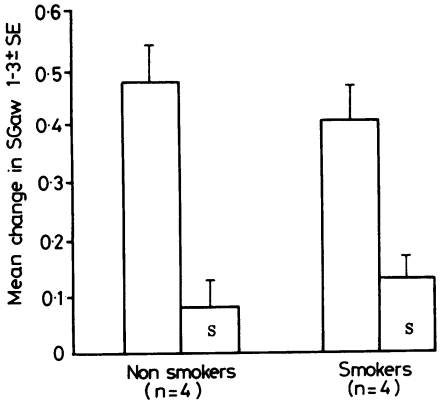

Fig 4 *The effect of 800 μg salbutamol (S) on the immediate response to inhalation of cigarette smoke in four smokers and four non-smokers. Each subject took three single inhalations of cigarette smoke and the response was assessed as the change from the baseline value of log sGaw for the first three measurements after each inhalation of smoke.*

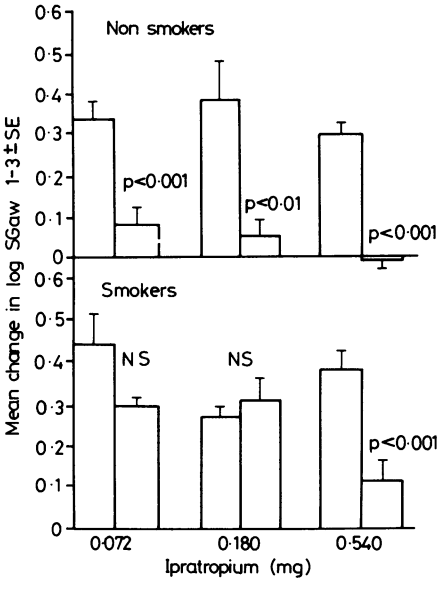

Fig 5 *The effect of 0·072 mg, 0·18 mg, and 0·54 mg ipratropium bromide on the immediate response to cigarette smoke inhalation in three smokers and three non-smokers. Changes with and without ipratropium were compared by paired t tests and significant values are shown above the appropriate columns.*

significantly decreased two to three minutes after smoking in any non-smokers but was on four occasions in smokers.

Discussion

The proportion of subjects found to have airway narrowing after inhalation of cigarette smoke has varied in previous studies. Several workers have found significant responses in a minority.[17–22] In those studies in which responses have been more common, deliberate, deep inhalations of cigarette smoke have often been used.[4 7–9] Apart from the dose and type of cigarette smoke used, the timing of measurements in relation to smoke inhalation has varied. Nadel and Comroe found a decrease in sGaw within one minute of the start of smoking a cigarette, with a decay of the observed response over 10–40 minutes. The maximum response was found at the first measurement made.[10] Our results indicate that measurements within 30 seconds of smoke exposure show consistent, reproducible changes. Differences in the timing of the measurements made may explain some of the inconsistencies in the reported studies.

Measurements of changes induced by cigarette smoke have usually been by measurement of resistance or spirometry. Spirometry measurements require inhalation to total lung capacity and maximal effort. The full inhalation may temporarily remove induced bronchoconstriction[23] and the maximum effort makes it difficult to perform a large number of manoeuvres in a short time. The computerised plethysmographic measurement of airways resistance, which was used in this study, is more reproducible than the manual method[11] and removes any possibility of observer bias in the results. Exposure to cigarette smoke with the subject already in the plethysmograph allows observation of immediate changes in airway calibre.

In lightly anaesthetised dogs Aviado and Palecek[24] found bronchoconstriction a few seconds after inhalation of cigarette smoke. They concluded that this was mainly a vagal reflex as it was decreased after cervical vagotomy. Recordings of single afferent fibres from airway receptors in animals show an immediate response to various irritant stimuli[25 26] and a proportion of these respond to cigarette smoke.[27] Vagal blockade[2] and sympathomimetic drugs[28] significantly decrease bronchoconstriction produced by lung irritants such as cigarette smoke in man and animals.

We found a significant decrease in the immediate response in smokers and non-smokers after 800 μg salbutamol inhaled as a dry powder. This blockade is presumed to be through a sympathomimetic action

on bronchial muscle, which makes it likely that most of the airway narrowing is occurring below the larynx, which contains striated muscle and would not be expected to be greatly affected by salbutamol. Ipratropium bromide, an anticholinergic agent, also reduced the immediate response. Sodium cromoglycate had no effect on airway narrowing. This does not support the reports of the action of cromoglycate as a bronchodilator[29] and in reversing vagally mediated bronchoconstriction.[30]

The airway narrowing which occurs immediately after inhalation of cigarette smoke is likely to be a nervously mediated reflex bronchoconstriction initiated by stimulation of irritant receptors with its pathway running in the vagus nerve. Such airway narrowing might be beneficial by increasing turbulent flow leading to impaction of particles or adsorption of gases higher in the bronchial tree or by helping the mechanics of coughing. While only a minority of smokers develop chronic airflow obstruction our studies show that airway narrowing almost invariably follows attempts to inhale cigarette smoke. These responses are usually transient but repeatable with further inhalations.

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