Smoking, carbon monoxide, and atherosclerotic diseases

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Summary and conclusions

Smoking habits and random measurements of the proportion of haemoglobin bound to carbon monoxide (COHb%) were examined for their association with atherosclerotic diseases in 1068 men aged 55 to 74 years from rural areas of Finland. COHb% and smoking history were similarly associated with claudication and coronary heart disease. Random measurements of COHb% did not show a better overall relation to the prevalence of atherosclerotic diseases than smoking history, though COHb% showed a stronger association with a probable previous myocardial infarction. Further studies are needed to clarify the role of carbon monoxide in atherosclerosis.

Introduction

Cigarette smoking is a known risk factor for atherosclerotic disease. Exposure to cigarette smoke has generally been estimated by interview techniques, the information being based on the amount of tobacco smoked daily. The risk of atherosclerosis, however, is probably related more to the amount of smoke inhaled than to the number of cigarettes smoked, but it is difficult to evaluate the depth of inhalation with interview methods.¹ Carbon monoxide constitutes about 4% of tobacco smoke and binds with haemoglobin to form a stable compound. Thus the proportion of haemoglobin bound to carbon monoxide (COHb%) should be a good indicator of the depth of inhalation.

We decided to evaluate random estimations of COHb% in a study of the prevalence of atherosclerotic disease. We also looked for a possible independent association between COHb and atherosclerotic disease.

Subjects and methods

In 1959, 1711 men aged 40-59 years from rural areas of eastern and south-west Finland were enrolled in a cohort study of coronary heart disease (CHD) and other atherosclerotic diseases.² In 1974, 1178 (96.2% of the survivors) were re-examined, and COHb measurements were available for 1068 (522 from east Finland, and 546 from west Finland).

The men attended for examination between 8 am and 2 pm. Venous blood samples were taken within half an hour of arrival. No instructions had been given about smoking before attendance, but subjects were not allowed to smoke while awaiting examination. Smoking on the day of examination was not recorded. COHb% was

estimated with a special spectrophotometer (182 CO-Oximeter, Instrumentation Laboratory Inc). Methods used to obtain clinical and other data as well as data on smoking habits and serum cholesterol concentrations have been described elsewhere.^{2,3} All clinical data were evaluated centrally and classified according to set rules.

Subjects were classified as having "definite" CHD when, in the absence of other heart disease (rheumatic, pulmonary, etc), there was a history of angina on effort or of a typical chest-pain attack of at least half an hour's duration⁴ or when a resting electrocardiogram (ECG) showed Minnesota code⁵ changes of infarction (code I, 1-3); ischaemic ST waves (IV, 1-3); negative T waves (V, 1, 2); abnormal atrioventricular or ventricular conduction (VI, 1, 2, 4; VII, 1, 2, 4); or atrial fibrillation. Two separate criteria were used to form subgroups of men with myocardial infarction—namely, a history of typical chest-pain attack (with or without ECG abnormalities at survey) and Minnesota code ECG changes I, 1, or I, 2 and V, 1, 2. A standard questionnaire was used⁴ to diagnose intermittent claudication, and the usual clinical criteria were used to diagnose stroke. Men with other types of heart disease; those with less definite symptoms or signs of CHD, claudication, or cerebrovascular disease; and those on whom data were incomplete were grouped separately. In the analyses of each disease manifestation in relation to smoking and COHb the unaffected men only served as controls.

The subjects were primarily divided into eight subgroups (two areas, four five-year age groups in each). The following categories were used for history of smoking: never smoked, stopped smoking, current smokers (1-9, 10-19, or 20 or more cigarettes a day), and pipe or cigar smokers (no cigarettes).

Partial correlation analysis was used to study the possibility that COHb% was independently associated with atherosclerotic disease. We chose this statistical procedure to avoid spurious results due to the strong association of the explanatory variables, cigarette consumption and COHb%. Categories were used for both cigarette consumption (as above) and COHb% ($\leq 0.5\%$; $0.6-2.0\%$; $\geq 2.1\%$). Thus the correlation coefficients indicate rank correlations between variables.

Results

Altogether 219 (42%) of the men from east Finland (EF) and 164 (30%) from west Finland (WF) were current smokers. The mean COHb concentration was 1.9% in east Finnish subjects and 1.7% in those from west Finland. The prevalence of definite atherosclerotic disease was higher in EF than in WF—claudication: EF 10%, WF 6%; stroke: EF 5%, WF 3%; CHD: EF 39%, WF 28%. The eight age- and area-specific subgroups and the total groups showed similarities in the association of atherosclerotic disease with smoking and COHb%; the results presented here are for the total groups only.

COHb% was strongly related to smoking. There were few differences between those who had never smoked and those who had stopped smoking in their distribution according to COHb% (table I). COHb concentrations above 2% were much more common in current smokers than in the other men. The prevalence of claudication was greater among current and former smokers than in those who had never smoked (table II). COHb concentrations above 2% were associated with an increased prevalence of claudication (table III). On partial correlation analysis the correlation between COHb% and claudication was low ($r=0.16$; $P<0.001$). When the effect of cigarette smoking was eliminated the coefficient was reduced by half ($r=0.08$; NS). The prevalence of stroke was inversely associated both with cigarette smoking and with COHb% (tables II and III). Nevertheless, only 38 of the men had a history of stroke, and the associations were not significant.

There was a weakly positive association between the prevalence of definite CHD and cigarette smoking, and between CHD and COHb%; the association was significant ($P<0.05$), however, only for COHb% (tables II and III). On partial correlation analysis COHb% was not correlated with CHD when the influence of cigarette smoking on the correlation coefficient was eliminated. Similarly the occurrence of angina pectoris was weakly associated with both smoking

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and COHb%; the associations tended to be significant for both (tables II and III). Smoking was not associated with a history of an attack of chest pain or with ECG signs of myocardial infarction (table II). Nevertheless, attacks of chest pain occurred at least twice as often in men with COHb concentrations above 0.5% compared with those with COHb concentrations of 0.5% or less (table III). The correlation between the COHb% and the occurrence of attacks was low ($r=0.13$; $P<0.001$). The correlation coefficient remained unchanged ($r=0.13$) on partial correlation analysis after eliminating the influence of smoking.

When studied separately in the three groups according to cigarette-smoking habit, the association of chest-pain attacks with raised COHb% was particularly clear in the ex-smokers (table IV). ECG signs of myocardial infarction tended to be associated with COHb concentrations above 0.5% (table III), but the numbers were small and the associations were not significant.

Systolic blood pressure was inversely correlated with cigarette consumption ($r=-0.14$; $P<0.001$). The correlation with COHb% was not significant ($r=-0.06$). Serum cholesterol concentration was not correlated with cigarette consumption or COHb%. The associations between atherosclerotic disease and smoking and COHb% were also studied separately in three subgroups according to blood pressure and serum cholesterol concentration—namely, systolic

blood pressure <141 , $141-160$, >160 mm Hg; serum cholesterol <5.8 mmol/l (<226 mg/100 ml), $5.8-7.1$ mmol/l ($226-275$ mg/100 ml), >7.1 mmol/l (>275 mg/100 ml)—and were found to be similar. Hence the associations did not seem to be mediated by these two risk factors.

Discussion

Wald *et al.*,⁶ who studied a group of 950 men and women aged 30-69, found that the prevalence of atherosclerotic disease correlated more with COHb concentrations than with smoking history. In our study randomly estimated COHb concentrations and cigarette consumption assessed by interview were similarly associated with the prevalence of atherosclerotic manifestations. Nevertheless, a history of an attack of chest pain was related more to COHb% than to smoking history. Wald *et al.* excluded men with more than one hour between smoking and venesection. The COHb% may thus have indicated the carbon monoxide dose of the last cigarette rather than the effect of longer duration of exposure to CO. In our study COHb measurements were

TABLE I—Distribution of men according to cigarette-smoking habit and COHb% (pipe and cigar smokers excluded)

	COHb %									
	0	0.1-	1.1-	2.1-	3.1-	4.1-	5.1-	6.1-	7.1-	≥ 8.1
No (%) who never smoked	87 (41.4)	55 (26.2)	53 (25.2)	6 (2.9)	7 (3.3)	1 (0.5)	1 (0.5)			
No (%) who had stopped smoking	189 (40.3)	131 (27.9)	101 (21.5)	29 (6.2)	6 (1.3)	9 (1.9)	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
No (%) of current smokers	23 (6.4)	34 (9.5)	51 (14.2)	49 (13.7)	64 (17.8)	60 (16.7)	34 (9.5)	20 (5.6)	9 (2.5)	15 (4.2)

TABLE II—Occurrence ratios of atherosclerotic diseases according to smoking habits (numbers of definitely affected and unaffected men given in parentheses). Men only possibly affected together with five others on whom data on smoking habit were not available are excluded

	Never smoked	Stopped smoking	Current smokers			
			No of cigarettes/day			Pipe or cigar only
			1-9	10-19	≥20	
Claudication	1.0 (4; 158)	3.3* (29; 329)	9.7*** (16; 51)	4.3** (10; 84)	8.8*** (20; 72)	8.7*** (3; 11)
Stroke	1.0 (9; 187)	1.0 (19; 402)	0.3 (1; 81)	0.9 (5; 115)	0.5 (3; 127)	0 (0; 23)
Definite CHD	1.0 (61; 123)	1.1 (151; 251)	1.3 (38; 48)	1.2 (50; 75)	1.1 (45; 82)	1.1 (7; 12)
Angina	1.0 (29; 123)	1.5* (102; 251)	1.7* (23; 48)	1.5 (31; 75)	1.5 (33; 82)	0.7 (2; 12)
ECG evidence of infarction	1.0 (8; 123)	1.3 (21; 251)	1.3 (4; 48)	0.8 (4; 75)	1.3 (7; 82)	1.3 (1; 12)
Chest-pain attack	1.0 (22; 123)	1.2 (57; 251)	1.2 (11; 48)	1.3 (19; 75)	1.0 (15; 82)	0.9 (2; 12)

* $P<0.05$; ** $P<0.01$; *** $P<0.001$ (χ^2 test).

†Fisher's exact test.

TABLE III—Occurrence ratios of atherosclerotic diseases according to COHb% (numbers of definitely affected and unaffected men given in parentheses). Men only possibly affected are excluded

	COHb %			
	≤ 0.5	0.6-2.0	2.1-4.0	> 4.0
Claudication	1.0 (17; 283)	1.4 (20; 235)	2.3** (16; 105)	4.5*** (29; 84)
Stroke	1.0 (20; 357)	0.7 (11; 284)	0.5 (4; 149)	0.4 (3; 146)
Definite CHD	1.0 (108; 237)	1.3* (118; 182)	1.3* (66; 91)	1.3* (62; 86)
Angina	1.0 (66; 237)	1.3 (74; 182)	1.5* (43; 91)	1.4* (39; 86)
ECG evidence of infarction	1.0 (12; 237)	1.8 (17; 182)	2.1 (10; 91)	1.4 (6; 86)
Chest-pain attack	1.0 (27; 237)	2.1*** (49; 182)	2.0** (24; 91)	2.4*** (28; 86)

* $P<0.05$; ** $P<0.01$; *** $P<0.001$ (χ^2 test).

TABLE IV—Association of previous chest-pain attack with COHb% according to cigarette-smoking habit (pipe and cigar smokers excluded)

COHb %:	No attack			Attack			DF	χ^2	P
	≤ 0.5	0.6-2.0	≥ 2.1	≤ 0.5	0.6-2.0	≥ 2.1			
No (%) who never smoked	105 (55.9)	69 (36.7)	14 (7.5)	10 (45.5)	11 (50.0)	1 (4.6)	2	1.54	NS
No (%) who had stopped smoking	232 (56.3)	143 (34.7)	37 (9.0)	15 (26.3)	31 (54.4)	11 (19.3)	2	18.99	<0.001
No (%) of current smokers	38 (12.1)	63 (20.1)	213 (67.8)		7 (15.6)	38 (84.4)	2	7.41	<0.05

Analysis by groups including COHb concentrations $\leq 2.0\%$ only—Never smoked: $\chi^2=1.25$; DF=1; NS. Stopped smoking: $\chi^2=14.46$; DF=1; $P<0.001$. Current smokers (Fisher's exact test): $z=1.60$; NS.

made at random, which gives a good indication of the mean COHb concentration in smokers.⁷

A history of an attack of chest pain suggesting myocardial infarction was associated with raised COHb concentrations; a similar relation was not found for smoking history. The association was unlikely to have been caused by greater frequency of "false" attacks of chest pain in men with raised COHb concentrations because a similar association was found for ECG signs of myocardial infarction. The association was mainly caused by slight rises in COHb concentration (0.6-2.0%). The finding of this association among ex-smokers was unexpected; occasional smokers who had already had a myocardial infarction may have denied their habit more often than the other men.

Because our subjects were middle-aged and older men from rural areas, we cannot make generalised conclusions. Furthermore, a cross-sectional study such as this has sources of bias: for instance, the men who had diseases associated with smoking

may have altered their smoking habits. A prospective population study is needed to clarify the role of carbon monoxide in atherosclerosis.

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Influence of induced abortion on gestational duration in subsequent pregnancies

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Summary and conclusions

We studied the effect of previous induced and spontaneous abortion on gestational duration in subsequent pregnancies in 12 obstetric departments in the Netherlands. Only primiparae were studied. Of 504 women who had had a previous induced abortion, 18 (3.6%) delivered before 32 weeks' gestational age. Forty of 1313 women with a history of spontaneous abortion (3.0%) and 259 of 12 678 women with no history of abortion (2.1%) also delivered before 32 weeks. The differences between the three groups were not significant.

In the Netherlands there are no significant indications that spontaneous midtrimester abortions or premature deliveries are caused by a previous induced abortion.

Introduction

Should women who have had induced abortions be afraid of additional risk in subsequent, wanted pregnancies? English¹⁻³ and eastern European⁴⁻⁷ studies show increased numbers of second-trimester spontaneous abortions and premature deliveries in women becoming pregnant after induced abortions. We aimed to evaluate the risks of such complications in Dutch women.

Since 1967 induced abortions have become more common in the Netherlands. In 1972-3 the estimated number of abortions was 20 000-30 000,⁸ decreasing to 16 000-18 000 in 1974, and 15 000 in 1975.^{9 10} This last figure gives a rate of approximately 5.5 abortions per 1000 women aged 15-44 years, or 81 per 1000

births. Not more than 5% of abortions are induced beyond 12 weeks' gestation, and 95% of all interventions are performed by minimal dilatation and vacuum aspiration.

Patients and methods

The analysis was carried out in the department of obstetrics, Wilhelmina Gasthuis, University of Amsterdam. From January 1972 to June 1976 we reviewed 3780 primiparae admitted to this department who delivered at 17 weeks' gestation or more. Of these women, 265 (7.0%) had had at least one previous induced abortion (group A). The second group consisted of 348 primiparae (9.2%) who had had at least one spontaneous abortion and no induced abortions (group B). A third group of 3167 women (83.8%) had had no abortions (group E).

Age-matched controls were selected for each woman in groups A and B from primiparae delivering immediately afterwards who had no history of abortion (groups C and D). We compared gestational age at delivery between these four groups and between groups A, B, and E. When the date of the last menstrual period was not exactly known, gestational age was estimated from information on prenatal care, birth weight, and Dubowitz score.

In addition to the material from our own department, we had at our disposal data kindly supplied by GVR (Gemeenschappelijke Verloskundige Registratie—that is, Co-operative Obstetric Registration). In this register, data are collected from 11 obstetric departments in various regions of the Netherlands.¹¹ By adding these data to our own, we could study material from 12 departments. From this we selected only primiparae for whom gestational age of pregnancy was known. We excluded women with multiple pregnancies and those who had undergone conisation of the cervix or had uterine scars or congenital malformations of the uterus.

Thus our total series included 14 495 primiparae, of whom 12 678 had no history of abortion (87.5%), 504 had had a previous induced abortion (3.4%), and 1313 a spontaneous abortion (9.1%). We compared gestational age at delivery in these larger groups.

Results

Table I shows gestational age at delivery in group A and its matched controls (C) and group B and its matched controls (D). In group A (previous induced abortion) the proportion of deliveries before 32

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