Gender difference in the influence of smoking on arterial wall thickness

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Abstract

Background: We hypothesized that arterial wall thickening, an early atherogenic alteration, might be associated with smoking differently according to gender, considering the cardiovascular protection of female sex hormones. Methods and results: We measured ultrasonographically carotid and femoral intima-media thickness (IMT) in 194 men and 330 women without risk factors other than smoking. In men: (i) current smokers had greater carotid and femoral IMT (P<0.01, P<0.001) and former smokers had greater femoral IMT (P<0.01) than never smokers; (ii) in pooled never, current and former smokers carotid and femoral IMT correlated to current daily smoking (P<0.01) and lifelong smoking (P<0.001); and (iii) carotid and femoral IMT correlated to age in never smokers (P<0.001), current smokers (P<0.01, P<0.001) and former smokers (P<0.01), with greater slopes in current than in former smokers at carotid site (P<0.05) and in current than in never smokers at femoral site (P<0.05). In women: (i) IMT did not differ by smoking status; (ii) in pooled smokers and non smokers femoral IMT correlated to current daily smoking (P<0.01) and lifelong smoking (P<0.01) with a lower slope than in men (P<0.001), while carotid IMT did not; and (iii) carotid and femoral IMT correlated to age in never smokers (P<0.001), current smokers (P<0.001, P<0.05) and former smokers (P<0.001, P<0.01) with no different slopes. Conclusion: Smoking-related increase in IMT existed in men but not in women, suggesting a possible protection of female gender from early structural arterial alteration of smoking. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Cigarette smoking; Intima-media thickness; Large artery

1. Introduction

Cigarette smoking is well recognized as a major risk factor for atherosclerosis in men and women [1,2]. However the understanding of smoking effect on atherogenesis remains incomplete, particularly at the initial step of arterial disease. Large artery intima-media thickness (IMT), a marker of early arterial alteration [3], can be measured non-invasively with considerable precision by coupling high-resolution B-mode ultrasonography with an automated, computerized system of image analysis [4,5]. Our objective was to use this technique to describe the relationship between IMT and cigarette smoking in a cross-sectional study of current and former smokers as compared with never smokers. All of them were recruited among a cohort of healthy adults, of both sexes and free from other major cardiovascular risk factors which may have a confounding effect on the IMT/smoking association. Special attention was given to the influence of gender and site of IMT measurement (carotid and femoral) because these two factors are likely to influence the response of the arterial wall to smoking.

2. Methods

2.1. Subjects

The study population is composed of 194 men and 330 women aged 17–65 years. They were drawn from
the cohort of the AXA study [5], a longitudinal survey of cardiovascular risk factors involving 788 volunteers of both sexes recruited from employees of an insurance company (AXA, La Défense, Paris, France). The greater number of women than in men in the study population reflected the gender distribution existing in employees of the tertiary sector in the ‘Ile de France’ area. The subjects in the present work were free from cardiovascular disease including stroke, transient ischemia, coronary heart disease, congestive heart failure and intermittent claudication. They were also free from major risk factors (except smoking) for cardiovascular disease: hypertension defined as an SBP ≥160 mmHg and/or an DBP ≥95 mmHg, the presence of antihypertensive drug treatment or a combination of these; hypercholesterolemia defined as a total cholesterol level ≥6.2 mmol/l, the use of lipid lowering drug or both; diabetes mellitus defined as a fasting blood glucose level ≥7.8 mmol/l, the use of antidiabetic drugs or both. Lastly information about the menopausal status was obtained by questioning the women. A woman was classified as postmenopausal when she reported natural menopause, i.e. the absence of any menstruation during the 6 months before the investigation, or hysterectomy with bilateral oophorectomy. In addition the questionnaire elicited information on use of hormonal replacement therapy in postmenopausal women.

2.2. Smoking status and classification

Occupational health medicine nurse (JJ) administered to each subject a standard oral questionnaire that included precise questions on smoking status. The subjects were classified into three groups on the basis of their smoking status at screening: (1) never smokers — those who have never smoked; (2) current smokers — those who currently smoke daily and have performed so for the previous 3 months, regardless of the amount smoked; and (3) former smokers — those who have smoked, but had quit 3 months ago or more. In addition, current smokers were asked about the average number of cigarettes they smoked per day. Current and former smokers were also asked about the total years smoked and the average pack of cigarettes per day smoked over these years and the life long smoking dose in pack years was calculated from the total years smoked times the average pack per day smoked. Measurement of salivary or serum cotinine levels for validation of baseline smoking status was not available in the present study.

2.3. Arterial investigation

The subjects were investigated by the same sonographic physician at the workplace with a real-time B-mode ultrasound imager (Ultramark 4, Advanced Technologies Laboratories) equipped with a 7.5 MHz probe. The sonographic physician was unaware of the smoking status of the subject investigated when the scan was performed.

The imaging of IMT of the distal segment of the common carotid artery and common femoral artery on both sides was performed according to a standardized procedure [4,5]. The IMT image, obtained in the far wall of each artery, consisted of two parallel echogenic lumen-intima and media- adventitia interfaces (double-line pattern) visible on at least 1 cm of longitudinal length. Such image did not include intrusive plaque because its presence would disrupt the double-line pattern. Therefore, our measurement of IMT applies to wall thickness before lesions intrude into the vessel (preintrusive IMT). Because of poor interface visualization, the IMT image obtained was not of sufficient quality in the femoral arteries (on both sides) of two men and of five women. Once the optimal quality image of far wall IMT was obtained, the image was frozen at end-diastole by ECG-triggering, transferred to a computer equipped with a software of digitization, and stored on disk for central off-line reading. Off-line blind measurements of IMT were performed by the same reader (JG), by means of an automated computerized edge-detection program (Iòtec, Iòdata, France) whose principles and description have been provided elsewhere [4,5]. This program located the two interfaces defining far wall IMT and calculated their distance every 100 µm by means of analysis of grey level density with special tissular recognition algorithms. Average IMT was calculated as the mean value of local IMT measures along at last 1 cm of length of artery. For each subject a total IMT (left + right)/2 was taken as measure of current wall thickness of the common carotid and common femoral arteries.

2.4. Statistical analysis

Values are expressed as mean ± S.D. (or S.E. for regression slopes). Comparisons of clinical variables and IMT by smoking status were performed in each sex by ANOVA and pairwise comparisons were performed by using the Student’s t-test. Linear regressions were used to analyze the relationships between IMT and age and between IMT and current daily and lifelong smoking dose. A multiple regression analysis was used for age-adjustment of IMT/smoking relationships. As the distribution of smoking dose was skewed, a logarithmic transformation was applied. The slopes of IMT/age and IMT/smoking relationships were compared between two groups by means of a general linear model relating IMT to age (or lifelong smoking), the group category, and the product of age (or lifelong smoking) with the group category. The statistical analysis was carried out on a computer (Apple Macintosh) with the use of JMP (SAS) and Excel (Microsoft) software.
3. Results

Table 1 shows the clinical characteristics of the study population by smoking status and by gender. No significant difference in any parameter existed between never smokers, current smokers, and former smokers except lifelong smoking dose lower in former smokers than in current smokers in both sexes \((P < 0.05)\). In women, the analysis of hormonal status showed that 49 were postmenopausal of whom 24 were receiving hormonal replacement therapy.

In men, carotid IMT was higher in current smokers than in never smokers \((P < 0.01)\) but no different between former smokers and never smokers and between former smokers and current smokers, while in women carotid IMT did not differ according to the smoking status (Table 2). In men, femoral IMT was higher in current smokers \((P < 0.001)\) and in former smokers \((P < 0.01)\) than in never smokers but no different between former smokers and current smokers, while in women femoral IMT did not differ according to the smoking status (Table 2).

In the whole population of men, carotid and femoral IMT did correlate with the current number of cigarettes per day \((r = 0.21, r = 0.19\) respectively, \(P < 0.01)\) and these correlations remained significant after age-adjustment \((P < 0.001, P < 0.01, \text{respectively})\).

In the male population carotid and femoral IMT did correlate with smoking pack-years \((r = 0.37, r = 0.38\) respectively, \(P < 0.001, \text{Fig. 1}\)), and these correlations remained significant after age-adjustment \((P < 0.001)\). The carotid and femoral IMT/pack-years relationships remained significant \((r = 0.28, r = 0.35, \text{respectively}, P < 0.001)\) when men who smoked more than 40 pack-years were excluded, and their regression slopes were similar to those obtained in the entire men population.

In the whole population of women, carotid IMT did not correlate with either the current number of cigarettes per day \((r = 0.04)\) or smoking pack-years \((r = 0.08, \text{Fig. 1})\). In the female population, femoral IMT did correlate with the current number of cigarettes per day \((r = 0.20, P < 0.01)\) and smoking pack-years \((r = 0.18, P < 0.01, \text{Fig. 1})\) and these correlations remained significant after age-adjustment \((P < 0.01)\). The slopes of regression between femoral IMT and either number of cigarettes per day or smoking pack-years, were lower in women than in men \((P = 0.08, P < 0.001, \text{respectively})\). In postmenopausal women, carotid and

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics by smoking status*</th>
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<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>(n)</td>
<td>80</td>
</tr>
<tr>
<td>Age, years</td>
<td>40 (\pm) 9</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.75 (\pm) 0.07</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 (\pm) 3</td>
</tr>
<tr>
<td>Systolic pressure, mmHg</td>
<td>133 (\pm) 9</td>
</tr>
<tr>
<td>Diastolic pressure, mmHg</td>
<td>82 (\pm) 8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.14 (\pm) 0.69</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>5.40 (\pm) 0.53</td>
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<tr>
<td>Current smoking, cigarette/day</td>
<td>–</td>
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<tr>
<td>Life long smoking, pack–years</td>
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</table>

* NS, never smokers; CS, current smokers; FS, former smokers; and \(n\), number of subjects. Values are mean \(\pm\) S.D.

* \(P < 0.05\) between CS and FS.

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Intima-media thickness (IMT) by smoking status*</th>
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<tbody>
<tr>
<td></td>
<td>NS (1)</td>
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<tr>
<td>Carotid IMT, mm</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.51 (\pm) 0.08</td>
</tr>
<tr>
<td>Women</td>
<td>0.49 (\pm) 0.07</td>
</tr>
<tr>
<td>Femoral IMT, mm</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.45 (\pm) 0.08</td>
</tr>
<tr>
<td>Women</td>
<td>0.42 (\pm) 0.05</td>
</tr>
</tbody>
</table>

* NS, never smokers; CS, current smokers; FS, former smokers; and \(n\), number of subjects. Values are mean \(\pm\) S.D. NS, non significant.
femoral IMT did not correlate with either the current number of cigarettes per day or smoking pack-years. Analysis of association of IMT and age showed that in men carotid IMT and age were correlated in never smokers \((P < 0.001)\), in current smokers \((P < 0.01)\), and in former smokers \((P < 0.01)\), but the slope of the regression line was higher \((P < 0.05)\) in current smokers than in former smokers (Fig. 2) and almost significantly higher \((P = 0.07)\) in current smokers than in never smokers. In women, carotid IMT and age were correlated in never smokers \((P < 0.001)\), in current smokers \((P < 0.001)\) and in former smokers \((P < 0.001)\), but the slopes of the regression lines were not different between groups (Fig. 2). In men, femoral IMT and age were correlated in never smokers \((P < 0.001)\), in current smokers \((P < 0.001)\) and in former smokers \((P < 0.01)\), but the slope of the regression line was higher in current smokers than in never smokers \((P < 0.05)\) (Fig. 2). In women, femoral IMT and age were correlated in never smokers \((P < 0.001)\), in current smokers \((P < 0.05)\) and in former smokers \((P < 0.01)\), and the slopes of the regression lines were not different between groups (Fig. 2).

4. Discussion

The main finding of our work was to demonstrate that when other cardiovascular risk factors (particularly hypertension and hypercholesterolemia) are absent, cigarette smoking was accompanied by an increase in carotid and femoral IMT in men but not in women. Such a result was obtained in a sample of healthy adults of both sexes recruited from a general population of employees in the Ile de France area and by using a B-mode IMT measurement, highly precise thanks to the standardization of image recording according to telediastole, the automated computerized measure without reader dependence, and the calculation of average IMT as the mean of a great number of local IMT measurements [5,6].

In men, both carotid and femoral IMT were increased in current smokers as compared with never smokers, in agreement with previous studies showing positive associations between arterial wall thickening, especially in carotid arteries, and cigarette smoking [7–10]. Also, as compared with never smokers, male former smokers had increased IMT. This increase
reached a statistical significance at the femoral site but not at the carotid site, supporting a higher sensitivity of the femoral artery wall to smoking [7,11]. Another important observation was that the difference in IMT at both sites of measurement was smaller between former smokers and never smokers than between current smokers and never smokers, suggesting that the smoking effects on arterial wall thickness may be partially reversible after cessation of smoking, as previously mentioned [12,13]. However, it is possible that the lower lifelong smoking dose in former smoker men than in current smokers may have produced a lower increase in IMT in former smokers. Indeed we have observed a dose dependence of current daily and lifelong smoking doses on carotid and femoral IMT in the pooled male population of never smokers, current smokers and former smokers, which is in favour of a causative role for smoking in arterial wall thickening. The precise mechanisms by which smoking may produce large artery wall thickening are unclear. A recent study of IMT in smokeless tobacco users suggests that the pathogenesis of arterial wall thickening in smokers seems related to components of tobacco other than nicotine [10]. Furthermore experimental studies in cockerels have shown that inhalation of sidestream cigarette smoke accelerates development of aortic atherosclerotic plaque and the plaque-promotion of environmental tobacco smoke may reside in the vapor phase which may induce smooth muscle cell proliferation [14,15]. Another result of the present work was that current smoking in men was associated with an acceleration of the normal age-related increase in carotid and overall femoral IMT. Indeed the analysis of the univariate correlations of IMT with age in men shows that the increase in femoral IMT per year was 2-fold greater in current smokers than in never smokers, and the same trend existed for the annual increase in carotid IMT between current and never smokers but without reaching statistical significance. This phenomenon of higher rate of progression of IMT was not observed in former smokers in whom the slope of IMT/age relationship did not differ from that of never smokers. These cross-sectional findings are in line with the results of a recent longitudinal study [16] showing that the 3-year progression rate of carotid IMT was 50% greater in current smokers than in never smokers while only 25% greater in former smokers than in never smokers.

Fig. 2. Slopes of the intima-media thickness (IMT)/age relationship with S.E. by smoking status, by site and by gender. *, †, ‡, mean P < 0.05, < 0.01, < 0.001, respectively, for the statistical significance of the regression slopes.
Surprisingly in women unlike men, we did not find that smoking (either current or former) was accompanied with increased IMT of both arteries examined. This lack of association was observed in the univariate analysis as well in multivariate model. Moreover age was significantly associated with IMT in women, but unlike men the slope of the IMT/age relationship did not differ between current, former and never smokers. Lastly, in contrast to men, current daily and lifelong smoking doses did not correlate with carotid IMT in women, while they were associated with femoral IMT. However the slope of the femoral IMT/pack–years relationships was lower in women than in men, as well as the slope of the relation between femoral IMT and current daily smoking but without reaching statistical significance. The gender differences in the slopes of the IMT/age relationships are not as a result of the fact that several men smoked more than 40 pack–years but no women, because they persisted when men with greater number than 40 pack–years smoking were excluded from the analysis. These results support the possibility that the sensitivity of the female large artery wall to smoking is attenuated at least at the early stage of disease. Although this finding has not been really emphasized in the literature until now, preliminary results of a substudy of the Monica project [17] have already pointed to the lack of association between cigarette smoking and ultrasonographic carotid plaque in women. Also it has been recently shown that the brachial artery flow-mediated dilation was not decreased in female current smokers compared with former smokers whereas it was decreased in male current smokers compared to former smokers [18], so suggesting a gender difference in early large artery alteration induced by smoking. The mechanisms of the relative protection of large artery wall of women from the thickening effect of smoking are unknown. Adverse effects of smoking [19–21] on endothelium, plasma fibrinogen and oxidative stress may be blunted by endogenous estrogens before menopause which are involved in the relative protection from cardiovascular disease in women [22]. Indeed, women in the present study are in a great majority premenopausal because only 49 women (15%) are post-menopausal. However, if the hypothesis that premenopausal female hormones are protective as regards smoking effect on IMT is correct, postmenopausal women would have significant relationships between IMT and smoking, like men. The fact that we did not observe such relationships in postmenopausal women does not support a major role of protective effect of female hormones on IMT. On the other hand the number of postmenopausal women is probably not sufficiently great to demonstrate significant correlations between IMT and smoking and the use of hormonal replacement therapy in 50% of postmenopausal women may blunt these correlations. Furthermore, the protective effect of female hormones may partly explain the discrepancy between our work and a previous study showing that cigarette smoking increased the development and progression of atherosclerosis in women [23]. In this study women were on average 10 years older that in the present work and post menopausal in the majority of cases; moreover atherosclerosis was characterized by the presence of radiographic calcified deposit in the aorta which is quite different from our pre-intrusive IMT measured in carotid and femoral arteries.

In conclusion, we have found marked differences in the influence of smoking on IMT between men and women. Firstly, IMT increased in the presence of smoking (current and even former) in men but not in women. Secondly, a dose dependence of current daily and lifelong smoking existed for IMT in men, but it was abolished for carotid IMT and clearly attenuated for femoral IMT in women. Thirdly, current smoking enhanced the normal age-related increase in IMT in men but not in women. All these findings concur for suggesting that gender modulates the early structural alterations of large artery walls in response to smoking. A practical implication is that carotid and overall femoral IMT may be a marker more appropriate in men than in women to detect and monitor early arterial effects of smoking.

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References


