

## Original Research

## The Acute and Chronic Effect of Cigarette Smoking on the Elastic Properties of the Ascending Aorta in Healthy Male Subjects

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**Introduction:** Aortic elastic properties are markers and prognosticators of cardiovascular risk. Smoking adversely affects arterial elastic properties. The acute and chronic effect of cigarette smoking on the elastic properties of the ascending aorta has not been determined.

**Methods:** The *chronic* part of the study included 130 healthy male subjects (age  $38.1 \pm 8.9$  years, 85 smokers and 45 non-smokers) with no other risk factors for cardiovascular disease. Twenty of the smokers (age  $40.0 \pm 4.2$  years) were also included in the *acute study*. In the *acute study* each subject was studied on two occasions: one while smoking one cigarette and the other during sham smoking. Ascending aortic distensibility was assessed by two-dimensional, guided, M-mode transthoracic echocardiography of the aortic root at baseline and at the end of smoking. In the *chronic study* the association was assessed between smoking status and ascending aortic distensibility.

**Results:** Smoking *acutely* increased systolic, diastolic, and pulse pressure. Furthermore, smoking decreased ascending aortic distensibility (by  $0.53 \pm 0.86 \text{ cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$ ,  $p < 0.05$ ). The *chronic study* showed that smokers had greater ascending aortic distensibility than non-smokers ( $2.22 \pm 0.93$  vs.  $2.75 \pm 1.07 \text{ cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$ , respectively,  $p < 0.05$ ). Aortic distensibility was independently associated with smoking ( $\beta = -0.293$ ,  $p < 0.001$ ) after controlling for possible confounders. No association of aortic distensibility with the intensity or duration of smoking was observed within the group of smokers.

**Conclusions:** Cigarette smoking results acutely in a deterioration of ascending aortic elastic properties in healthy male subjects. On a chronic basis, smokers have decreased ascending aortic distensibility compared to non-smokers. This effect of smoking on aortic distensibility is not related to dose or duration.

**A**ortic elastic properties are important determinants of left ventricular load and coronary blood flow<sup>1,2</sup> and have been identified as prognosticators of cardiovascular risk.<sup>3-6</sup> The ascending aorta is the part of the aorta with the greatest distensibility. It stores a significant proportion of the blood ejected from the left ventricle during systole and forwards it to the periphery during diastole. Therefore, normal function of the ascending aorta is of paramount importance for

the proper cushioning function of the large arteries. Distensibility of the ascending aorta is decreased in patients with coronary artery disease<sup>7,8</sup> and in the presence of various coronary risk factors<sup>9,10</sup> and is influenced by several pharmacologic interventions.<sup>11</sup>

Smoking is the most important modifiable risk factor for coronary artery disease. Almost one in five adults is a current smoker in western societies and the numbers are higher in developing countries,

with cigarette smoking being the commonest form of smoking.<sup>12</sup> We<sup>13-16</sup> and others<sup>17-20</sup> have shown, using both invasive and non-invasive methods, that smoking adversely affects arterial elastic properties, both acutely and on a chronic basis. However, the effect of cigarette smoking on the distensibility of the ascending aorta has not been specifically determined. Accordingly, the purpose of this study was to assess both the acute and the chronic effect of cigarette smoking on the distensibility of the ascending aorta in male subjects.

## Methods

### Subjects

One hundred-and-thirty healthy male subjects, aged  $38.1 \pm 8.9$  years, comprised the study population. Of those, 85 (65%) were smokers and 45 (35%) were non-smokers. All of the subjects were assessed for investigation of the chronic effect of smoking in the *chronic* part of the study. In addition, twenty of the smokers, aged  $40.0 \pm 4.2$  years, were also included in the *acute study*. None of the subjects had hypertension, diabetes, or a family history of premature vascular disease. In all participants, total cholesterol plasma level was below 240 mg/dl. Their clinical examination and electrocardiogram were normal and they were under no cardiovascular medication.

### Study protocol

In the *acute study* each subject underwent evaluation of the aortic elastic properties on two separate occasions: one while smoking one standard cigarette (1.1 mg nicotine, 12 mg tar) over 5 minutes, and another during sham smoking. Measurements were made at baseline and were repeated at the end of smoking.

In the *chronic study* the association between smoking status and ascending aortic distensibility was assessed by measurements under resting conditions.

Before measurements, subjects abstained from smoking and from caffeine and ethanol intake for at least 12 hours. Measurements were obtained in a quiet, temperature-controlled room at 23°C, after the participants had fasted for at least 8 hours. Following a 20-minute rest period in the supine position, during which participants were encouraged to relax with lights lowered and ambient noise reduced, measurements were made for the evaluation of aortic distensibility.

### Assessment of aortic root function

In order to evaluate the elastic properties of the ascending aorta, aortic diameters were measured from cross-sectional echocardiographic images 3 cm above the aortic valve, using two-dimensional, guided, M-mode transthoracic echocardiography of the aortic root in the left parasternal long-axis view, as described elsewhere.<sup>9</sup> All studies were performed using a Sonos 5500 phased array ultrasound system (Hewlett-Packard, Andover, MA). Aortic systolic diameter (AoS) was measured at the time of full opening of the aortic valve, and diastolic (AoD) diameter at the peak of the QRS complex on the simultaneous electrocardiogram recording.

Ascending aortic distensibility was calculated from the measurements of AoS, AoD, and pulse pressure (PP) as:  $\text{Distensibility} = 2 \times (\text{AoS} - \text{AoD}) / (\text{AoD} \times \text{PP})$  ( $\text{cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$ ). PP was obtained simultaneously, by cuff sphygmomanometry of the left brachial artery, as systolic minus diastolic blood pressure, using Korotkoff phase V for diastolic pressure. The interobserver and intraobserver variability for the calculation of aortic distensibility in our laboratory are 3.2 and 5.8%, respectively.<sup>10</sup>

The study was approved by the local ethics committee, and all the patients gave written informed consent.

### Statistical analysis

Numerical data are expressed as mean  $\pm$  standard deviation, while qualitative variables are presented as absolute and relative frequencies. All variables were tested for homogeneity of variance and normal distribution before any statistical analysis was applied. Normality tests were applied using the Kolmogorov-Smirnov criterion.

#### Acute study

Baseline parameters were compared between the two sessions using the Student t-test for paired measures. In order to evaluate the effect of smoking on the parameters studied, an overall  $2 \times 2$  analysis of variance (ANOVA) for repeated measures was performed (2 periods [baseline and after the intervention]  $\times$  2 interventions [smoking and sham smoking]).

#### Chronic study

Comparisons between normally distributed continuous variables were made using the independent sam-

ples Student t-test. To examine if there was a difference in aortic distensibility between smokers and non-smokers an analysis of covariance (ANCOVA) was applied. Two different models of multiple regression analysis were used to determine whether there was an association between aortic distensibility (dependent variable) and intensity or duration of smoking. In the first, smokers were subdivided into three groups according to the number of cigarettes smoked per day (independent variable): a light smoker group (1-19 cigarettes/day), a moderate smoker group (20-39 cigarettes/day) and a heavy smoker group ( $\geq 40$  cigarettes/day). In the second model, smokers were subdivided into three groups (tertiles) according to pack-years of smoking (independent variable). All the multivariate models used (ANCOVA and multiple regression analysis) included variables that have been found to correlate with aortic distensibility, as well as those known to be biologically relevant to it.

A p-value  $< 0.05$  was considered statistically significant. Data analysis was performed using the SPSS statistical package for Windows (version 10.0, SPSS Inc., Chicago, Illinois).

## Results

### Acute study

Baseline measurements in both sessions and measurements after smoking or sham smoking are shown in Table 1. No difference was observed in any parameter between the baseline measurements in the two sessions. The acute effect of smoking on each variable is better described as the *response* of each variable, defined as change from baseline after smoking minus change from baseline after sham smoking. Accord-

ly, p-values refer to the significance of the repeated-measures analysis of variance between the smoking and sham smoking sessions.

Smoking resulted in a significant increase in systolic, diastolic, pulse, and mean pressure (systolic pressure by  $10.2 \pm 5.8$  mmHg, diastolic pressure by  $4.4 \pm 4.2$  mmHg, pulse pressure by  $5.8 \pm 4.3$  mmHg, mean pressure by  $6.3 \pm 4.4$  mmHg,  $p < 0.001$  for all). Furthermore, smoking resulted in a significant increase in systolic and diastolic aortic diameter (systolic diameter by  $0.62 \pm 0.66$  mm, diastolic diameter by  $0.75 \pm 0.69$  mm,  $p < 0.001$  for both) and a decrease in ascending aortic distensibility (by  $0.53 \pm 0.86$   $\text{cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$ ,  $p < 0.05$ ).

### Chronic study

The demographic and clinical characteristics of the study population are reported in Table 2. Smokers had similar age, body mass index, pulse and mean pressure, total cholesterol, triglycerides, and plasma glucose compared to non-smokers. On the other hand, smokers had decreased high density lipoprotein (HDL) cholesterol ( $49.5 \pm 10.5$  vs.  $53.4 \pm 8.8$  mg/dl,  $p < 0.05$ ), decreased systolic diameter ( $31.4 \pm 3.5$  vs.  $33.1 \pm 4.1$  mm,  $p < 0.02$ ), a trend for decreased diastolic diameter ( $29.9 \pm 3.4$  vs.  $31.2 \pm 4.0$  mm,  $p = 0.055$ ), and decreased distensibility of the ascending aorta ( $2.22 \pm 0.93$  vs.  $2.75 \pm 1.07$   $\text{cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$ ,  $p < 0.05$ ).

Aortic distensibility was independently associated with smoking status ( $p < 0.001$ ) after controlling for possible confounders, such as age, body mass index, HDL cholesterol, glucose, and mean pressure. However, no association between aortic distensibility and the intensity or duration of smoking was observed (for cigarettes smoked per day,  $\beta = -0.019$ ,  $p = 0.851$ ;

**Table 1.** Acute study of 20 smokers.

	Smoking session		Sham-procedure session	
	Baseline	After smoking	Baseline	After sham smoking
Systolic pressure, mmHg	$114.4 \pm 9.6$	$125.0 \pm 9.5$	$114.1 \pm 10.7$	$114.5 \pm 8.9$
Diastolic pressure, mmHg	$81.3 \pm 6.1$	$86.5 \pm 5.3$	$79.7 \pm 5.3$	$80.6 \pm 4.5$
Pulse pressure, mmHg	$33.1 \pm 6.6$	$38.5 \pm 7.0$	$34.4 \pm 8.4$	$34.0 \pm 7.4$
Mean pressure, mmHg	$92.3 \pm 6.8$	$99.3 \pm 6.2$	$91.2 \pm 6.4$	$91.9 \pm 5.3$
Systolic diameter, mm	$30.8 \pm 2.3$	$31.5 \pm 2.4$	$30.7 \pm 2.3$	$30.8 \pm 2.4$
Diastolic diameter, mm	$29.3 \pm 2.4$	$30.2 \pm 2.6$	$29.2 \pm 2.3$	$29.3 \pm 2.4$
Pulsatile diameter, mm	$1.48 \pm 0.45$	$1.31 \pm 0.63$	$1.54 \pm 0.49$	$1.49 \pm 0.40$
Distensibility ( $\text{cm}^2 \times \text{dyne}^{-1} \times 10^{-6}$ )	$2.36 \pm 0.81$	$1.72 \pm 0.82$	$2.42 \pm 0.98$	$2.32 \pm 0.74$

**Table 2.** Characteristics of the study participants in the chronic study.

	Smokers n=85	Non-smokers n=45	p-value
Age, years	38.0 ± 8.4	38.4 ± 9.7	0.829
Body mass index, Kg/m <sup>2</sup>	26.6 ± 2.8	26.5 ± 3.7	0.894
Total cholesterol, mg/dl	196.3 ± 22.9	191.1 ± 31.5	0.278
Triglycerides, mg/dl	95.8 ± 30.8	87.4 ± 33.2	0.152
HDL cholesterol, mg/dl	49.5 ± 10.5	53.4 ± 8.8	<b>&lt;0.05</b>
Glucose, mg/dl	96.4 ± 11.3	98.0 ± 10.8	0.435
Systolic pressure, mmHg	119.4 ± 12.4	119.8 ± 11.7	0.850
Diastolic pressure, mmHg	81.9 ± 6.2	84.1 ± 6.4	0.06
Pulse pressure, mmHg	37.5 ± 8.9	35.7 ± 9.0	0.285
Mean pressure, mmHg	94.5 ± 7.67	96.03 ± 7.41	0.254
Systolic diameter, mm	31.4 ± 3.5	33.1 ± 4.1	<b>&lt;0.02</b>
Diastolic diameter, mm	29.9 ± 3.4	31.2 ± 4.0	0.055
Pulsatile diameter, mm	1.54 ± 0.48	1.92 ± 0.58	<b>&lt;0.001</b>
Distensibility, cm <sup>2</sup> × dyne <sup>-1</sup> × 10 <sup>-6</sup>	2.22 ± 0.93	2.75 ± 1.07	<b>&lt;0.005</b>
Years of smoking	16.67 ± 8.15	–	–
Packs of cigarettes	1.17 ± 0.49	–	–
Pack-years	20.65 ± 14.90	–	–

HDL–high density lipoprotein.

for pack-years,  $\beta = -0.018$ ,  $p = 0.897$ ) after controlling for the aforementioned parameters.

## Discussion

This is the first study to investigate the acute and the chronic effect of cigarette smoking on the distensibility of the ascending aorta. According to our results, smoking has both an acute and a chronic detrimental effect on ascending aortic distensibility. Our results are in line with previous studies that examined the effect of smoking on vascular function. In detail, as we<sup>13-16</sup> and others<sup>17-20</sup> have shown, both active and passive smoking result in impaired arterial elastic properties. Smoking one cigarette,<sup>13,16,20</sup> or cigar,<sup>15</sup> or exposure to environmental smoke<sup>14</sup> acutely increases blood pressure, aortic stiffness, and wave reflections. The same acute detrimental effects are observed in the carotid and radial arteries.<sup>18</sup> Under baseline conditions, smokers have increased carotid stiffness, carotid-femoral pulse wave velocity, and wave reflections compared to non-smokers.<sup>17,19,20</sup> Findings from invasive studies show that both active and passive smoking affect the intrinsic aortic elastic properties and that the deterioration in arterial elastic properties observed is independent of the rise in blood pressure.<sup>13,14</sup>

## Mechanisms

There are some 4000 different chemical substances in

cigarette smoke, many of which have not yet been examined. Nicotine is probably the main vasoactive substance; however, carbon monoxide and other deleterious chemicals and oxidant gases interact with the cardiovascular system.<sup>21</sup>

Mechanisms through which smoking may decrease aortic distensibility include sympathetic activation and inflammation. It is well known that smoking results in sympathetic activation.<sup>22,23</sup> As has been demonstrated, norepinephrine infusion results in a great increase in peripheral and central pulse pressure and in aortic stiffness.<sup>24</sup> Furthermore, active smoking induces systemic inflammation.<sup>25,26</sup> Findings from the ATTICA study<sup>27</sup> suggest that this is also true for passive smoking.<sup>28</sup> Systemic inflammation is associated with increased aortic stiffness in population studies<sup>29</sup> and, as we have recently demonstrated, this is due to a cause-and-effect relationship.<sup>30</sup>

Given the regulatory role of the endothelium for arterial elastic properties,<sup>31</sup> endothelial dysfunction, which both active and passive smoking induce acutely and chronically, may also be involved in the deterioration of arterial elastic properties. Smoking one cigarette results acutely in a decrease in endothelium-dependent dilatation of the brachial artery, which lasts for at least one hour.<sup>32</sup> This effect is still significant with light cigarettes.<sup>33</sup> Acute smoking-induced endothelial dysfunction is eliminated by sildenafil<sup>34</sup> and red wine consumption.<sup>35</sup> On a chronic basis, both

active and passive chronic smokers have decreased endothelium-dependent dilatation,<sup>36-38</sup> which is potentially reversible after smoking cessation.<sup>39</sup>

### **Association with the intensity/duration of smoking**

In the present study we found no association between the intensity or duration of smoking (cigarettes smoked per day or pack-years) and aortic distensibility in smokers. Our results imply that smoking *per se* has an adverse effect on aortic function, without a clear dose-related effect. This result is in line with previous findings; no significant dose-related association could be found between smoking and cardiovascular risk in the Edinburgh Artery Study.<sup>40</sup> Furthermore, the effect of smoking on endothelium dependent dilatation and on C-reactive protein levels was not found to be dose-related in two other studies.<sup>38,41</sup>

### **Clinical implications**

Our study has important clinical implications. Aortic elastic properties are important determinants of left ventricular load and coronary blood flow<sup>1,2</sup> and have been identified as prognosticators of cardiovascular risk.<sup>3-6</sup> The ascending aorta is the part of the arterial system with the greatest ability to absorb the pulse generated by the ejection of the left ventricle.<sup>1,7</sup> Detection of abnormalities of ascending aortic function by echocardiography is easy to perform and adds valuable information to the evaluation of patients with increased cardiovascular risk.<sup>8,10</sup>

Smoking is the most important modifiable risk factor for coronary artery disease. As our study demonstrates, smoking has a detrimental acute and chronic effect on the distensibility of the ascending aorta, which is not related to dose or duration.

### **Limitations**

The method we used to evaluate aortic root function yields results closely related to those obtained by direct invasive measurements.<sup>7,9</sup> However, pressure was measured in the brachial artery instead of the aorta and those two pressures (peripheral, central) may not be identical because of pulse pressure amplification from centre to periphery.<sup>1,2,42</sup>

Our study population consisted only of young male subjects, so our results may not be applicable to other population groups.

### **Conclusions**

Cigarette smoking results acutely in a deterioration of ascending aortic elastic properties in healthy male subjects. On a chronic basis, smokers have decreased ascending aortic distensibility compared to non-smokers. This effect of smoking on aortic distensibility is not related to dose or duration. These findings provide important information about the effect of smoking on cardiovascular system.

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