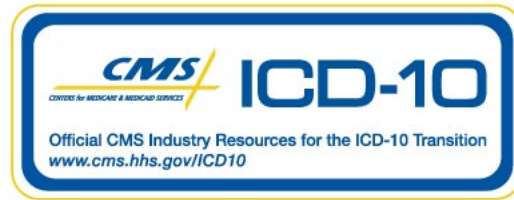


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Does Passive Smoking Impair Endothelium-Dependent Coronary Artery Dilation in Women?

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Objectives. This study sought to examine whether passive smoking is associated with endothelial dysfunction in the coronary arteries.

Background. Long-term exposure to cigarette smoking has been reported to suppress endothelium-dependent arterial dilation in humans. Endothelial dysfunction is an early feature of atherogenesis, and the impairment of acetylcholine (ACh)-induced coronary artery dilation indicates coronary endothelial dysfunction.

Methods. We studied 38 women (40 to 60 years old) who had no known risk factors for coronary artery disease other than tobacco smoking: 11 nonsmokers who had never smoked and had never been regularly exposed to environmental tobacco smoke; 19 passive smokers with self-reported histories of exposure to environmental tobacco smoke of ≥ 1 h/day for ≥ 10 years; and 8 active smokers. We examined the response of the epicardial coronary artery diameters (proximal and distal segments of the left anterior descending [LAD] and left circumflex [LCx] coronary arteries) to the intracoronary injection of ACh into the left coronary artery by means of quantitative coronary angiography.

Results. ACh significantly dilated the distal segment in nonsmokers (percent change from baseline diameter: LAD $13.7 \pm 3.4\%$, $p < 0.05$; LCx $18.8 \pm 2.9\%$, $p < 0.01$) but not the proximal segment (LAD $7.4 \pm 3.5\%$; LCx $3.1 \pm 5.0\%$). ACh significantly constricted all segments of the left coronary artery in passive smokers (LAD: proximal $-20.3 \pm 3.7\%$, $p < 0.05$; distal $-22.3 \pm 4.1\%$, $p < 0.01$; LCx: proximal $-20.8 \pm 3.1\%$, $p < 0.05$; distal $-17.3 \pm 2.9\%$, $p < 0.01$) and active smokers (LAD: proximal $-14.8 \pm 3.4\%$, $p < 0.05$; distal $-27.2 \pm 6.0\%$, $p < 0.01$; LCx: proximal $-14.5 \pm 6.6\%$, $p < 0.05$; distal $-22.4 \pm 4.0\%$, $p < 0.01$). Thus, ACh constricted most coronary arteries in both passive and active smokers and dilated the coronary arteries in nonsmokers.

Conclusions. Impairment of ACh-induced coronary artery dilation, indicating coronary endothelial dysfunction, may occur diffusely in passive smokers as well as in active smokers.

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Cigarette smoking has been recognized as one of the major risk factors for cardiovascular disease in both men and women (1). Furthermore, recent studies have demonstrated that environmental exposure to tobacco smoke (passive smoking), which includes exposure to both sidestream smoke from burning cigarettes and exhaled mainstream smoke, has been associated with an increase in frequency of coronary heart disease (2-7). Studies in experimental animals have shown that passive smoking may accelerate atherosclerosis (8) and that it increases platelet aggregation, which induces the likelihood of thrombus formation (9). The resulting increase in platelet aggregation and atherosclerosis may contribute to the devel-

opment of ischemic heart disease. Recently, Celermajer et al. (10) measured the brachial artery diameter in response to reactive hyperemia in healthy young adults and reported that passive smoking is associated with endothelial damage. Because endothelial dysfunction is an early feature of atherogenesis (11), it may represent an important marker of early vascular damage. However, few studies have assessed the effect of passive smoking on coronary endothelial function in humans.

We previously showed (12,13) that intracoronary injection of acetylcholine (ACh) induces coronary spasm in patients with coronary spastic angina. The arterial response to ACh is determined by the balance between the dilator action of endothelium-derived substances, including nitric oxide, and direct constrictor action on smooth muscle (14,15). The enhanced constrictor response to ACh is at least partly explained by decreased nitric oxide bioactivity during ACh stimulation (16,17). Therefore, the impairment of ACh-induced coronary artery dilation indicates coronary endothelial dysfunction.

We examined whether endothelial function of the coronary arteries was modulated by prolonged exposure to environmental tobacco smoke in women who had no known risk factors for coronary artery disease.

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Abbreviations and Acronyms

ACh	= acetylcholine
ECG	= electrocardiogram, electrocardiographic
HDL	= high density lipoprotein
LAD	= left anterior descending coronary artery
LCx	= left circumflex coronary artery
NTG	= nitroglycerin

Methods

Study patients. The study included a consecutive series of 11 lifelong nonsmokers (mean age 55 years, range 42 to 59), 19 passive smokers (mean age 56 years, range 43 to 60) and 8 active smokers (mean age 55 years, range 40 to 60) who were admitted at Kumamoto Rosai Hospital. All patients underwent diagnostic cardiac catheterization for evaluation of atypical chest pain. We examined only women. Because cigarette smoking is highly prevalent in men compared with women in Japan, the three groups for gender could not be matched had we examined both men and women. The passive smokers were lifelong nonsmokers with a self-reported history of exposure to environmental tobacco smoke at home or at work, or both, for ≥ 1 h/day for ≥ 10 years; the active smokers were current smokers who had smoked ≥ 20 cigarettes/day for >10 years. Cotinine levels measured in urine (18) on the day of admission were not detectable (<5.0 ng/ml) in nonsmokers and were 9.1 ± 0.5 ng/ml in passive smokers and $1,350 \pm 60$ ng/ml in active smokers. All patients had no other coronary risk factors, such as hypercholesterolemia (>240 mg/dl), hypertension ($>140/90$ mm Hg or antihypertensive treatment), diabetes mellitus, low high density lipoprotein (HDL) cholesterol levels (<35 mg/dl) or a family history of premature coronary artery disease, except for advancing age. No study subjects had significant coronary artery stenosis ($>25\%$) or coronary spasm (associated with chest pain, ischemic electrocardiographic [ECG] changes and narrowing [$>90\%$] of the epicardial coronary arteries) provoked by the intracoronary injection of ACh (12,13). No patient had congestive heart failure, allergy, active peptic ulcer, chronic obstructive lung disease, history of gynecologic operation or other clinically serious diseases. All medications that could have affected coronary vasomotor reactivity to ACh were withdrawn ≥ 7 days before the study. Written informed consent was obtained from all patients before the study, which was in agreement with the guidelines approved by the ethics committee of our institution.

Cigarette smoke is reported (19–21) to contain various chemicals, such as nicotine, nitric oxide-derived free radicals, carbon monoxide and large amounts of oxygen free radicals, that directly or indirectly cause short-term effects on coronary artery tone and hemodynamic variables. Because we aimed to determine the intrinsic functional integrity of the coronary arteries, in the present study, active smokers refrained from cigarette smoking and passive smokers from environmental tobacco smoke for ≥ 24 h before the study to avoid the possible

effects of the vasoactive substances contained in cigarette smoke.

Study protocol. *Cardiac catheterization and angiographic study.* After the control coronary angiography of the left coronary artery in the right anterior oblique caudal projection was performed, a pacing catheter (USCI tripolar electrode catheter) was inserted into the right ventricular apex for temporal pacing. The pacing rate was set in the demand mode at 50 beats/min to prevent bradyarrhythmia during intracoronary injection of ACh. Relations among focal spot, patient and height of image tube were kept constant during the angiographic study. Recordings from 12 ECG leads were made at appropriate intervals. Intracoronary injection of ACh was performed as previously described (12,13). In brief, incremental doses (50 and 100 μg) of ACh were injected into the left main coronary artery, and left coronary angiography was performed 1 min after each injection. The injection time of each dose of ACh was 20 s, and the time interval between injections was 5 min. Finally, left coronary arteriograms were obtained in multiple projections after administration of nitroglycerin (NTG) (0.3 mg).

Quantitative coronary angiography. The lumen diameter of the coronary artery was quantitatively measured using a computer-assisted coronary angiographic analysis system (Hicor, Siemens, Erlangen, Germany) as previously reported (14–17). Briefly, automated contour detection was performed at a digital angiographic work station (Siemens) (22). Measurements were obtained by investigators (H.W., M.D.) who had no knowledge of the characteristics of the study patients.

The lumen diameters were measured at the proximal, middle and distal segments of the left anterior descending (LAD) and left circumflex (LCx) coronary arteries. Angiographic measurements were performed at baseline and after administration of ACh and nitroglycerin (NTG). A Judkins catheter was used to calibrate the arterial diameter in millimeters. Special care was taken to perform all measurements at the same sites by use of anatomic references.

The response of the coronary artery diameter to the ACh and NTG was expressed as the percent change from baseline coronary diameter.

Statistical analysis. Results are shown as mean value \pm SE. The percent diameter changes in all coronary segments, age, total serum cholesterol levels, blood pressure and other variables were statistically compared among the groups with one-way analysis of variance followed by the Scheffé test. Variables and frequencies between two groups were statistically compared by an unpaired *t* test and by chi-square analysis, respectively. A *p* value <0.05 was considered statistically significant.

Results

Baseline characteristics. There was no significant difference in age, blood pressure, total cholesterol level and low density lipoprotein and HDL cholesterol levels among the three groups (Table 1). There was no significant difference in

Table 1. Baseline Characteristics of Nonsmokers, Passive Smokers and Active Smokers*

	Non-Smokers (n = 11)	Passive Smokers (n = 19)	Active Smokers (n = 8)
Age (yr)	53 ± 2	56 ± 2	55 ± 2
SBP (mm Hg)	120 ± 5	115 ± 3	124 ± 3
DBP (mm Hg)	75 ± 4	71 ± 2	74 ± 2
Total-C (mg/dl)	182 ± 5	187 ± 5	184 ± 4
HDL-C (mg/dl)	52 ± 4	54 ± 4	52 ± 2
LDL-C (mg/dl)	116 ± 4	113 ± 4	109 ± 7

*p = NS for all comparisons. Data presented are a mean value ± SE. DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; SBP = systolic blood pressure; Total-C = total cholesterol.

frequencies of postmenopausal state among the three groups (i.e., 9 [82%] of 11 nonsmokers, 6 [75%] of 8 active smokers, 15 [79%] of 19 passive smokers). No study patient had any hormone replacement therapy. There was no significant difference in the self-reported hours of aerobic exercise (e.g., sports, walking, cycling, jogging) among the three groups (4.1 ± 0.3 h/week in nonsmokers, 3.9 ± 0.2 h/week in passive smokers, 3.7 ± 0.4 h/week in active smokers, p = NS among the three groups).

In the 19 passive smokers, exposure to environmental tobacco smoke was light in 10 patients (3.7 ± 1.4 h/day) and heavy in the remaining 9 patients (7.8 ± 2.6 h/day). The 10 light passive smokers had been exposed to environmental tobacco smoke at home; 5 of the 9 heavy passive smokers had been exposed at work; and the remaining 4 of the heavy smokers both at home and at work. There was no significant difference in age, blood pressure and serum cholesterol levels between light and heavy passive smokers.

Comparison of response to ACh. Figure 1 shows the diameter changes at the proximal, middle and distal segments of the left coronary artery in response to 100 µg of ACh in the nonsmokers, passive smokers and active smokers. In the nonsmokers, ACh significantly dilated the distal segment of the LAD

Figure 1. Percent change (mean ± SE) in lumen diameters from baseline values in proximal, middle and distal segments of the LAD (left) and LCx (right) in response to intracoronary injection of ACh (100 µg) in nonsmokers, passive smokers and active smokers. *p < 0.05, †p < 0.01.

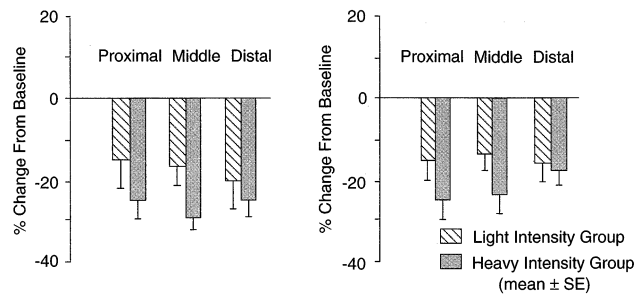
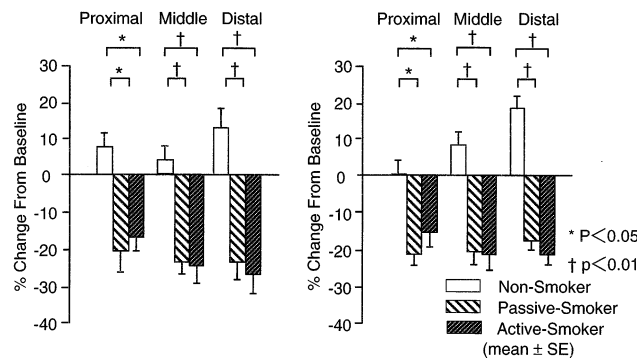


Figure 2. Percent change (mean ± SE) in lumen diameters from baseline values in proximal, middle and distal segments of the LAD and LCx in response to intracoronary injection of ACh (100 µg) in light and heavy passive smokers. There was no significant difference between the two groups.

(percent change from the baseline: 13.7 ± 3.4%, p < 0.05 vs. baseline diameter), but it did not significantly change the proximal and middle segments as a whole (7.4 ± 3.5% and 4.6 ± 3.4%, respectively). ACh significantly dilated the middle and distal segments of the LCx (9.7 ± 3.4%, p < 0.05 and 18.8 ± 2.9%, p < 0.01, respectively, vs. baseline diameter) but did not significantly change the proximal segments (3.1 ± 5.0%) (Fig. 1). In the passive smokers, ACh significantly constricted all segments of the left coronary artery (% change from baseline: LAD proximal -20.3 ± 3.7%, p < 0.05; LAD middle -23.1 ± 3.3%, p < 0.01; LAD distal -22.3 ± 4.1%, p < 0.01; LCx proximal -20.8 ± 3.1%, p < 0.05; LCx middle -19.1 ± 13.1%, p < 0.01; LCx distal -17.3 ± 2.9%, p < 0.01) (Fig. 1). In the active smokers, ACh significantly constricted all segments of both the LAD and LCx (percent change from the baseline: LAD proximal -14.8 ± 3.4%, p < 0.05; LAD middle -26.3 ± 4.6%, p < 0.01; LAD distal -27.2 ± 6.0%, p < 0.01; LCx proximal -14.5 ± 6.6%, p < 0.05; LCx middle -21.8 ± 5.4%, p < 0.01; LCx distal -22.4 ± 4.0%, p < 0.01).

Figure 1 also shows a significantly greater constriction of the coronary arteries in response to ACh injection at all segments in both the passive and active smokers than those in the nonsmokers. The degree of ACh-induced coronary constriction was similar in both the passive and the active smokers. The degree of constriction of the coronary arteries of heavy passive smokers was comparable to that in light passive smokers (Fig. 2).

Comparison of response to NTG. NTG increased the coronary artery diameter of all segments in the active, passive and nonsmokers. The percent increase in coronary diameter after NTG injection was comparable among the three groups (Fig. 3).

Discussion

Active smoking has long been established as one of the major coronary risk factors (1). Furthermore, exposure to environmental tobacco smoke, so-called passive smoking, may also have deleterious cardiovascular effects (2-9). The present study demonstrated that passive smoking is strongly associated

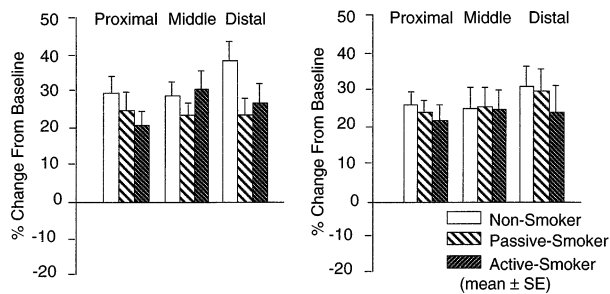


Figure 3. Percent change (mean \pm SE) in lumen diameters from baseline values in proximal, middle and distal segments of the LAD and LCx in response to sublingual NTG in nonsmokers, passive smokers and active smokers. There was no significant difference among the three groups.

with impairment of endothelium-dependent coronary artery dilation.

Passive smoking and coronary endothelial vasomotor function. The endothelium is an important modulator of coronary vasodilation, mainly through the release of endothelium-derived nitric oxide, and the arterial response to ACh depends on the integrity of this tissue (23). Endothelium-dependent vasodilation in response to ACh is impaired during the atherosclerotic process (14,15,24,25), and smoking and other coronary risk factors have been shown (16,26) to be associated with impairment of ACh-induced endothelium-dependent arterial dilation in asymptomatic adults. The present study shows that ACh constricted all coronary artery segments in both the active and passive smokers but dilated most of coronary artery segments in the nonsmokers. However, the degree of NTG-induced coronary dilation was comparable among the three groups. Thus, on the basis of our previous study (16), the enhanced constrictor response to ACh may be at least partly explained by the decrease in endothelial nitric oxide bioactivity during ACh stimulation. Therefore, not only active smoking but also passive smoking seems to be one of the important risk factors of endothelium dysfunction in the coronary arteries, an early feature of atherosclerosis. It is also possible that the supersensitivity of smooth muscle to the constrictor effect of ACh may also partly contribute to the enhanced constrictor response to ACh.

There was no significant difference in the diameter changes of all segments between heavy and light passive smokers. This result suggests that some of the effects of cigarette smoke on coronary artery vasomotor reactivity may reach a saturation point when exposure to environmental tobacco smoke is ≥ 1 h/day for ≥ 10 years, so that a monotonic dose-response effect may not exist. However, it is possible that the lack of the dose-response effect may be due to the small number of patients studied. Furthermore, the intensity of exposure to environmental tobacco smoke depends on a large number of variables, such as the number of hours of exposure per day, the proximity to active smokers in the home or at work and the size and ventilation of the rooms in which passive smoking occurs. The intensity of the passive smoking is also difficult to quantify

exactly by the self-reporting system of the passive smoking. Further studies will be necessary to resolve this issue because whether there is a dose-response relation between exposure to environmental tobacco smoke and death due to the environmental tobacco smoke (6,27) is still controversial.

Possible mechanisms of endothelial dysfunction in passive smokers. In the present study, the degree of ACh-induced coronary constriction was similar in the passive and active smokers. Although this may indicate equivalent exposure to smoking-related products between the two groups, it allows comparison of the susceptibility of the coronary artery wall to damage from active smoking with that from passive smoking. Environmental tobacco smoke consists of sidestream smoke (from the burning ends of cigarettes), exhaled mainstream smoke and a vaporphase of components that diffuse through cigarette paper into the environment. Approximately 85% of passive smoke exposure is from sidestream smoke, and 15% of that is from mainstream smoke (5). Because cigarettes burn at high temperatures during inhalation, combustion is complete, and some toxic components of tobacco smoke are broken down or filtered out before inhalation. For example, the concentration of carbon monoxide is 2.5 times higher in sidestream smoke than in mainstream smoke (4). More than 4,000 chemicals have been found, and >50 substances have been identified as carcinogens in environmental tobacco smoke (28). The particles in sidestream smoke have a smaller diameter than those in mainstream smoke and are more likely to be deposited in the most distant alveolar portions of the lung (29). Exposure to environmental tobacco smoke may cause endothelial dysfunction in part from the injurious effect of these small compounds or from secondary chemical reactions on the vascular endothelium, or both.

Large-scale epidemiologic studies (2-7) have consistently linked passive smoking to an excess risk of atherosclerotic heart disease. The present study showed that not only active smokers but also passive smokers have significantly impaired coronary endothelial function, an early process of atherosclerosis. Therefore, passive smoking may be a relevant risk factor for heart disease morbidity and mortality.

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