

Acute Effects of Passive Smoking on the Coronary Circulation in Healthy Young Adults

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PASSIVE SMOKING HAS BEEN IDENTIFIED as an important risk factor for cardiovascular disease.¹⁻⁶ In 1992, the American Heart Association concluded that the risk of death due to heart disease is increased by about 30% among those exposed to environmental tobacco smoke at home, and could be much higher in those exposed at the workplace, where higher levels of environmental tobacco smoke may be present.¹ There is evidence that exposure of nonsmokers to environmental tobacco smoke breaks down the serum antioxidant defenses⁷ and is associated with impairment of endothelium-dependent function of arterial walls.⁸ However, the acute effects of passive smoking on the coronary circulation in nonsmokers have not been evaluated.

Coronary flow velocity reserve (CFVR), a measure of endothelial function in the coronary circulation, can be noninvasively measured in the left anterior descending coronary artery (LAD) using transthoracic Doppler ech-

Context Recent studies have shown that passive smoking is a risk factor for ischemic heart disease and may be associated with vascular endothelial dysfunction. The acute effects of passive smoking on coronary circulation in nonsmokers are not known.

Objective To determine the acute effects of passive smoking on coronary circulation using coronary flow velocity reserve (CFVR), assessed by noninvasive transthoracic Doppler echocardiography.

Design, Setting, and Participants Cross-sectional study conducted from September 2000 to November 2000 among 30 Japanese men (mean age, 27 years; 15 healthy nonsmokers and 15 asymptomatic active smokers) without history of hypertension, diabetes mellitus, or hyperlipidemia.

Main Outcome Measures Coronary flow velocity reserve, calculated as the ratio of hyperemic to basal coronary flow velocity induced by intravenous infusion of adenosine triphosphate and measured in each participant before and after a 30-minute exposure to environmental tobacco smoke.

Results Heart rate and blood pressure responses to adenosine triphosphate infusion were not affected by passive smoking exposure in either group. Passive smoking exposure had no effect on basal coronary flow velocity in either group. Mean (SD) CFVR in nonsmokers was significantly higher than that in active smokers before passive smoking exposure (4.4 [0.91] vs 3.6 [0.88], respectively; $P = .02$), while CFVR after passive smoking exposure did not differ between groups ($P = .83$). Passive smoking exposure significantly reduced mean (SD) CFVR in nonsmokers (4.4 [0.91] vs 3.4 [0.73], respectively; $P < .001$).

Conclusions Passive smoking substantially reduced CFVR in healthy nonsmokers. This finding provides direct evidence that passive smoking may cause endothelial dysfunction of the coronary circulation in nonsmokers.

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ocardiography (TTDE).⁹⁻¹³ The purpose of this study was to determine the acute effects of passive smoking on coronary circulation using measurement of CFVR by TTDE.

METHODS

Subjects

We studied 30 healthy Japanese men (mean [SD] age, 27 [4] years) including 15 nonsmokers and 15 asymptomatic active smokers from September 2000

to November 2000. These subjects were recruited from the students of Osaka City University Medical School. All were clinically well and had no history of hypertension, diabetes mellitus, hyperlipid-

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emia, or left ventricular hypertrophy (septal or posterior wall thickness at diastole >12 mm). Nonsmokers lived in smoke-free homes, worked in smoke-free environments, and had no exposure to environmental tobacco smoke for more than 12 hours. Subjects were considered active smokers if they regularly smoked at least 20 cigarettes per day; the average (SD) duration of smoking was 6.8 (2.7) years. Active smokers had refrained from smoking for more than 12 hours before this study in order to minimize effects of acute smoking on study measurements. All subjects gave informed consent to the protocol, which was approved by the Committee for the Protection of Human Subjects in Research at Osaka City University Medical School.

Blood Sampling

From all subjects, blood samples were taken into a heparinized syringe by venipuncture for determination of plasma carboxyhemoglobin level (HbCO), total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol levels. Plasma HbCO level was determined by spectrophotometry as a parameter of exposure to passive smoking.

Passive Smoking

After baseline hemodynamic and echocardiographic recording, all subjects spent 30 minutes in the smoking room (450 cm × 300 cm with a 250-cm ceiling) in our hospital. When this room was used for the study, some individuals who were not among the study participants visited to smoke on their own accord. The air concentrations of carbon monoxide in the echocardiographic laboratory and smoking room were determined by averaging values measured every 5 minutes in each room using Indoor Pollution Evaluating System Model IES-1000 (constant-potential electrolysis, Sibata Scientific Technology, Ltd, Tokyo, Japan).

Hemodynamic Measurements

All subjects underwent heart rate and echocardiographic monitoring continuously and blood pressure measure-

ment every 1 minute during echocardiographic examinations. We calculated mean arterial pressure and heart rate–blood pressure product as indices of cardiac work.^{14,15}

Coronary Flow Velocity Reserve Measurements by TTDE

Before and after passive smoking, we measured echocardiographic parameters with a digital ultrasound system (Acuson Sequoia 512, Acuson Corporation, Mountain View, Calif) using a frequency of 5 to 12 MHz (Doppler frequency, 3.5 MHz). For color Doppler flow mapping, the velocity range was set at ± 12 to ± 25 cm/s. The color gain was adjusted to provide optimal imaging. The acoustic window was around the midclavicular line in the fourth and fifth intercostal spaces in the left lateral decubitus position. The left ventricle was imaged in the long-axis cross-section and the ultrasound beam was inclined laterally. Next, coronary blood flow in the distal portion of the LAD was searched for under color Doppler flow mapping guidance. With a sample volume (1.5 or 2.0 mm wide) positioned on the color signal in the LAD, we recorded Doppler spectral tracings of the flow velocity by fast Fourier transformation analysis. Adenosine triphosphate¹⁶ was administered (140 μ g/kg per minute) for 2 minutes to record spectral Doppler signals during hyperemic conditions. All studies were continuously recorded on videotape and clips of stopped frames were also stored digitally on magneto-optical disks (230 MB) for subsequent off-line analysis. Coronary flow velocity was measured at baseline and at peak hyperemic conditions by tracing contours of spectral Doppler signals using the software incorporated in the ultrasound system. These measurements were made by the investigators who were blinded to the subjects' smoking status. Each parameter was averaged over 3 consecutive cycles. Coronary flow velocity reserve was calculated as the ratio of hyperemic to basal coronary flow velocity.

Statistical Analysis

Baseline characteristics including age, total cholesterol, triglycerides, and HDL cholesterol in the 2 groups at baseline were compared with the unpaired *t* test; $P < .05$ was considered significant. To compare effects of adenosine triphosphate administration and passive smoking, we used repeated measures analysis of variance (ANOVA) for hemodynamic parameters, the air concentration of carbon monoxide, HbCO level, coronary flow velocity, and CFVR over adenosine triphosphate administration before and after passive smoking. Where appropriate, directed pairwise comparisons of individual groups were conducted using the unpaired *t* test. We used a paired *t* test for directed comparisons of passive smoking effect in each group. For all analyses, we used SAS software version 6.12 (SAS Institute, Cary, NC). Lipid values are reported in conventional units. To convert total and HDL cholesterol from mg/dL to mmol/L, multiply by 0.0259. To convert triglycerides from mg/dL to mmol/L, multiply 0.0113.

RESULTS

Baseline Characteristics

Patient age did not significantly differ in nonsmokers and active smokers (mean [SD], 27 [4] years for both groups; $P = .82$). Other baseline characteristics including heart rate, blood pressure, mean arterial pressure, and heart rate–blood pressure product were also similar in nonsmokers and active smokers (TABLE 1). Total cholesterol, triglycerides, and HDL levels did not significantly differ in nonsmokers and active smokers (167 [33] mg/dL vs 163 [43] mg/dL, $P = .78$; 102 [35] mg/dL vs 90 [30] mg/dL, $P = .53$; and 56.1 [7.8] mg/dL vs 55.0 [13.5] mg/dL, $P = .19$, respectively).

Hemodynamics

None of the subjects experienced any symptoms or had any electrocardiogram change during either passive smoking or adenosine triphosphate administration. Passive smoking had

Table 1. Hemodynamic Change Due to Passive Smoking*

	HR, beats/min	SBP, mm Hg	DBP, mm Hg	MAP, mm Hg	RPP
Nonsmokers					
Before passive smoking					
Baseline	61.1 (8.3)	108.6 (10.6)	64.3 (7.3)	86.5 (8.6)	5264.4 (797.2)
Hyperemia	64.2 (9.6)	104.9 (10.2)	59.2 (8.7)	82.1 (8.7)	5257.9 (922.2)
After passive smoking					
Baseline	61.8 (8.5)	110.2 (11.1)	62.3 (5.9)	86.2 (8.1)	5329.1 (912.1)
Hyperemia	64.2 (9.8)	106.9 (12.0)	60.6 (6.0)	83.8 (8.5)	5360.2 (890.6)
Smokers					
Before passive smoking					
Baseline	58.9 (5.7)	105.4 (11.7)	63.3 (10.1)	84.3 (10.4)	4956.5 (724.9)
Hyperemia	64.7 (10.6)	102.6 (11.4)	58.9 (10.3)	80.7 (10.4)	5251.1 (1271.4)
After passive smoking					
Baseline	62.3 (7.8)	107.1 (12.0)	64.1 (10.5)	85.6 (11.0)	5359.4 (1086.6)
Hyperemia	65.9 (11.2)	104.5 (10.5)	59.8 (8.8)	82.1 (9.4)	5429.8 (1222.9)
Repeated Measures ANOVA†					
Group	.97	.46	.97	.65	.87
Passive smoking	.20	.24	.78	.36	.13
Group × passive smoking	.34	>.99	.53	.79	.39
Adenosine	.01	.001	<.001	<.001	.26
Group × adenosine	.44	.66	.55	.95	.32
Passive smoking × adenosine	.21	.81	.24	.37	.36
Passive smoking × group × adenosine	.52	.91	.27	.43	.20

*HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; RPP, rate pressure product (beats per minute × mm Hg); and ANOVA, analysis of variance. Data presented as mean (SD).
 †Data presented as P values.

Table 2. Carbon Monoxide Level in Air and Carboxyhemoglobin Level in Blood*

	Setting	
	Echocardiographic Laboratory	Smoking Room
CO, ppm		
Nonsmokers	0.40 (0.21)	6.02 (0.88)
Smokers	0.52 (0.17)	6.32 (0.88)
	Status	
	Before Passive Smoking	After Passive Smoking
Hbco, %		
Nonsmokers	0.24 (0.18)	1.57 (0.32)
Smokers	2.49 (1.78)	2.67 (1.79)
Repeated Measures ANOVA		
	F Value	P Value
CO, ppm		
Group effect	1.6	.22
Setting effect	1271.2	<.001
Interaction effect	0.3	.58
Hbco, %		
Group effect	13.6	.001
Passive smoking effect	65.2	<.001
Interaction effect	37.9	<.001

*Data presented as mean (SD). For each statistic, df = 1, 28. CO indicates carbon monoxide; Hbco, carboxyhemoglobin level; and ANOVA, analysis of variance.

no effect on hemodynamic parameters including heart rate, blood pressure, mean arterial pressure, and heart rate–blood pressure product in each group (Table 1).

Carbon Monoxide and Hbco Level

The results of repeated measures ANOVA analysis for carbon monoxide level in air and HbCO level in blood are presented in TABLE 2. Carbon monox-

ide level in the smoking room was higher than that in the echocardiographic laboratory for both nonsmokers and active smokers. There were significant group, passive smoking, and interaction effects on HbCO level over passive smoking between both groups. Before passive smoking, the HbCO level in the blood was significantly lower in nonsmokers than in active smokers. Passive smoking significantly increased HbCO level in nonsmokers but did not significantly increase HbCO level in active smokers.

Coronary Flow Velocity

Coronary flow velocity could be observed at baseline and during hyperemia in all subjects. There was a significant interaction effect between the 2 groups over adenosine triphosphate administration before and after passive smoking (TABLE 3 and FIGURE 1). Coronary flow velocity during hyperemia in nonsmokers was significantly higher than that in active smokers before passive smoking. This parameter was quite similar in the 2 groups after passive smoking. Thus, CFVR in nonsmokers was significantly higher than that in ac-

tive smokers before passive smoking ($P=.02$), whereas CFVR did not differ between the 2 groups after passive smoking ($P=.83$). Coronary flow velocity reserve in nonsmokers was significantly reduced by passive smoking ($P<.001$) (TABLE 4 and FIGURE 2).

COMMENT

Our data revealed that temporary passive smoking abruptly reduced CFVR in nonsmokers but did not affect CFVR in active smokers. This provides direct evidence of a harmful effect of passive smoking on the coronary circulation in nonsmokers.

Comparison With Previous Studies

Cigarette smoking is one of the major risk factors for cardiovascular disease.^{17,18} This may be the result of structural¹⁹ or functional changes^{18,20} in the coronary artery produced by smoking. Some epidemiological studies have linked passive smoking to excess risk for atherosclerotic heart disease.^{1,21-25} It is thought that some premature deaths of nonsmokers may be related to passive smoking, with the majority of such deaths due to cardiac ischemia.^{1,21-25} Celermajer et al⁸ have shown that passive smoking is associated with dose-related impairment of endothelium-dependent dilatation of the brachial artery in healthy young adults. Dilatation mediated by brachial artery flow is endothelium-dependent, mediated by the release of nitric oxide. Although endothelial dysfunction in the brachial artery appears to be well correlated with both coronary endothelial physiological function and the degree of coronary atherosclerosis, flow-mediated dilatation of brachial artery does not evaluate response of the coronary circulation directly.

Reduction of CFVR by Passive Smoking in Nonsmokers

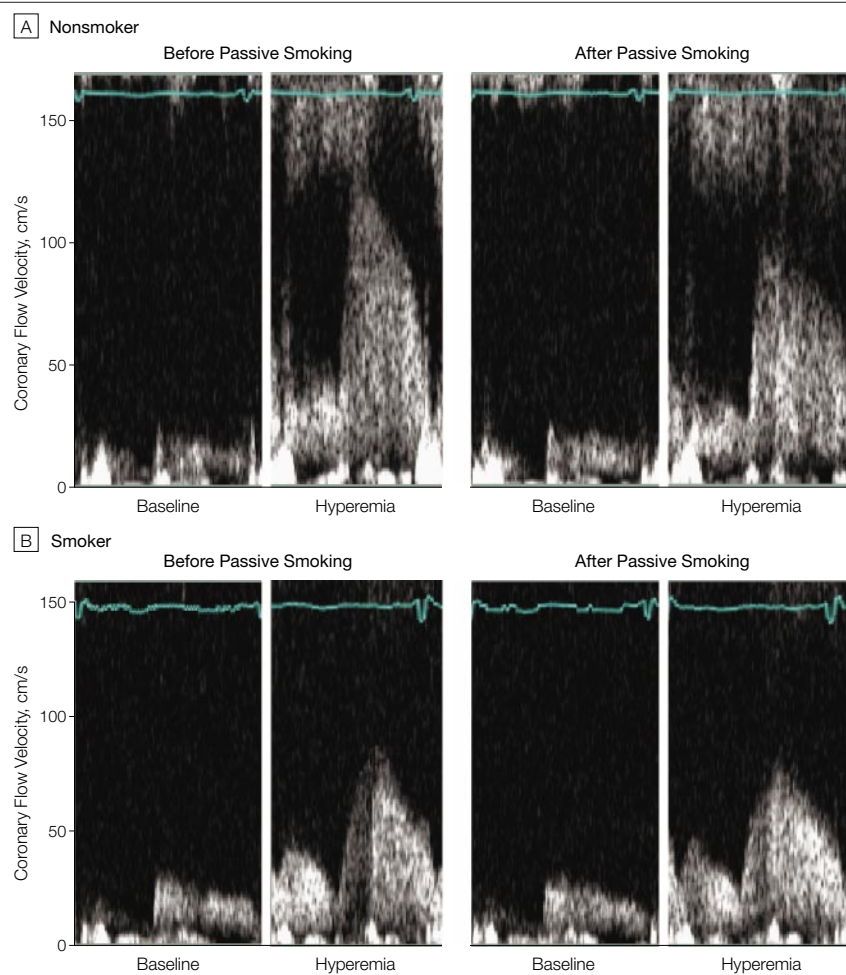
The predictive association of coronary endothelial function with clinical outcome of patients with coronary artery disease supports the concept that endothelial function may serve as an integrating index of overall coronary risk

Table 3. Flow Velocity Data*

	Status	
	Before Passive Smoking	After Passive Smoking
Nonsmokers, cm/s		
Baseline	20.2 (6.8)	20.7 (5.9)
Hyperemia	86.6 (27.4)	68.8 (22.7)
Smokers, cm/s		
Baseline	19.2 (4.0)	20.5 (4.6)
Hyperemia	67.1 (15.0)	66.7 (14.6)
Repeated Measures ANOVA		
	F Value	P Value
Group	1.8	.19
Passive smoking	8.4	.007
Group × passive smoking	10.3	.003
Hyperemia	295.9	<.001
Group × hyperemia	2.8	.10
Passive smoking × hyperemia	27.7	<.001
Group × passive smoking × hyperemia	18.9	<.001

*Data presented as mean (SD). For all analyses, $df = 1, 28$. ANOVA indicates analysis of variance.

Figure 1. Doppler Tracing of Left Anterior Descending Coronary Artery Flow in 2 Subjects



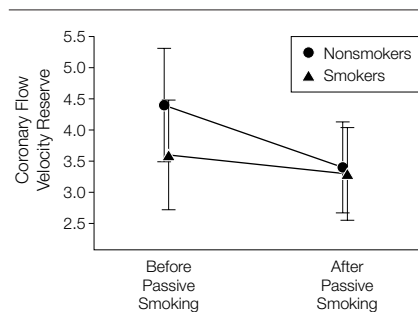
A, In the nonsmoker, coronary flow velocity at baseline did not change after passive smoking, but coronary flow velocity during hyperemia was reduced after passive smoking. B, In the smoker, coronary flow velocity at baseline and during hyperemia did not change after passive smoking.

Table 4. Coronary Flow Velocity Reserve*

	Coronary Flow Velocity Reserve	
	Before Passive Smoking	After Passive Smoking
Nonsmokers	4.4 (0.91)	3.4 (0.73)
Smokers	3.6 (0.88)	3.3 (0.74)

Group	Repeated Measures ANOVA	
	F Value	P Value
Group	2.4	.14
Passive smoking	69.7	<.001
Group × passive smoking	24.9	<.001

*Data presented as mean (SD); see "Methods" section for calculation of coronary flow velocity reserve. For all analyses, $df = 1, 28$. ANOVA indicates analysis of variance.

Figure 2. Coronary Flow Velocity Reserve Values

Data are mean (SD). Coronary flow velocity reserve (CFVR) before passive smoking was significantly higher in nonsmokers than in smokers. However, CFVR after passive smoking was reduced significantly in nonsmokers, but only slightly among smokers.

factor stress. Thus, assessment of coronary endothelial vasoreactivity may be an important diagnostic and prognostic tool.²⁶ Coronary flow reserve has been proposed as a parameter of physiological changes in the coronary circulation reflecting the function of large epicardial arteries and microcirculation.^{27,28} Impaired coronary flow reserve has been suggested as a surrogate measure of subclinical coronary atherosclerosis, providing an integrated measure of both vascular endothelial function and smooth muscle relaxation.²⁹ Recent studies have found a good agreement between CFVR as assessed with Doppler guide wire and the results of perfusion scintigraphy and positron emission tomography.^{30,31}

Tanaka et al³² found that smoking a cigarette with a high nicotine content abruptly reduced CFVR. Sumida et al³³ found that long-term exposure to envi-

ronmental tobacco smoke impaired acetylcholine-induced coronary artery dilatation, indicating coronary endothelial dysfunction. However, CFVR has previously been measured only by invasive or semi-invasive procedures^{18,27,28,34-36} and few findings have been reported on the direct impact of passive smoking on coronary circulation in healthy nonsmokers. CFVR can now be measured noninvasively by TTDE,⁹⁻¹³ and good agreement has been found between CFVR as assessed with TTDE and the results of Doppler guide wire examination.³⁷ Thus, CFVR measurement by TTDE has become a clinical tool for noninvasive and physiological assessment of coronary circulation.

In this study, CFVR before passive smoking was lower in active smokers than in nonsmokers. This difference was also found in recent studies of CFVR in active smokers.^{32,38} Kaufmann et al³⁸ found that mean (SD) CFVR values in nonsmokers and active smokers were 4.55 (0.84) and 3.79 (0.60), respectively ($P < .05$). In the present article, CFVR in nonsmokers was reduced to the same level as in active smokers after passive smoking. On the other hand, CFVR in active smokers was not significantly reduced by passive smoking. The present study is the first to demonstrate that passive smoking may have a stronger adverse effect on CFVR in nonsmokers than in active smokers.

Environmental tobacco smoke includes many toxic constituents, such as carbon monoxide, benzopyrene, and more than 4000 chemicals.^{1,39} One or some of these toxic constituents may injure the arterial wall.²¹⁻²³ Allred et al⁴⁰

found that increased carbon monoxide level induced by short-term exposure to environmental tobacco smoke resulted in more rapid onset of angina in patients with coronary artery disease as a result of endothelial dysfunction. In the present article, short-term exposure to environmental tobacco smoke increased the level of HbCO in nonsmokers, but in active smokers no difference in HbCO was found before and after passive smoking. This may be one of the reasons why passive smoking had a stronger adverse effect on CFVR in nonsmokers than in active smokers.

We measured changes in coronary flow velocity, not changes in coronary blood flow. However, it has been reported that changes in coronary flow velocities induced by coronary vasodilatation closely reflect changes in coronary blood flow.⁴¹ Furthermore, we cannot exclude the possibility that some of the volunteers in this study had epicardial coronary artery disease. This may have been ruled out only with coronary angiography, the performance of which seemed unjustified in these asymptomatic volunteers. However, none of the subjects had hypertension, diabetes, hyperlipidemia, or a history of coronary artery disease. Thus, their clinical risk for coronary artery disease was considered low.

A limitation in our study was that our design did not allow us to comment on long-term effects of passive smoking or the duration of the CFVR reduction after passive smoking; these effects may be worth testing in a large-scale trial.

In healthy individuals without coronary artery disease, reduction of CFVR can result from dysfunction of the coronary microcirculation.^{27,28} The present findings suggest that reduction of CFVR after passive smoking may be caused by endothelial dysfunction of the coronary circulation, an early process of atherosclerosis, and that this change may be one reason why passive smoking is a risk factor for cardiac disease morbidity and mortality in nonsmokers.

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