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

Ryo Otsuka, MD
Hiroyuki Watanabe, MD
Kumiko Hirata, MD
Kotaro Tokai, MD
Takashi Muro, MD
Minoru Yoshiyama, MD
Kazuhide Takeuchi, MD
Junichi Yoshikawa, MD

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.

JAMA. 2001;286:436-441
Plasma HbCO level was determined by lipoprotein (HDL) cholesterol levels.

exposure to passive smoking.

Technology, Ltd, Tokyo, Japan).

potential electrolysis, Sibata Scientific System Model IES-1000 (constant-

measured every 5 minutes in each room

determination was by averaging values

graphic laboratory and smoking room

boxyhemoglobin level (HbCO), total cho-

puncture for determination of plasma car-

From all subjects, blood samples were

Blood Sampling

All subjects underwent heart rate and elec-

trocardiographic monitoring con-

Hemodynamic Measurements

All subjects underwent heart rate and elec-

trocardiographic monitoring con-

Coronary Flow Velocity Reserve Measurements by TTDE

Before and after passive smoking, we measured echocardiographic param-

eters with a digital ultrasound system (Acuson Sequoia 512, Acuson Corpo-

ration, Mountain View, Calif) using a frequency of 5 to 12 MHz (Doppler

frequency, 3.5 MHz). For color Dop-

pler 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, the

coronary blood flow in the distal por-

tion of the LAD was searched for under color Doppler flow mapping guid-

eance. 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 µg/kg per minute) for 2 minutes to record spectral Dop-

pler signals during hyperemic condi-
tions. All studies were continuously recorded on videotape and clips of

stopped frames were also stored digi-
tally on magneto-optical disks (230

MB) for subsequent off-line analysis. Coronary flow velocity was measured

at baseline and at peak hyperemic con-
ditions 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 con-

secutive 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 unpair-
ted 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 param-

ters, the air concentration of carbon

monoxide, HbCO level, coronary flow

velocity, and CFVR over adenosine tri-

phosphate administration before and

after passive smoking. Where appro-

priate, 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 con-

vert triglycerides from mg/dL to

mmol/L, multiple 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 char-

acteristics 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 electrocardio-

gram change during either passive

smoking or adenosine triphosphate

administration. Passive smoking had

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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 monoxide 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. This may be the result of structural or functional changes in the coronary artery produced by smoking. Some epidemiological studies have linked passive smoking to excess risk for atherosclerotic heart disease. 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. Celermajer et al 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

<table>
<thead>
<tr>
<th>Status</th>
<th>Before Passive Smoking</th>
<th>After Passive Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmokers, cm/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>20.2 (6.8)</td>
<td>20.7 (5.9)</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>86.6 (27.4)</td>
<td>68.8 (22.7)</td>
</tr>
<tr>
<td>Smokers, cm/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>19.2 (4.0)</td>
<td>20.5 (4.6)</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>67.1 (15.0)</td>
<td>66.7 (14.6)</td>
</tr>
</tbody>
</table>

*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.
Coronary flow reserve (CFVR) has been proposed as a parameter of physiological assessment of coronary circulation.29 Recent studies have 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.

**Author Contributions:** Study concept and design: Otsuka, Watanabe, Muro, Yoshiyama, Takeuchi, Yoshikawa. Acquisition of data: Otsuka, Watanabe, Hirata, Tokai.
Analysis and interpretation of data: Otsuka, Watanabe.

CRITICAL REVISION OF THE MANUSCRIPT FOR IMPORTANT INTELLECTUAL CONTENT: Otsuka, Watanabe, Hirata, Yoshiyama, Takeuchi, Yoshikawa.

STATISTICAL EXPERTISE: Otsuka, Watanabe, Hirata.

ADMINISTRATIVE, TECHNICAL, OR MATERIAL SUPPORT: Otsuka, Watanabe, Hirata, Tokai, Muro.

STUDY SUPERVISION: Watanabe, Yoshiyama, Takeuchi, Yoshikawa.

REFERENCES


