Smoking Cessation Normalizes Coronary Endothelial Vasomotor Response Assessed with ^{15}O-Water and PET in Healthy Young Smokers

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Cigarette smoking is one of the risk factors of cardiovascular diseases and is related to abnormal peripheral and coronary vascular vasomotion. Coronary vascular endothelial dysfunction is caused by chronic smoking in smokers without epicardial coronary artery stenosis. The coronary endothelial vasomotion abnormality is restored by interventions such as L-arginine or vitamin C infusion. However, to our knowledge, the effect of smoking cessation on coronary vasomotor response has not been elucidated. Therefore, the aim of this study was to assess the effect of smoking cessation on coronary vasomotor response by quantitative myocardial blood flow (MBF) measurement using ^{15}O-water and PET. **Methods:** Fifteen young smokers (Brinkman index $>$ 100; mean age $\pm$ SD, 26 $\pm$ 4 y) with no evidence of heart disease or cardiovascular risk factors, except for smoking, and age-matched nonsmokers (n = 12) were enrolled in this study. MBF was measured at rest, during the cold pressor test (CPT), before and at 1 and 6 mo after smoking cessation. In addition, MBF measurement during adenosine triphosphate (ATP) infusion was performed before and at 6 mo after smoking cessation. In nonsmokers, MBF was measured at rest, during ATP infusion, and during the CPT. **Results:** MBF at rest and during ATP infusion did not differ between smokers and nonsmokers (0.73 $\pm$ 0.12 vs. 0.80 $\pm$ 0.15 mL/g/min and 3.15 $\pm$ 1.43 vs. 3.69 $\pm$ 0.76 mL/g/min, respectively; P = not significant). In contrast, MBF during the CPT in smokers was lower than that in nonsmokers (0.90 $\pm$ 0.19 vs. 1.12 $\pm$ 0.28 mL/g/min; $P < 0.05$). There was no significant difference in MBF either at rest or during ATP infusion between before and after smoking cessation, but MBF during the CPT increased at 1 mo in comparison with before cessation of smoking (0.90 $\pm$ 0.19 vs. 1.02 $\pm$ 0.22 mL/g/min; $P < 0.01$). An improvement of MBF response to the CPT was preserved at 6 mo after smoking cessation. **Conclusion:** Coronary vasomotor abnormality assessed by MBF response to the CPT was improved at 1 mo after smoking cessation. These findings indicate that coronary endothelial dysfunction may be reversible within 1 mo after smoking cessation in healthy young smokers.

Key Words: myocardial blood flow; cigarette smoking; cold pressor test; coronary vascular endothelium; PET; ^{15}O-water; cardiovascular disease

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Vascular endothelium has a very important role in regulating the integrity and metabolism of the vascular wall and encompasses the vascular structure and permeability, vasomotor tone, and homeostasis. The functional integrity of the vascular endothelium exerts important antiatherosclerotic and antithrombotic effects (*1,2*). Endothelial dysfunction is shown in the early stage of atherosclerosis (*3–5*). There is a significant inverse correlation between the extent of atherosclerosis and flow-mediated blood-flow response. It is reported that endothelial dysfunction is closely related to the prognosis of ischemic heart disease (*6–8*). Patients with coronary endothelial dysfunction are reported to have a higher cardiovascular event rate than those with normal coronary vasomotion (*8*). Therefore, the endothelial dysfunction is a significant predictor of cardiovascular events (*7*). The endothelial vasomotor abnormality seems to be important in assessing cardiovascular risk factors, such as hypercholesterolemia, cigarette smoking, diabetes mellitus, and hypertension. Thus, it appears that coronary endothelial dysfunction may reflect a mechanistic link that confers an increased risk of adverse cardiovascular events in smokers.

In clinical situations, coronary endothelial function is assessed by measurement of vasomotor response to intracoronary acetylcholine infusion during coronary angiography (CAG) (*3,9*). The cold pressor test (CPT) is used to assess coronary endothelial function (*10*). These methods are limited in patients with a high probability of coronary artery disease, because it is difficult to perform CAG in patients with a low likelihood of coronary artery disease. Therefore, repeated noninvasive methods that may be applicable in patients without coronary artery disease are required in clinical situations. Absolute myocardial blood flow (MBF)

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measurement at rest and during a CPT is used to assess coronary endothelial dysfunction (*11–15*).

Smoking cessation improves peripheral vasomotor response, and higher vasomotor response is shown in former passive smokers in comparison with passive smokers (*16*). However, an effect of cigarette smoking cessation is not fully elucidated and the time course of improvement of endothelial function after smoking cessation is unknown. Therefore, the aim of this study was to evaluate the effects of smoking cessation on coronary endothelial dysfunction in young smokers without cardiac diseases and cardiovascular risk factors, except for cigarette smoking.

MATERIALS AND METHODS

Study Subjects

Fifteen consecutive male volunteers (age range, 22−37 y; mean age ± SD, 25.8 ± 3.7 y) who had been smoking >5 y (range, 5−17 y), with 6.4 ± 2.2 pack-years (1 pack-year is defined as smoking of 20 cigarettes per day for 1 y or the equivalent), and who agreed to stop smoking for at least 6 mo were enrolled prospectively in this study. The Brinkman index was 136 ± 35, which was calculated as the number of cigarettes per day × the years of cigarette smoking. The volunteers had no cardiovascular risk factors, except for cigarette smoking. All of them agreed to refrain from cigarette smoking for at least 6 mo after the first PET study. Twelve nonsmokers' data (mean age ± SD, 26.3 ± 3.3 y) from our historical database of 46 healthy subjects without a smoking history served as control subjects. Inclusion criteria of the controls were healthy male subjects < 37 y old without cardiovascular disease and medications. Repeated MBF measurements were not performed in nonsmokers, because their data were derived from the historical database. None of the subjects had a history of cardiovascular disease, hyperlipidemia, hypertension, or diabetes mellitus, and none was receiving any medication. All had normal electrocardiograms at rest and during a stress test. All subjects refrained from caffeine-containing beverages for at least 24 h before the PET scan. The smokers refrained from smoking for at least 4 h before the first PET study. The purpose and potential risks of this study were explained to all subjects, and written informed consent was obtained. The study was approved by The Ethics Committee of Hokkaido University Graduate School of Medicine.

MBF Measurement with PET

PET data acquisition was performed using a whole-body scanner (ECAT/EXACT HR+; Siemens/CTI) as shown in Figure 1. Briefly, a dynamic ^{15}O-water PET data acquisition for 6 min was performed after obtaining a transmission scan with an external ^{68}Ge/^{68}Ga source and a ventricular blood-pool scan with ^{15}O-CO inhalation. MBF was measured using a method as previously described (*11,17–20*). MBF was quantified using software previously reported (*21*). Briefly, regions of interest (ROIs) were drawn on the whole left ventricular (LV) myocardium and within the LV cavity. The ROIs projected onto the dynamic ^{15}O-water images. Arterial and myocardial tissue activity curves were derived with spillover correction and were fitted to a single-tissue-compartment tracer kinetic model to calculate MBF at rest and during adenosine triphosphate (ATP) infusion and the CPT. MBF measurement during the CPT was performed as previously reported (*11,17*). Briefly, the CPT was started after the subject's right foot was immersed in ice water. Sixty seconds later, the ^{15}O PET scan was started, and the CPT was continued for at least 4 min. The analysis was performed blinded.

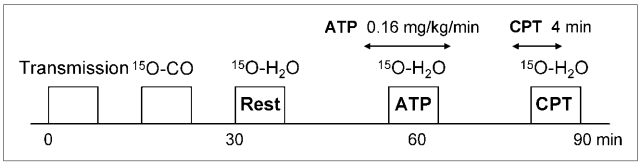

FIGURE 1. PET data acquisition is shown. MBF was measured at rest and was followed during hyperemic flow–induced adenosine triphosphate (ATP) infusion and CPT.

Refrain from Smoking and PET Scan Protocols

Fifteen subjects refrained from smoking after the first PET scan. MBF measurement was performed at 1 and 6 mo after smoking cessation. A time course and PET scan protocol are shown in Figure 2. All subjects had interviews and measurements of expiratory CO concentration randomly to ensure smoking cessation. MBF was measured at rest and during ATP infusion and the CPT before and at 6 mo after smoking cessation. MBF was assessed at rest and during the CPT at 1 mo after smoking cessation. At 6 mo after smoking cessation, PET was performed in 12 subjects, because 3 subjects abandoned smoking cessation between 2 and 5 mo after beginning smoking cessation. On the PET scan, expiratory CO concentration and plasma cotinine level were measured to evaluate a history of smoking. In addition, plasma cholesterol, high-density lipoprotein (HDL), glucose, and caffeine concentrations were measured.

Statistical Analysis

All data are presented as mean ± SD. The Mann–Whitney *U* test was used to compare values between smokers and nonsmokers. The changes in MBF, hemodynamics, smoking parameters, and lipid profiles before and after smoking cessation were compared using 1-way ANOVA for repeated measurements with Scheffé and Bonferroni/Dunn procedures in 12 subjects who completed smoking cessation for 6 mo. All P values < 0.05 were considered to be statistically significant.

RESULTS

PET scans were performed in all enrolled smokers and nonsmokers. Although all 15 smokers underwent PET scans before and 1 mo after smoking cessation, 3 subjects

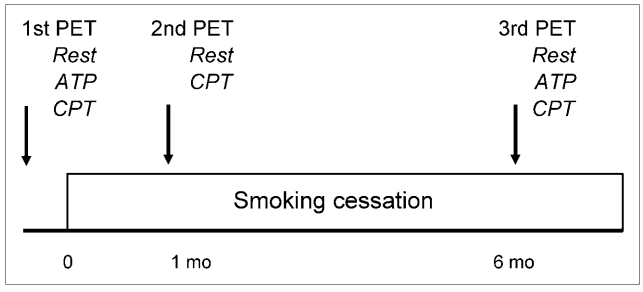

FIGURE 2. PET scan protocol before and after smoking cessation is shown. ATP = adenosine triphosphate.

abandoned smoking cessation between 2 and 5 mo after starting smoking cessation. Three subjects did not undergo PET scans at 6 mo after smoking cessation because of a continuation of smoking after the second PET scans at 1 mo. There were no significant differences in clinical characteristics between smokers and nonsmokers. All procedures were well tolerated apart from common side effects caused by ATP, such as flushing and a feeling of tightness in the chest. Clinical characteristics of 27 subjects are shown in Table 1.

Hemodynamic and Smoking Parameters

All procedures were well tolerated by all volunteers. Table 2 shows blood pressure, heart rate, and rate·pressure product (RPP) at rest, during hyperemia, and during the CPT. Heart rate and RPP were significantly increased during pharmacologic vasodilation and the CPT in the smokers and the nonsmokers. Additionally, blood pressure was increased during the CPT. There were no significant differences between the smokers and the nonsmokers. None of the subjects had abnormal blood lipid profiles, elevated fasting plasma glucose level, or elevated hemoglobin A_{1c} percentage. Cigarette smoking parameters are shown in Table 2. The smokers had an elevated serum cotinine level of 191 ± 81.8 ng/mL (range, 75−290 ng/mL) and an expiratory CO percentage of 1.7% ± 0.6% (range, 0.7%−2.7%). Serum cotinine levels were variable, depending on cigarette smoking exposure. The normal value of serum cotinine of nonsmokers was zero. The serum cotinine was not detected in 14 subjects after 1 mo of smoking cessation, expect for 1 subject who used nicotine patches after smoking cessation. The normal value of expiratory CO concentration was 0.4% ± 0.2% (range, 0.2%−0.7%).

Comparison Between Smokers and Nonsmokers

MBF of the smokers and the nonsmokers is shown in Table 3. There were no significant differences in MBF at rest and during ATP infusion between smokers and nonsmokers. Hyperemic flow in smokers tended to be lower than that of nonsmokers ($P = 0.064$). However, myocardial blood flow reserve (MFR) did not differ between smokers and nonsmokers. MBF during the CPT in smokers was significantly lower than that of nonsmokers (0.90 ± 0.19 vs. 1.12 ± 0.28; $P < 0.05$), indicating coronary endothelial vasomotor abnormality in the smokers.

TABLE 1
Clinical Characteristics of 27 Subjects

Characteristic	Smokers (n = 15)	Nonsmokers (n = 12)	P
Age (y)	25.8 ± 3.7	26.3 ± 3.3	NS
Total cholesterol (mg/dL)	171 ± 31	163 ± 44	NS
LDL cholesterol (mg/dL)	105 ± 24	84 ± 41	NS
HDL cholesterol (mg/dL)	50 ± 7.4	62 ± 10	0.052
Height (cm)	174 ± 5.7	173 ± 5.5	NS
Body weight (kg)	65 ± 8	69 ± 11	NS
BMI (kg/m^2)	21.4 ± 2.1	23.0 ± 3.0	NS
Smoking (y)	7.3 ± 2.9		
Pack-years	6.8 ± 1.7		

NS = not significant; LDL = low-density lipoprotein; BMI = body mass index (kg/m^2).

Effects of Smoking Cessation on Hemodynamics, Smoking Parameters, and MBF Dynamics

Smoking and hemodynamic parameters before and after smoking cessation are shown in Table 2. Serum cotinine level declined significantly from 191 ± 81.8 ng/mL to 2.1 ± 8.1 ng/mL after a 1-mo smoking cessation. At 1 mo after smoking cessation, 14 subjects had no detectable serum cotinine level. One subject showed a slightly elevated serum cotinine level of 31 ng/mL, due to use of nicotine patches to prevent smoking, but the expiratory CO concentration declined to a level of nonsmokers. Furthermore, the expiratory CO percentage decreased after starting smoking cessation from 1.7% ± 0.6% to 0.5% ± 0.2%. At 6 mo after smoking cessation, serum cotinine was not detected in any of the 12 subjects. In hemodynamic parameters, there were no significant differences between before and after smoking cessation. At 1 mo after smoking cessation, the heart rate tended to be higher than that before cessation. Therefore, the RPP at rest tended to be higher than that before cessation. Although the percentage increase of the RPP during the CPT versus that of the resting condition tended to decrease after a 1-mo smoking cessation, there were no significant differences between before and after smoking cessation.

Time Course of Vasomotor Response After Smoking Cessation

The time course of MBF changes is shown in Table 4. In addition, individual data of MBF response to the CPT and hemodynamic parameters are shown in Table 5. There were no significant changes in rest and hyperemic MBF before and after smoking cessation. On the other hand, MBF during the CPT increased after a 1-mo smoking cessation in comparison with that before smoking cessation, which was virtually similar to the level of nonsmokers. There was no significant difference in MBF during the CPT between exsmokers and nonsmokers. The increase in MBF during the CPT from MBF at rest and the ratio of MBF during the CPT to that at rest increased at 1 mo after smoking cessation. The improved coronary vasomotor response to the CPT was preserved for 6 mo after smoking cessation in 12 subjects who completed smoking cessation (ANOVA for repeated measurements).

Clinical Characteristics and Lipid Profiles

None of the subjects had abnormal serum lipid profiles, elevated blood glucose, or elevated glycohemoglobin A_{1c} levels. There were no significant differences in body weight, body mass index, and lipid profiles, except for HDL cholesterol between smokers and nonsmokers. HDL cholesterol

TABLE 2
Smoking and Hemodynamic Parameters Before and After Smoking Cessation and in Nonsmokers

Parameter	Smokers			Nonsmokers
	Before (n = 15)	1 mo (n = 15)	6 mo (n = 12)	(n = 12)
Cotinine	191.6 ± 81.8	2.1 ± 8.1*	0*	
CO	1.7 ± 0.6	0.5 ± 0.2*	0.3 ± 0.3*	
Rest				
SBP	109.1 ± 6.6	106.0 ± 7.4	109.3 ± 7.0	103.0 ± 5.2
mBP	75.8 ± 5.1	80.1 ± 6.6	75.8 ± 6.8	68.3 ± 3.6
DBP	59.1 ± 5.3	61.7 ± 7.0	59.0 ± 7.1	51.1 ± 4.4
HR	60.6 ± 9.3	64.3 ± 11.0	60.7 ± 6.8	59.2 ± 8.0
RPP	6,623 ± 1,167	7,559 ± 1,692	6,678 ± 1,023	6,073 ± 750
ATP				
SBP	110.3 ± 6.6		111.2 ± 11.9	101.2 ± 11.3
mBP	72.5 ± 5.8		75.9 ± 8.9	66.0 ± 8.4
DBP	53.5 ± 6.6		58.2 ± 7.6	48.8 ± 7.7
HR	85.1 ± 8.5†		82.7 ± 14.7†	82.2 ± 14.6†
RPP	9,412 ± 1,280†		7,964 ± 4,306†	8,369 ± 1,785†
CPT				
SBP	138.0 ± 15.4‡	141.3 ± 14.2‡	142.7 ± 9.4‡	128.8 ± 7.2‡
mBP	97.0 ± 16.4‡	99.4 ± 10.0‡	100.8 ± 6.7‡	88.8 ± 6.1‡
DBP	76.5 ± 17.8‡	78.5 ± 10.3‡	79.9 ± 7.2‡	67.6 ± 10.3‡
HR	81.2 ± 16.9‡	82.3 ± 16.6‡	77.3 ± 16.9‡	72.8 ± 8.8‡
RPP	11274 ± 3012‡	11,701 ± 3,163‡	11,193 ± 2,588‡	9,236 ± 1,356‡
% increase in RPP during CPT				
ΔRPP	71.7 ± 44.1	55.1 ± 22.2	69.4 ± 38.4	53.5 ± 26.3

*$P < 0.05$, vs. before smoking cessation.
†$P < 0.05$, rest vs. ATP.
‡$P < 0.05$, rest vs. CPT.
Cotinine = serum cotinine level (ng/mL); CO = % expiratory CO; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; MBP = mean blood pressure; ATP = adenosine triphosphate.

of smokers tended to be lower than that of nonsmokers (50 ± 7.4 vs. 62 ± 10 mg/dL; $P = 0.052$). However, all smokers enrolled in this study had normal values of serum HDL cholesterol (normal range, 41−86 mg/dL). Furthermore, changes in serum lipid profiles before and after smoking cessation are shown in Table 6. There were no significant changes in lipid profiles before and after smoking cessation (ANOVA for repeated measurements; Table 6). Serum caffeine levels were also measured in all subjects at the time of MBF measurements. In all subjects, serum caffeine was not detected.

TABLE 3
MBF in Smokers and Nonsmokers

	Smokers (n = 15)	Nonsmokers (n = 12)	P
Rest	0.73 ± 0.12	0.80 ± 0.14	NS
ATP	3.15 ± 0.70	3.69 ± 0.76	NS (0.064)
MFR	4.35 ± 0.94	4.72 ± 1.30	NS
CPT	0.90 ± 0.19*	1.12 ± 0.28	0.015
RPP at CPT	11,274 ± 3,012	9,237 ± 1,356	NS
% increase	71.7 ± 44.1	53.5 ± 26.3	NS

*$P < 0.05$, smokers vs. nonsmokers.
NS = not significant; MBF = myocardial blood flow (mL/g/min); MFR = myocardial flow reserve; RPP = rate·pressure product (mm Hg/min); % increase = % increase of RPP from rest to CPT.

DISCUSSION

The present study demonstrates that young healthy smokers have impaired coronary endothelial vasomotor dysfunction, which is reversible within 1 mo after smoking cessation, and the improvement is preserved at 6 mo after cessation. The improvement of coronary endothelial function is shown to be at the level of nonsmokers. Smoking cessation may prevent cardiovascular events via normalized vascular endothelial function. Although there is a possibility that smoking cessation in young smokers reduces future cardiovascular events, further long-term confirmations may be needed.

Effect of Cigarette Smoking on MBF Dynamics

Cigarette smoking is one of the important modifiable risk factors for cardiovascular diseases. It is well known that chronic cigarette smoking causes vascular endothelial dysfunction even in young smokers (*11,13*). Smoking causes

TABLE 4
MBF Before and After Smoking Cessation

	Before (n = 15)	1 mo (n = 15)	6 mo (n = 12)
Rest	0.73 ± 0.12	0.72 ± 0.13	0.74 ± 0.10
ATP	3.15 ± 0.70		3.30 ± 0.57
CPT	0.90 ± 0.19	1.02 ± 0.22*	1.04 ± 0.18*
ΔMBF	0.17 ± 0.14	0.30 ± 0.16*	0.29 ± 0.10*
CPT/rest	1.24 ± 0.20	1.42 ± 0.22*	1.39 ± 0.11*

*$P < 0.01$ vs. before smoking cessation.
MBF (mL/g/min); ΔMBF = MBF increase during CPT from resting condition; CPT/rest = MBF during CPT divided by that at rest.

not only endothelium-dependent vasomotor abnormality but also endothelium-independent vasomotor abnormality induced by adenosine or dipyridamole infusion (*22*). In this study, impaired coronary vasomotor response to the CPT was shown in smokers in comparison with nonsmokers. On the other hand, hyperemic flow induced by ATP infusion tended to be lower than that of nonsmokers in this study. The mechanisms of slightly impaired myocardial hyperemic flow in smokers may be due to an early stage of coronary atherosclerosis and impaired endothelium-dependent vasodilatation via flow-mediated vasodilatation. Some part of abnormal hyperemic flow response is attributed to coronary endothelial dysfunction (*23*). In the other words, impaired hyperemic flow response in smokers may be caused partially by vascular endothelial dysfunction. It may be difficult to exclude exposure of tobacco smoke for 6 mo after smoking cessation, but the possibility of smoke exposure may be low, because all subjects showed normal expiratory CO concentration and no detectable serum cotinine on the third PET scan. In addition, abnormal MBF response to CPT was normalized at 1 mo and preserved for 6 mo after smoking cessation.

Mechanisms of Endothelial Dysfunction and Reversibility by Smoking Cessation

It has been reported recently that abnormal coronary vascular function may progress from an impairment of endothelium-dependent coronary vasomotion to an impairment of the coronary vasodilatory capacity in young individuals with increasing body weight (*24*), which is reversible with exercise and diet modification (*25*). Thus, there is also a possibility that the vascular alterations in the current study population of young healthy smokers were still confined to the endothelium and had yet not affected vascular smooth muscle function. There is much evidence that cigarette smoking causes vascular endothelial damage assessed by peripheral and coronary vasomotor response (*13,26–29*). It is known that cigarette smoking causes abnormal coronary blood flow response to the CPT, indicating that the endothelium is the main site of toxic effects on the vascular system (*28,29*). Many compounds in cigarette smoke are harmful to vascular endothelium, including nicotine and CO. In this study, the serum cotinine level as a nicotine

TABLE 5
MBF Response and Hemodynamics Before and After Smoking Cessation

		Before smoking cessation						1 mo after smoking cessation						6 mo after smoking cessation					
	Age	MBF			RPP			MBF			RPP			MBF			RPP		
No.	(y)	Rest	CPT	ΔMBF	Rest	CPT	ΔRPP	Rest	CPT	ΔMBF	Rest	CPT	ΔRPP	Rest	CPT	ΔMBF	Rest	CPT	ΔRPP
1	27	0.66	0.85	0.19	5,616	9,656	71.9	0.55	0.77	0.23	6,148	9,472	54.1	0.65	0.90	0.25	5,300	9,230	74.2
2	24	0.64	0.86	0.23	6,380	15,755	146.9	0.67	0.72	0.05	7,564	11,868	56.9	0.65	0.91	0.26	5,824	13,442	130.8
3	23	1.04	1.27	0.24	8,162	16,500	102.2	1.10	1.48	0.38	12,350	20,875	69.0	0.99	1.46	0.47	8,500	17,440	105.2
4	25	0.92	1.13	0.21	6,954	10,419	49.8	0.62	1.12	0.50	6,048	9,570	58.2	0.90	1.20	0.30	6,720	9,513	41.6
5	28	0.67	1.03	0.36	9,890	16,653	68.4	0.77	0.95	0.18	9,272	14,616	57.6						
6	37	0.65	0.75	0.10	6,720	9,030	34.4	0.79	1.10	0.32	7,424	8,640	16.4	0.77	1.07	0.30	7,236	10,152	40.3
7	26	0.67	1.11	0.43	6,440	9,792	52.0	0.80	1.40	0.60	7,986	10,716	34.2	0.67	1.08	0.42	6,215	11,840	90.5
8	24	0.64	0.75	0.11	6,270	9,933	58.4	0.62	0.78	0.16	6,325	11,592	83.3	0.66	0.82	0.15	6,136	8,804	43.5
9	30	0.65	0.62	-0.02	5,141	15,012	192.0	0.65	0.97	0.32	6,528	12,936	98.2	0.70	0.93	0.23	7,245	11,178	54.3
10	23	0.79	0.84	0.05	5,452	8,733	60.2	0.69	0.85	0.16	5,508	9,009	63.6						
11	23	0.82	0.89	0.08	6,710	9,792	45.9	0.68	1.21	0.53	8,500	14,308	68.3	0.74	1.15	0.41	8,487	10,584	24.7
12	25	0.72	0.85	0.13	6,213	10,578	70.3	0.77	1.01	0.24	8,496	12,012	41.4	0.78	1.10	0.32	6,565	9,730	48.2
13	25	0.63	0.69	0.05	7,198	9,856	36.9	0.66	0.82	0.16	6,545	10,875	66.2	0.69	0.87	0.18	5,750	13,770	139.5
14	22	0.72	1.10	0.38	6,270	8,772	39.9	0.71	1.08	0.37	7,437	10,413	40.0						
15	25	0.73	0.76	0.03	5,936	8,636	45.5	0.79	1.09	0.29	7,250	8,618	18.9	0.74	0.98	0.24	6,160	8,636	40.2
Mean	25.8	0.73	0.90	0.17	6,623	11,274	71.7	0.72	1.02	0.30	7,559	11,701	55.1	0.74	1.04	0.29	6,678	11,193	69.4
SD	3.7	0.12	0.19	0.14	1,167	3,012	44.1	0.13	0.22	0.16	1,692	3,163	22.2	0.10	0.18	0.10	1,023	2,588	38.4
Statistics*									*	*					*	*			

*$P < 0.01$ vs. before smoking cessation.
MBF (mL/g/min); ΔMBF = increase during CPT from resting condition; ΔRPP = % increase during CPT from resting condition.

TABLE 6
Serum Lipid Profiles Before and After Smoking Cessation

Lipid profile	Before (n = 15)	1 mo (n = 15)	6 mo (n = 12)
Total cholesterol (mg/dL)	171 ± 31	177 ± 21	185 ± 28
LDL cholesterol (mg/dL)	106 ± 24	103 ± 24	110 ± 27
HDL cholesterol (mg/dL)	50 ± 7	55 ± 9	55 ± 13
Triglyceride (mg/dL)	130 ± 55	136 ± 74	105 ± 43

LDL = low-density lipoprotein.

metabolite and expiratory CO declined after smoking cessation. However, improved coronary endothelial vasomotor response abnormality after smoking cessation may not be fully accounted for by a decrease in nicotine and CO concentration. Nicotine alone also causes endothelial structural damage in experimental models exposed to extremely high nicotine levels, comparable with a human smoking 50–100 cigarettes per day (*30*). In smokers, it was demonstrated that nicotine alone causes acute endothelial dysfunction, although to a lesser extent than smoking a cigarette of the same nicotine yield (*31*). Our present study subjects had no history of markedly heavy cigarette smoking. Additionally, coronary vasomotor response to the CPT improved to the level of nonsmokers within 1 mo after smoking cessation. Therefore, impaired coronary endothelial function in smokers may be a functional abnormality with reversibility, especially in young healthy smokers. Abnormal MBF response to the CPT in smokers was normalized by an infusion of L-arginine as a precursor of nitric oxide (NO), suggesting functional endothelial abnormality via NO production impairment in chronic smokers (*14*). In addition, impaired hyperemic flow response in smokers was normalized by vitamin C injection (*22*). Recently, Schindler et al. showed a precise chronologic change of myocardial vasomotor response to the CPT after starting vitamin C administration, suggesting short-term and long-term effects of vitamin C intake (*15*). Therefore, endothelial dysfunction in smokers is a functional abnormality, which is improved or normalized by acceleration of NO production through antioxidative interventions using vitamin C. In lipid-lowering therapy, lipid profile changes have been reported to affect MBF dynamics (*32*), but there were no lipid profile changes after smoking cessation in this study, indicating that the lipid profile may not contribute to improvement of MBF response to the CPT. Considering these findings, endothelial dysfunction in smokers seems to be a functional deterioration that is reversible, and lifestyle modifications, such as smoking cessation, may be important to improve endothelial dysfunction, reducing the rate of cardiovascular events.

Clinical Implications

The current study provides important noninvasive mechanistic insight into the early functional stages of the development of coronary artery disease in smokers. Furthermore, the functional recovery of coronary endothelial dysfunction after smoking cessation was determined in serial PET studies. The data of the current study emphasize the importance of smoking cessation in smoking-related endothelial dysfunction in young healthy smokers, which should be regarded as an important strategy for altering the cardiovascular risk at an early age (*25*). This study demonstrated that coronary endothelial dysfunction is normalized within 1 mo of smoking cessation in young smokers, which may encourage young smokers to refrain from cigarette smoking. On the other hand, it seems that >1 mo may be required to improve endothelial dysfunction in middle-age or old-age smokers, because atherosclerosis may have progressed or they may have other cardiovascular risk factors.

Limitations

One of the major limitations of the current study is the small number of subjects. In addition, females and elderly smokers were not enrolled in this study. However, a significant improvement in response to the CPT at 1 mo after smoking cessation was obtained with the current number of subjects. Hyperemic MBF was not measured at 1 mo in this study to reduce radiation exposure. In this study, hyperemic MBF was not significantly decreased in smokers compared with nonsmokers, in spite of a trend of impaired hyperemic flow in smokers. Myocardial hyperemic flow was reported to be attenuated in middle-age smokers, which may be partially caused by endothelial dysfunction attributed to chronic smoking (*22*). There may be a discrepancy in the time course between hyperemic and endothelial functional improvement in middle-age or old-age smokers. In the present study, young male smokers were enrolled mainly to exclude the effects of humoral factors, such as estrogen. Further study is necessary to evaluate the effect of smoking cessation in females. This may require a reproducibility study to confirm the MBF response to the CPT. The measurement of MBF using ^{15}O-water PET has been well validated (*33,34*). Moreover, a close relationship between MBF response and coronary vasomotion was clearly validated by assessing the correlation between quantitative coronary angiography and the CPT (*35*). In addition, excellent repeatability of the MBF response to CPT has been reported (*36*). However, considering these findings, the MBF response to the CPT may be reliable, because there was no difference in the MBF during the CPT between 1 mo and 6 mo after smoking cessation.

CONCLUSION

Coronary vasomotor abnormality assessed by MBF response to the CPT was improved at 1 mo after smoking cessation. The findings indicate that coronary endothelial dysfunction may be reversible within 1 mo after smoking cessation in healthy young smokers.

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REFERENCES

1. Nabel EG. Biology of the impaired endothelium. *Am J Cardiol.* 1991;68:6C–8C.
2. Vallance P, Chan N. Endothelial function and nitric oxide: clinical relevance. *Heart.* 2001;85:342–350.
3. Zeiher AM, Drexler H, Wollschlager H, Just H. Modulation of coronary vasomotor tone in humans: progressive endothelial dysfunction with different early stages of coronary atherosclerosis. *Circulation.* 1991;83:391–401.
4. Zeiher AM, Drexler H, Wollschlager H, Just H. Endothelial dysfunction of the coronary microvasculature is associated with coronary blood flow regulation in patients with early atherosclerosis. *Circulation.* 1991;84:1984–1992.
5. Gould KL, Martucci JP, Goldberg DI, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease: a potential noninvasive marker of healing coronary endothelium. *Circulation.* 1994; 89:1530–1538.
6. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation.* 2000;101:1899–1906.
7. Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation.* 2000;101:948–954.
8. Halcox JP, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation.* 2002;106:653–658.
9. Zeiher AM, Krause T, Schachinger V, Minners J, Moser E. Impaired endothelium-dependent vasodilation of coronary resistance vessels is associated with exercise-induced myocardial ischemia. *Circulation.* 1995;91:2345–2352.
10. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. *Circulation.* 1988;77:43–52.
11. Iwado Y, Yoshinaga K, Furuyama H, et al. Decreased endothelium-dependent coronary vasomotion in healthy young smokers. *Eur J Nucl Med Mol Imaging.* 2002;29:984–990.
12. Meeder JG, Peels HO, Blanksma PK, et al. Comparison between positron emission tomography myocardial perfusion imaging and intracoronary Doppler flow velocity measurements at rest and during cold pressor testing in angiographically normal coronary arteries in patients with one-vessel coronary artery disease. *Am J Cardiol.* 1996;78:526–531.
13. Campisi R, Czernin J, Schoder H, et al. Effects of long-term smoking on myocardial blood flow, coronary vasomotion, and vasodilator capacity. *Circulation.* 1998;98:119–125.
14. Campisi R, Czernin J, Schoder H, Sayre JW, Schelbert HR. L-Arginine normalizes coronary vasomotion in long-term smokers. *Circulation.* 1999;99: 491–497.
15. Schindler TH, Nitzsche EU, Munzel T, et al. Coronary vasoregulation in patients with various risk factors in response to cold pressor testing: contrasting myocardial blood flow responses to short- and long-term vitamin C administration. *J Am Coll Cardiol.* 2003;42:814–822.
16. Raitakari OT, Adams MR, McCredie RJ, Griffiths KA, Celermajer DS. Arterial endothelial dysfunction related to passive smoking is potentially reversible in healthy young adults. *Ann Intern Med.* 1999;130:578–581.
17. Furuyama H, Odagawa Y, Katoh C, et al. Assessment of coronary function in children with a history of Kawasaki disease using ^{15}O-water positron emission tomography. *Circulation.* 2002;105:2878–2884.
18. Iida H, Kanno I, Takahashi A, et al. Measurement of absolute myocardial blood flow with $H_2{}^{15}O$ and dynamic positron-emission tomography: strategy for quantification in relation to the partial-volume effect. *Circulation.* 1988;78:104–115.
19. Iida H, Rhodes CG, de Silva R, et al. Use of the left ventricular time-activity curve as a noninvasive input function in dynamic oxygen-15-water positron emission tomography. *J Nucl Med.* 1992;33:1669–1677.
20. Katoh C, Ruotsalainen U, Laine H, et al. Iterative reconstruction based on median root prior in quantification of myocardial blood flow and oxygen metabolism. *J Nucl Med.* 1999;40:862–867.
21. Katoh C, Morita K, Shiga T, Kubo N, Nakada K, Tamaki N. Improvement of algorithm for quantification of regional myocardial blood flow using ^{15}O-water with PET. *J Nucl Med.* 2004;45:1908–1916.
22. Kaufmann PA, Gnecchi-Ruscone T, di Terlizzi M, Schafers KP, Luscher TF, Camici PG. Coronary heart disease in smokers: vitamin C restores coronary microcirculatory function. *Circulation.* 2000;102:1233–1238.
23. Buus NH, Bottcher M, Hermansen F, Sander M, Nielsen TT, Mulvany MJ. Influence of nitric oxide synthase and adrenergic inhibition on adenosine-induced myocardial hyperemia. *Circulation.* 2001;104:2305–2310.
24. Tounian P, Aggoun Y, Dubern B, et al. Presence of increased stiffness of the common carotid artery and endothelial dysfunction in severely obese children: a prospective study. *Lancet.* 2001;358:1400–1404.
25. Woo KS, Chook P, Yu CW, et al. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation.* 2004;109:1981–1986.
26. Czernin J, Sun K, Brunken R, Bottcher M, Phelps M, Schelbert H. Effect of acute and long-term smoking on myocardial blood flow and flow reserve. *Circulation.* 1995;91:2891–2897.
27. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation.* 1993;88:2149–2155.
28. Czernin J, Waldherr C. Cigarette smoking and coronary blood flow. *Prog Cardiovasc Dis.* 2003;45:395–404.
29. Puranik R, Celermajer DS. Smoking and endothelial function. *Prog Cardiovasc Dis.* 2003;45:443–458.
30. Zimmerman M, McGeachie J. The effect of nicotine on aortic endothelium: a quantitative ultrastructural study. *Atherosclerosis.* 1987;63:33–41.
31. Neunteufl T, Heher S, Kostner K, et al. Contribution of nicotine to acute endothelial dysfunction in long-term smokers. *J Am Coll Cardiol.* 2002;39:251–256.
32. Guethlin M, Kasel AM, Coppenrath K, Ziegler S, Delius W, Schwaiger M. Delayed response of myocardial flow reserve to lipid-lowering therapy with fluvastatin. *Circulation.* 1999;99:475–481.
33. Kaufmann PA, Gnecchi-Ruscone T, Yap JT, Rimoldi O, Camici PG. Assessment of the reproducibility of baseline and hyperemic myocardial blood flow measurements with ^{15}O-labeled water and PET. *J Nucl Med.* 1999;40:1848–1856.
34. Kaufmann PA, Camici PG. Myocardial blood flow measurement by PET: technical aspects and clinical applications. *J Nucl Med.* 2005;46:75–88.
35. Schindler TH, Nitzsche EU, Olschewski M, et al. PET-measured responses of MBF to cold pressor testing correlate with indices of coronary vasomotion on quantitative coronary angiography. *J Nucl Med.* 2004;45:419–428.
36. Siegrist PT, Gaemperli O, Koepfli P, et al. Repeatability of cold pressor test-induced flow increase assessed with $H_2{}^{15}O$ and PET. *J Nucl Med.* 2006;47:1420–1426.