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Evaluation of coronary endothelial dysfunction in healthy young smokers: Cold pressor test using [^{15}O]H_2O PET

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ABSTRACT

The purpose of this study was to investigate coronary endothelial dysfunction in young healthy smokers by measuring myocardial blood flow (MBF) using [^{15}O]H_2O-PET. The study population was 18 young male volunteers consisted of 9 smokers (age: 23.8±1.1 yr) and 9 non-smokers (age: 25.0±2.5 yr). The smokers had been smoking cigarettes for 6.6±2.5 pack years. Myocardial [^{15}O]H_2O-PET was performed at rest, during cold (5 °C) pressor stimulation and during adenosine infusion. Left ventricular (LV) input function and tissue time–activity curves were obtained by drawing region of interest (ROI) on the LV blood pool and myocardium images obtained by non-negative matrix factorization (NMF) of dynamic [^{15}O]H_2O-PET data, and MBF was calculated using these time–activity curves and single compartmental model. There were no significant difference in resting MBF between two groups (smokers: 1.43±0.41 and non-smokers: 1.37±0.41 ml/g/min; P = NS). However, during cold pressor stimulation, MBF in smokers was significantly lower than that in non-smokers (1.25±0.33 vs. 1.59±0.29 ml/g/min; P = 0.019). MBF changed to 90±24% of resting MBF in smokers and 122±28% in non-smokers. The difference in the ratio of cold pressor MBF to basal MBF between two groups was also significant (P = 0.024). During adenosine infusion, however, hyperemic MBF did not differ significantly between smokers and non-smokers (5.81±1.99 vs. 5.03±1.27 ml/g/min; P = NS). This study shows that [^{15}O]H_2O PET analysis can reveal that endothelial dysfunction occurs in even young smokers of about 6 pack years.

1. Introduction

The vascular endothelium regulates vascular smooth muscle tone by releasing vasoactive mediators, mainly nitric oxide (NO) synthesized by the enzyme NO synthase from the amino acid L-arginine (Vallance, 1992). It is known that a variety of risk factors for coronary artery disease (CAD) are related to the impairment of coronary endothelium-dependent vasodilator function (Egashira et al., 1993; Vita et al., 1990; Reddy et al., 1994). To evaluate the vasodilator function by coronary endothelium, coronary blood flow (CBF) after intracoronary infusion of acetylcholine or during cold pressor test (CPT) has been measured (Nabel et al., 1988; Zeiher et al., 1989) by invasive methods such as quantitative coronary angiography or coronary doppler ultrasonography. Recently, non-invasive positron emission tomography (PET) was introduced to measure myocardial blood flow (MBF) during CPT in patients with coronary artery obstructive disease (CAOD) or subjects with the risk factor of CAOD (Meeder et al., 1996; Campisi et al., 1998; Di Carli et al., 1999; Drzezga et al., 2000). Smoking is one of well-known risk factors for CAOD and known to impair endothelial-dependent coronary vasomotion (Nitenberg et al., 1993; Zeiher et al., 1995). It has been reported that endothelial-dependent vasodilator function is decreased in smokers when the MBF was measured using PET during the CPT (Iwado et al., 2002). This study was designed to compare MBF at rest, during CPT and during adenosine-induced hyperemia between young healthy smokers (with smoking history of about 6 pack years) and non-smokers using [^{15}O]H_2O PET and to demonstrate impaired endothelial-dependent coronary vasomotion in smokers.

2. Materials and methods

2.1. Study population

Study population of this study (Table 1) included 9 male young healthy smokers (23.8±2.9 year) and 9 male young healthy

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Table 1
Demographic data of study populations.

	Smokers	Non-smokers	*P*-Value
Number	9	9	NS
Age (yr)	23.8±1.1	25.0±2.5	NS
Height (cm)	176.0±5.9	174.2±7.7	NS
Weight (kg)	72.7±7.6	72.3±11.3	NS
Body mass index (kg/m^2)	23.4±1.8	23.8±2.9	NS
Smoking history (Pack years)	6.6±2.5		NS

NS: statistically not significant.

non-smokers (25.0±2.5 year). All smokers had smoked over 10 cigarettes per day for more than 5 years (6.6±2.5 pack year). None of the study participants had a history of cardiovascular disease and any risk factor such as hypertension, diabetes mellitus, hyperlipidemia, or family history of CAOD. None were receiving any medication.

All participants refrained from intake of caffeine-containing food or beverages for at least 24 h before the study. The smokers abstained from smoking for at least 4 h before the PET study. This study was approved by the Institutional Review Board in the hospital and all participating subjects signed statements of informed consent.

2.2. Imaging protocol

PET was performed using a whole-body scanner (Siemen/CTI ECAT 47; Knoxville, USA) equipped with germanium-68 line sources for transmission scans. Myocardial [^{15}O]H_2O PET was performed at rest, during cold pressor stimulation and adenosine infusion. At first resting dynamic PET scanning (12×5, 9×10, and 3×30 s) was started simultaneously with the bolus injection of [^{15}O]H_2O into the antecubital vein of the subject. After the resting scan, one hand of the participant was submerged in ice water (5 °C) from 60 s before the PET scan to 60 s after the start of the scan. Finally, adenosine of 0.14 mg/kg/min was continuously infused for 7 min, [^{15}O]H_2O was injected 3 min after the start of adenosine infusion. PET acquisition was accomplished for 4 min. Pulse rate, blood pressure, and EKG were monitored throughout the experiment in all subjects.

2.3. Image analysis

To obtain left ventricular (LV) blood pool and myocardium image from the dynamic PET data, non-negative matrix factorization (NMF) method (Paatero and Tapper, 1997; Lee and Seung, 1999; Lee et al., 2001) was used since the method has the theoretical advantages vs. the conventional factor analysis.

LV input function and tissue time–activity curves were obtained by drawing region of interest (ROI) on the LV blood pool and myocardium images, and MBF was calculated using these time–activity curves and single compartmental model in which the correction terms for partial volume and spillover effects were incorporated (Fig. 1).

Coefficient of variation was calculated in total 54 images—three times per person—from 18 subjects to evaluate the reproducibility of our algorithm. Calculated coefficient of variation was 9.8%. Calculated MBF was standardized with rate–pressure product (RPP).

2.4. Statistical analysis

Student's *t*-test for the demographic characteristics and the Wilcoxon signed-rank sum test for MBF data in two groups were performed. The data were expressed as means±standard error. MBF was corrected by the rate–pressure product at rest, during CPT, and during adenosine-induced hyperemia: The standardized MBF = {MBF × 10,000}/{pulse rate × mean systolic pressure}. Data were analyzed using the SPSS 11.0. Statistical significance was set at $P<0.05$.

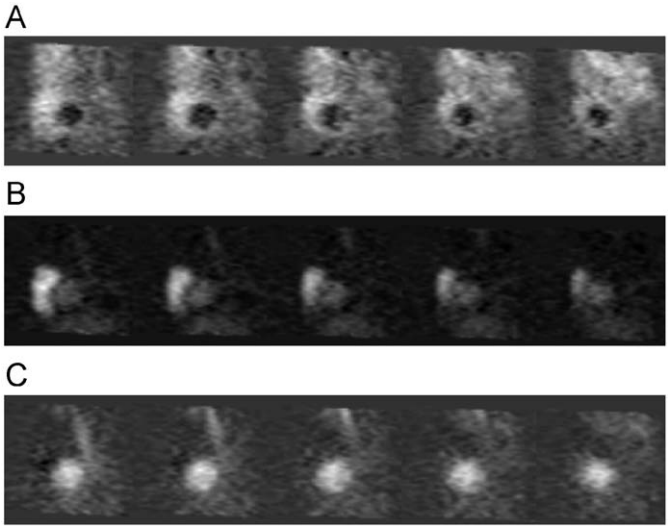

Fig. 1. Factor images using NMF methods: (A) myocardium, (B) right ventricle and (C) left ventricle.

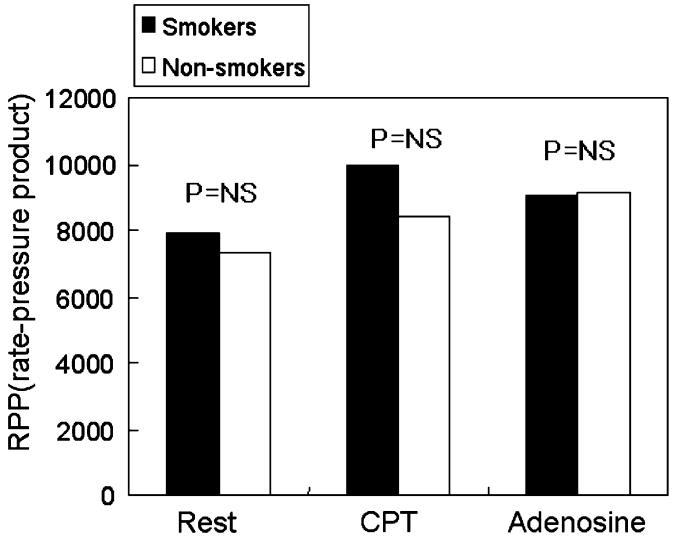

Fig. 2. Rate–pressure product (RPP) at rest, during cold pressor stimulation, and during adenosine infusion in smokers and non-smokers.

3. Results

3.1. Hemodynamic findings

In the smokers, pulse rate during CPT was significantly higher than that in the non-smokers ($P<0.02$). However, there was no significant difference in RPP at rest, during cold pressor test and during adenosine-induced hyperemia between the smokers and the non-smokers (Fig. 2 and Table 2).