Acute Effects of Smoking Light Cigarettes on Coronary Microvascular Functions

Ozgur Ciftci, MD; Mustafa Caliskan, MD; Hakan Gullu, MD; Dogan Erdogan, MD; Semra Topcu, MD; Ozgen Guler, MD; Aylin Yildirir, MD; Haldun Muderrisoglu, MD
Department of Cardiology (Ciftci, Caliskan, Gullu, Erdogan,Topcu, Yildirir, and Muderrisoglu); Department of Radiology (Guler), Baskent University School of Medicine, Ankara, Turkey

Address for correspondence:
Ozgur Ciftci, MD
Department of Cardiology
Baskent University Konya Teaching and Medical Research Center
Hoca Cihan Mah, Saray Cad
No: 1, Selcuklu, Konya, Turkey
drozgurciftci@gmail.com

ABSTRACT

Background: To date, there has been no study comparing the possible acute effects on coronary microvascular functions of smoking light cigarettes (those with low tar and nicotine yield) and regular cigarettes.

Methods: Twenty healthy volunteers (8 women and 12 men; mean age, 25.8 ± 5.8 years) were included in a single-blind, open-label, cross-over study to compare the effects of smoking light cigarettes (containing 0.6 mg nicotine, 8 mg tar, 9 mg carbon monoxide) and smoking regular cigarettes (containing 0.9 mg nicotine, 12 mg tar, 12 mg carbon monoxide) on coronary flow reserve (CFR). For each participant, CFR values were measured at baseline, after smoking 2 regular or light cigarettes, and 15 days later after smoking 2 cigarettes of the other kind.

Results: After smoking 2 cigarettes, CFR values declined from 2.8 ± 0.56 (baseline) to 2.31 ± 0.51 after smoking light cigarettes ($P = .003$), and from 2.8 ± 0.56 (baseline) to 2.21 ± 0.45 after smoking regular cigarettes ($P < .001$). After smoking light and regular cigarettes, CFR values were similar ($P = .678$).

Conclusions: Light cigarette smoking has similar acute detrimental effects on coronary microvascular function and CFR as does regular cigarette smoking.

Introduction

Smoking is the leading preventable cause of death from cardiovascular diseases.[1,2] Although the main toxic components of cigarette smoke are nicotine and carbon monoxide, cigarette smoke contains thousands of additional toxic components. These toxins mainly target the endothelium, especially the coronary endothelium.[3,4] Cigarette smoking acutely causes vasoconstriction of the epicardial coronary arteries and increases coronary resistance vessel tone.[5,6] Nicotine increases endothelial cell proliferation and intimal hyperplasia,[7] and increased serum carbon monoxide levels have been shown to increase the number of endothelial cells circulating in human blood.[8] It is known that amounts of nicotine smaller than those in cigarette smoke can cause acute endothelial dysfunction.[1] Therefore, it is expected that smoking fewer or more cigarettes daily has a similar adverse effect on endothelial function.[9] Free radicals contained in the cigarette smoke tar can damage the vascular endothelium.[3] Although the notion of a safe cigarette is an illusion, commercially available so-called light cigarettes are increasingly being smoked. To the general population, smoking light (low-tar, low-nicotine cigarettes) looks less hazardous than smoking regular cigarettes.

To date, no study has comprehensively investigated the cardiovascular effects of smoking light cigarettes. Therefore, in the present study, we aimed to investigate the possible acute effect of smoking light versus regular cigarettes on coronary microvascular functions.

Methods

Study Population

Twenty healthy volunteers (8 women and 12 men; mean age, 25.8 ± 5.8 years) from our hospital staff participated in this study. Inclusion criteria were nonsmoker (total number of cigarettes smoked during a lifetime 1 to 100),[10] free of coronary risk factors, and regular menstrual cycle (women). Exclusion criteria were having any disease (eg, hypertension, diabetes mellitus, hyperlipidemia [low density lipoprotein cholesterol >160 mg/dL, triglyceride >200 mg/dL]) that could impair coronary flow reserve (CFR), a family history of coronary heart disease, body mass index greater than 35 kg/m^2, left ventricular mass index ≥125 g/m^2 for men and ≥110 g/m^2 for women, electrocardiographic changes implicating coronary artery disease, and drinking alcohol. Additionally, subjects using vasoactive drugs were excluded from the study.

The study was conducted according to the recommendations set forth by the Declaration of Helsinki on biomedical research involving human subjects. The institutional ethics committee approved the study protocol, and each subject provided written informed consent.

Study Design

Twenty subjects fulfilling the inclusion criteria were included in a single-blinded, cross-over, open-label study. On the first day of the study, to determine the baseline measurement of CFR, each participant underwent an echocardiographic examination after a 12-hour fasting period. The second day, each participant smoked 2 light cigarettes (containing 0.6 mg nicotine, 8 mg tar, 9 mg carbon monoxide) or 2 regular cigarettes (containing 0.9 mg nicotine, 12 mg tar, 12 mg carbon monoxide) in a closed room within 15 minutes. Then, within 20 to 30 minutes, each participant underwent an echocardiographic examination that included a CFR measurement to determine the acute effects on CFR of smoking the cigarettes. Then, 15 days later, a second

Clin. Cardiol. 32, 4, 210–214 (2009)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20343

Received: June 8, 2007
Accepted with revision: November 11, 2007

run of the study was performed. The same procedure was repeated and each participant smoked 2 cigarettes of the other kind within 15 minutes of each other in a closed room. Then, within 20 to 30 minutes, each participant underwent an echocardiographic examination including CFR measurement to determine the acute effects of smoked cigarettes on CFR.

CFR Measurement

In this study, a transthoracic Doppler harmonic echocardiographic examination was performed on each subject using an Acuson Sequoia C256 Echocardiography System (Acuson Corp, Mountain View, CA) equipped with a broadband transducer with second harmonic capability (5V2c). Visualization of the distal left anterior descending (LAD) coronary artery was performed using a modified, foreshortened, 2-chamber view obtained by sliding the transducer on the upper part and medially, from an apical 2-chamber view. Subsequently, coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall, with the color Doppler velocity set in the range of 9.0 to 24.0 cm/second. The acoustic window was around the midclavicular line, in the fourth and fifth intercostal spaces, with the subject in the left lateral decubitus position.[11–13] By placing the sample volume on the color signal, spectral Doppler of the LAD showed a characteristic biphasic flow pattern, with larger diastolic and smaller systolic components. Coronary diastolic peak flow velocities (DPFV) were measured at baseline and after dipyridamole infusion (0.56 mg/kg over 4 minutes). By averaging the 3 highest Doppler signals for each measurement, CFR was defined as the ratio of hyperemic to baseline diastolic peak velocities.[12,13] CFR measurements for all subjects are shown in Figure 1.[11–13] One investigator, blinded to

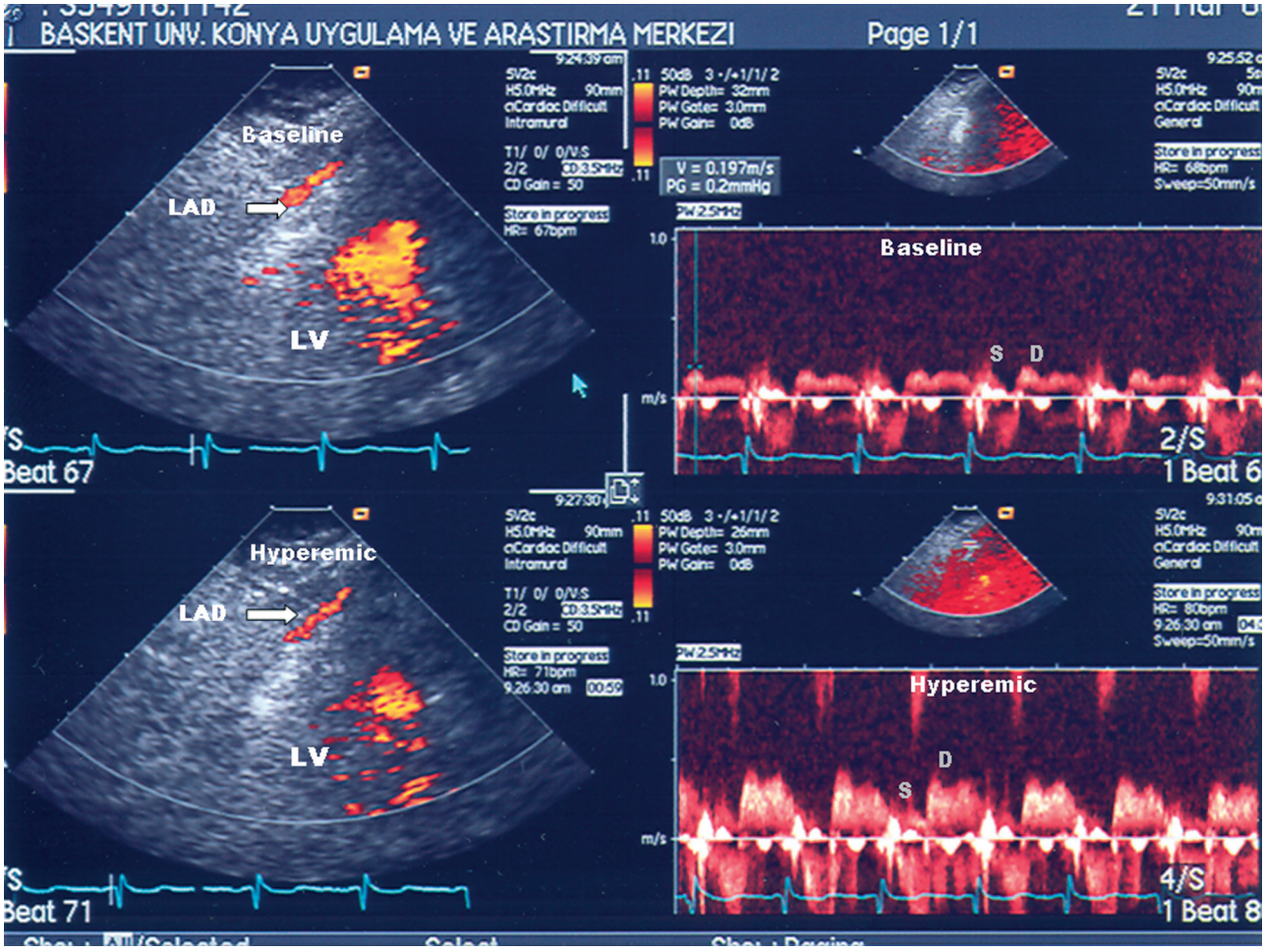

Figure 1. Coronary blood flow in the mid to distal segment of the LAD in color-coded transthoracic Doppler echocardiography and spectral Doppler analyses. D = diastole; LAD = left anterior descending artery; LV = left ventricle; S = systole.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20343

the study's parameters, performed all the measurements. Echocardiographic images were recorded on video tapes. To check the reproducibility of the CFR measurements, the CFR measurements of 5 participants were repeated after 15 days. The intraobserver, intraclass correlation coefficient for CFR measurement was 0.935.

Statistical Analyses

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 10.0, SPSS Inc., Chicago, IL). Numeric values are expressed as means ± SD. Baseline measurements and measurements after smoking light and regular cigarettes were compared using a Kruskal-Wallis test, and differences among the groups were assessed with a Mann-Whitney *U* test with a Bonferroni correction. Changes in the measurements after smoking light and regular cigarettes compared with baseline measurements were tested using a Wilcoxon *t test*. A P value $< .05$ was considered statistically significant.

Results

Demographic, biochemical, and baseline echocardiographic measurements of the participants are shown in Table 1. As shown in Table 2, compared with baseline measurements, systolic and diastolic blood pressure (BP) values were slightly, but not significantly, increased after smoking both light and regular cigarettes. Heart rate, and therefore rate pressure, product values were significantly increased after smoking both kinds of cigarettes (Table 2). Basal DPFV values were significantly increased by smoking light cigarettes from 24.15 ± 5.69 to 28.40 ± 6.91, and smoking regular cigarettes from 24.15 ± 5.69 to 27.65 ± 4.96 (Table 2). Hyperemic DPFV values were modestly decreased after smoking both kinds of cigarettes. Therefore, CFR values were significantly decreased by smoking light and regular cigarettes (Table 2). When the CFR values after smoking light and regular cigarettes were adjusted according to differences in rate pressure product values, decreases in CFR values remained statistically significant ($F = 6.558$, $P = .015$ and $F = 14.180$, $P = .001$; light and regular cigarettes, respectively). The results of a comparison analysis using the Mann-Whitney *U* test between groups are shown in Table 3. The Mann-Whitney *U* test showed that the basal DPFV and the hyperemic DPFV values were similar between the after light cigarette smoking and after regular cigarette smoking values. Therefore, after light cigarette smoking and after regular cigarette smoking CFR values were similar (2.31 ± 0.51 versus 2.21 ± 0.45, $P = .678$) (Table 3).

Smoking the 2 kinds of cigarettes only slightly decreased the mitral E/A ratio, which reflects left ventricular diastolic function (Table 2). Compared with the baseline, smoking 2 light cigarettes significantly decreased the mitral E/A ratio. However, the decrease in the mitral E/A ratio after smoking regular cigarettes did not reach statistical significance (Table 3). Systolic BP, diastolic BP, heart rate, and rate pressure product values were increased by smoking both light and regular cigarettes (Table 3).

Table 1. Demographic, Biochemical, and Echocardiographic Characteristics of the Participants

	Mean n = 20	SD
Age (year)	25.80	5.88
BMI (kg/m²)	24.50	3.78
Baseline SBP (mm Hg)	112.00	11.97
Baseline DBP (mm Hg)	68.50	6.71
Baseline heart rate (bpm)	70.50	10.21
Glucose (mg/dL)	90.50	3.29
Total cholesterol (mg/dL)	153.70	31.26
Triglyceride (mg/dL)	88.70	88.70
HDL chol (mg/dL)	41.35	6.95
LDL chol (mg/dL)	95.50	24.09
hsCRP (mg/L)	.87	.54
LVMI (g/m²)	74.73	15.43
Basal DPFV(cm/s)	24.15	5.69
Hyperemic DPFV(cm/s)	66.60	13.43
CFR	2.82	.56
Mitral E max (cm/s)	84.35	11.72
Mitral A max (cm/s)	52.45	10.29
Mitral E/A ratio	1.66	.33

BMI = Body mass index; CFR = coronary flow reserve; DBP = diastolic blood pressure; DPFV = coronary diastolic peak flow velocity; HDL = high-density lipoprotein; hsCRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; LVMI = left ventricular mass index; SBP = systolic blood pressure.

Discussion

Smoking both light and regular cigarettes impairs coronary microvascular functions and acutely impairs CFR to the same degree. Our study is the first to demonstrate the similar acute hazardous effects of smoking light and regular cigarettes on coronary microvascular functions.

Koskenvuo et al[14] compared transthoracic echocardiography and magnetic resonance imaging for measuring the LAD flow velocity and CFR. Saraste et al[15] compared transthoracic echocardiography and positron emission tomography for measuring CFR. These studies demonstrated an excellent correlation of transthoracic

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20343

Table 2. Before Smoking and After Smoking Hemodynamic and Coronary Flow Measurements of Light Cigarette Smokers and Regular Cigarette Smokers

	Basal	After Light Cigarette	After Regular Cigarette	*P*
SBP	112 ± 11.97	118.75 ± 17.24	119.90 ± 19.30	.303
DBP	68.50 ± 6.71	72.25 ± 10.94	72.25 ± 11.30	.380
Heart rate	70.50 ± 10.21	77.51 ± 9.51	80.35 ± 9.22	.012
RPP	7892.50 ± 1357.32	9425.00 ± 1970.87	9653.25 ± 2009.61	.012
Basal DPFV	24.15 ± 5.69	28.40 ± 6.91	27.65 ± 4.96	.030
Hyperemic DPFV	66.60 ± 13.43	63.85 ± 12.69	59.90 ± 10.68	.162
CFR	2.82 ± 0.56	2.31 ± 0.51	2.21 ± 0.45	.001
Mitral E/A ratio	1.66 ± 0.33	1.43 ± 0.37	1.51 ± 0.33	.130

CFR = coronary flow reserve; RPP = rate pressure product; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 3. Before Smoking and After Smoking Hemodynamic and Coronary Flow Measurements of the Light Cigarette Smokers and Regular Cigarette Smokers and Differences Between the Groups

	Basal	After Light	After Regular	Basal vs Light *P*	Basal vs Regular *P*	Light vs Regular *P*
SBP	112 ± 11.97	118.75 ± 17.24	119.90 ± 19.30	.034	.032	.925
DBP	68.50 ± 6.71	72.25 ± 10.94	72.25 ± 11.30	.215	.196	.862
Heart rate	70.50 ± 10.21	77.51 ± 9.51	80.35 ± 9.22	.0001	.0001	.277
RPP	7892.50 ± 1357.32	9425.00 ± 1970.87	9653.25 ± 2009.61	.001	.0001	.583
Basal DPFV	24.15 ± 5.69	28.40 ± 6.91	27.65 ± 4.96	.002	.014	.862
Hyperemic DPFV	66.60 ± 13.43	63.85 ± 12.69	59.90 ± 10.68	.136	.029	.201
CFR	2.82 ± 0.56	2.31 ± 0.51	2.21 ± 0.45	.003	.001	.678
Mitral E/A	1.66 ± 0.33	1.43 ± 0.37	1.51 ± 0.33	.011	.126	.341

Abbreviations: CFR = coronary flow reserve; RPP = rate pressure product; DBP = diastolic blood pressure; SBP = systolic blood pressure.

echocardiography to magnetic resonance imaging and positron emission tomography for measuring CFR.

The term *light* is a powerful word; it usually implies that the food contains fewer harmful ingredients. Adding the term *light* on a cigarette pack might lead people to believe that the lower tar and nicotine content is accompanied by lower cardiovascular disease risks.[16] Light cigarettes can be subject to full compensation for reduced yield due to changes in smoking behavior. Smokers can transform even the lowest tar cigarettes into much higher tar cigarettes by taking more or larger puffs on each cigarette or by blocking filter air dilution vents with their fingers or lips.[17,18] In our study, participants were nonsmokers and therefore, it was unlikely that they breathed the light cigarette smoke deeper than the regular cigarette smoke.

Kozlowski et al[16] have shown that many light cigarette smokers smoke light cigarettes to reduce the hazardous effects of smoking and/or as a step toward quitting. However, our study clearly demonstrates that smoking light cigarettes has similar hazardous effects on coronary microvascular functions. These light cigarette smokers are mostly unaware that 1 light cigarette only has less tar, nicotine, and CO. However, cigarette smoke contains thousands of noxious molecules, and these ingredients may be responsible for the hazardous effects of smoking light cigarettes. Borland et al[19] have reported that mistaken beliefs about the possible benefits of light cigarettes are widespread in Australia, Canada, the United Kingdom and the United States.

Tanaka et al[20] have investigated the acute effects of smoking low nicotine (less than 1 mg) and high nicotine (more than 1 mg) cigarettes on CFR in 8 and 6 nonsmokers, respectively. They found no difference in baseline coronary flow velocity before and after smoking in either group. In the

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20343

high nicotine cigarette group, after injection of papaverine, CFR was reduced after smoking. There was no significant change in CFR after smoking in the low nicotine cigarette group. The authors measured coronary flow velocity 5 minutes after index smoking; however, 5 minutes might not have been long enough for complete hemodynamic results of cigarette smoking to emerge. Additionally, that study with the low nicotine cigarette, which is not commercially available for smokers, does not shed light on the possible hazards of smoking light cigarettes. Neunteufl et al[1] have suggested that nicotine causes acute endothelial dysfunction in long-term smokers, and that there may be some ingredients of cigarette smoke that contribute to this adverse effect. In the same manner, we observed that light cigarette smoking impairs CFR independently from the nicotine and tar content of the cigarette smoked.

Papamichael et al[21] reported that prompt increments in heart rate and BP were observed during the first 5 minutes after smoking. These changes have been attributed to an increase in circulating and locally released catecholamines. Plasma catecholamines are maximal at the end of 10 minutes. To avoid sympathoneuronal stimulation in the current study, all participants smoked 2 cigarettes, and we measured CFR and hemodynamic parameters 20 to 30 minutes after smoking.

In conclusion, compared with regular cigarettes, smoking light cigarettes has similar hazardous effects on coronary microvascular functions.

References

1. 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.
2. Heliovaara M, Karvonen MJ, Vilhunen R, Punsar S. Smoking, carbon monoxide, and atherosclerotic diseases. *Br Med J.* 1978;1: 268–270.
3. Pittilo, MR. Cigarette smoking, endothelial injury and cardiovascular disease. *Int J Exp Pathol.* 2000;1:219–230.
4. Czernin J, Waldherr C. Cigarette smoking and coronary blood flow. *Prog Cardiovasc Dis.* 2003;45:395–404.
5. Esen AM, Barutcu I, Acar M, et al. Effect of smoking on endothelial function and wall thickness of brachial artery. *Circ J.* 2004;68: 1123–1126.
6. Quillen JE, Rossen JD, Oskarsson HJ, et al. Acute effect of cigarette smoking on the coronary circulation: constriction of epicardial and resistance vessels. *J Am Coll Cardiol.* 1993;22:642–647.
7. Hamasaki H, Sato J, Masuda H, et al. Effect of nicotine on the intimal hyperplasia after endothelial removal of the rabbit carotid artery. *Gen Pharmacol.* 1997;28:653–659.
8. Davis JW, Shelton L, Eigenberg DA, Hignite CE, Watanabe IS. Effects of tobacco and non-tobacco cigarette smoking on endothelium and platelets. *Clin Pharmacol Ther.* 1985;37:529–533.
9. Barua RS, Ambrose JA, Eales-Reynolds LJ, et al. Heavy and light cigarette smokers have similar dysfunction of endothelial vasoregulatory activity: an in vivo and in vitro correlation. *J Am Coll Cardiol.* 2002;39:1758–1763.
10. Pomerleau CS, Pomerleau OF, Snedecor SM, Mehringer AM. Defining a never-smoker: results from the nonsmokers survey. *Addict Behav.* 2004;29:1149–1154.
11. Caiati C, Zedda N, Montaldo C, Montisci R, Iliceto S. Contrast-enhanced transthoracic second harmonic echo Doppler with adenosine: a noninvasive, rapid and effective method for coronary flow reserve assessment. *J Am Coll Cardiol.* 1999;34:122–130.
12. Lambertz H, Tries HP, Stein T, Lethen H. Noninvasive assessment of coronary flow reserve with transthoracic signal-enhanced Doppler echocardiography. *J Am Soc Echocardiogr.* 1999;12:186–195.
13. Korcarz CE, Stein JH. Noninvasive assessment of coronary flow reserve by echocardiography: technical considerations. *J Am Soc Echocardiogr.* 2004;17:704–707.
14. Koskenvuo JW, Saraste M, Niemi P, et al. Correlation of transthoracic Doppler echocardiography and magnetic resonance imaging in measuring left anterior descending artery flow velocity and time-course of dipyridamole-induced coronary flow increase. *Scand J Clin Lab Invest.* 2003;63:65–72.
15. Saraste M, Koskenvuo J, Knuuti J, et al. Coronary flow reserve: measurement with transthoracic Doppler echocardiography is reproducible and comparable with positron emission tomography. *Clin Physiol.* 2001;21:114–122.
16. Kozlowski LT, Goldberg ME, Yost BA, et al. Smokers' misperceptions of light and ultra-light cigarettes may keep them smoking. *Am J Prev Med.* 1998;15:9–16.
17. Kozlowski LT, Heatherton TF, Frecker RC, Nolte HE. Self-selected blocking of vents on low-yield cigarettes. *Pharmacol Biochem Behav.* 1989;33:815–819.
18. Kozlowski LT, Rickert WS, Pope MA, Robinson JC, Frecker RC. Estimating the yield to smokers of tar, nicotine, and carbon monoxide from the 'lowest yield' ventilated filter-cigarettes. *Br J Addict.* 1982;77:159–165.
19. Borland R, Yong HH, King B, et al. Use of and beliefs about light cigarettes in four countries: findings from the International Tobacco Control Policy Evaluation Survey. *Nicotine Tob Res.* 2004; 6:S311–S321.
20. Tanaka T, Oka Y, Tawara I, Sada T, Kira Y. Acute effects of nicotine content in cigarettes on coronary flow velocity and coronary flow reserve in men. *Am J Cardiol.* 1998;82:1275–1278, A9.
21. Papamichael CM, Aznaouridis KA, Stamatelopoulos KS, et al. Endothelial dysfunction and type of cigarette smoked: the impact of 'light' versus regular cigarette smoking. *Vasc Med.* 2004;9:103–105.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20343