ENDOTHELIAL FUNCTION

Light cigarette smoking impairs coronary microvascular functions as severely as smoking regular cigarettes

Hakan Gullu, Mustafa Caliskan, Ozgur Ciftci, Dogan Erdogan, Semra Topcu, Erkan Yildirim, Aylin Yildirir, Haldun Muderrisoglu

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See end of article for authors' affiliations

Correspondence to: Dr H Gullu, Baskent University, Konya Teaching and Medical Research Centre, Cardiology Department, Hoca Cihan Mah, Saray Cad, No 1, 42080, Selcuklu, Konya, Turkey; gulluhakan@hotmail.com

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Background: Smoking is the most prevalent and most preventable risk factor for cardiovascular diseases. Smoking low-tar, low-nicotine cigarettes (light cigarettes) would be expected to be less hazardous than smoking regular cigarettes owing to the lower nicotine and tar yield.

Objective: To compare the chronic and acute effects of light cigarette and regular cigarette smoking on coronary flow velocity reserve (CFVR).

Methods: 20 regular cigarette smokers (mean (SD) age 24.8 (5.0)), 20 light cigarette smokers (mean age 25.6 (6.4)), and 22 non-smoker healthy volunteers (mean age 25.1 (4.2)) were included. First, each subject underwent echocardiographic examination, including CFVR measurement, after a 12 hour fasting and smokeless period. Two days later, each subject smoked two of their normal cigarettes in a closed room within 15 minutes. Finally, within 20–30 minutes, each subject underwent an echocardiographic examination, including CFVR measurement.

Results: Mean (SD) CFVR values were similar in light cigarette and regular cigarette smokers and significantly lower than in the controls (2.68 (0.50), 2.65 (0.61), 3.11 (0.53), p = 0.013). Before and after smoking a paired *t* test showed that smoking two light cigarettes acutely decreased the CFVR from 2.68 (0.50) to 2.05 (0.43) (p = 0.001), and smoking of two regular cigarettes acutely decreased CFVR from 2.65 (0.61) to 2.18 (0.48) (p = 0.001).

Conclusion: Smoking low-tar, low-nicotine cigarettes impairs the CFVR as severely as smoking regular cigarettes. CFVR values are similar in light cigarette and regular cigarette smokers and significantly lower than in controls.

Smoking is the most prevalent and most preventable risk factor for cardiovascular diseases, resulting in a twofold increase in the risk of coronary artery disease.[1] Cigarette smoking is responsible for one-fifth of all cardiovascular deaths and increases the risk of heart failure threefold.[1–3] The two most toxic constituents of cigarette smoke are nicotine and carbon monoxide; however, cigarette smoke contains about 2000 additional toxic components. Cigarette smoke exerts the most marked detrimental effects on the endothelial system and especially on the coronary endothelial system.[3 4] Nicotine causes increased endothelial cell proliferation and intimal hyperplasia,[5] and increased serum carbon monoxide levels have been shown to cause increased endothelial cells circulating in human blood.[6] Smaller amounts of nicotine than that found in cigarette smoke can cause acute endothelial dysfunction.[7] Free radicals contained in the cigarette smoke tar can damage the vascular endothelium.[4] It is known that the adverse effect on the endothelial functions is the same whether a small or large number of cigarettes is smoked a day.[8]

So called ''light cigarettes'', commercially available in recent years, are increasingly smoked. Smoking low-tar, low-nicotine cigarettes (light cigarettes) would be expected to be less hazardous than smoking regular cigarettes in view of the description ''light'' used to define these cigarettes. However, to date, no study has comprehensively investigated the cardiovascular effects of light cigarettes.

In this study, considering the previous emphasis on the effects of nicotine and tar on the cardiovascular system, we proposed the hypothesis that ''light'' cigarettes with lower nicotine and low tar yield might be less hazardous for coronary microvascular functions than ''regular'' cigarettes with their higher nicotine and tar content.

METHODS

Study population

For this study, participants were otherwise healthy ''regular cigarette'' (12 mg tar, 0.9 mg nicotine and 12 mg CO) smokers and ''light cigarette'' (8 mg tar, 0.6 mg nicotine, and 9 mg CO) smokers consecutively registered from our hospital staff or healthy volunteers, or both. Inclusion criteria were smoking steadily the same kind of cigarette for at least 3 years, age 18–40 years, absence of coronary risk factors, and for women, a regular menstrual cycle. Exclusion criteria were having any disease that could cause coronary flow velocity reserve (CFVR) impairment (eg, hypertension, diabetes mellitus and family history of coronary artery disease), drinking alcohol and obesity (body mass index >30 kg/m^2). Subjects using any vasoactive drug, those with ECG changes omplying coronary heart disease, and subjects who had any pulmonary disease were also excluded. Subjects who were planning to stop smoking were excluded because of a concern that they might change their usual smoking habit, such as incomplete inspiration of smoke.

Subjects who fulfilled all inclusion and exclusion criteria—20 light cigarette smokers (mean (SD) age 25.6 (6.4), 12 female), 20 regular cigarette smokers (mean age 24.8 (5.0), 12 female) and 22 healthy non-smoker volunteers (mean age 25.1 (4.2), nine female)—were consecutively included in the study.

A complete physical examination was performed. Peripheral arterial pulses and carotid bruits were searched for in particular, and sitting blood pressure was recorded. Each subject was questioned about alcohol consumption, and again asked about major cardiovascular risk factors. Women were

Abbreviations: CFVR, coronary flow velocity reserve; DPFV, diastolic peak flow velocity; LAD, left anterior descending artery

Table 1 Demographic, biochemical, and echocardiographic characteristics of the three groups

Characteristics	Light cigarette smokers (n = 20)	Regular cigarette smokers (n = 20)	Controls (n = 22)	p Value
Age (years)	24.8 (5.0)	25.6 (6.4)	25.1 (4.2)	0.495
Male/female	8/12	11/9	10/12	
BMI (kg/m^2)	24.8 (3.0)	23.8 (3.5)	23.9 (3.3)	0.532
Smoked cigarette (pack×year)	7.43 (3.4)	9.10 (6.44)		0.31 (*t* test)
Baseline SBP (mm Hg)	117.5 (12.6)	119.5 (11.4)	112.9 (13.3)	0.208
Baseline DBP (mm Hg)	72.2 (8.0)	69.5 (9.4)	72.0 (7.7)	0.506
Baseline heart rate (bpm)	68.2 (11.0)	69.8 (8.4)	71.9 (11.0)	0.491
Glucose (mmol/l)	4.8 (0.2)	4.8 (0.3)	4.9 (0.3)	0.840
Total cholesterol (mmol/l)	4.05 (0.85)	4.10 (0.85)	4.20 (0.95)	0.923
Triglyceride (mmol/l)	1.18 (0.82)	1.18 (0.80)	1.20 (0.82)	0.997
HDL cholesterol (mmol/l)	1.10 (0.20)	1.10 (0.20)	1.15 (0.20)	0.977
LDL cholesterol (mmol/l)	2.40 (0.50)	2.40 (0.50)	2.50 (0.55)	0.811
hsCRP (mg/l)	1.51 (1.06)	1.57 (1.2)	1.76 (1.4	0.770
LVMI (g/m^2)	69.0 (16.3)	76.3 (12.6)	75.1 (14.4)	0.240
Basal DPFV(cm/s)	24.6 (5.8)	24.9 (4.7)	22.5 (3.1)	0.223
Hyperaemic DPFV(cm/s)	63.7 (8.0)	64.55 (12.1)	69.8.8 (11.4)	0.143
CFVR	2.68 (0.50)*	2.65 (0.61)**	3.11 (0.53)	0.013
Mitral E max (cm/s)	88.7 (13.7)	85.5 (18.0)	82.5 (9.5)	0.341
Mitral A max (cm/s)	49.8 (8.3)	53.0 (7.1)	54.1 (7.5)	0.166
Mitral E/A ratio	1.7 (0.3)	1.6 (0.3)	1.6 (0.2)	0.225

BMI, body mass index; CFVR, coronary flow velocity 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.
Post hoc Scheffé test results: *p = 0.049 versus control group; **p = 0.030 versus control group.
Results are shown as mean (SD).

evaluated at the follicular phase of the menstrual cycle. Blood glucose, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol levels in at least a 12 hour fasting state were determined. Plasma high sensitivity C reactive protein levels were measured by a highly sensitive sandwich ELISA technique. Each subject underwent transthoracic echocardiographic examination, including CFVR measurement. The study was conducted according to the recommendations of 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

At baseline, each subject underwent echocardiographic examination, including CFVR measurement after a 12 hour fasting and smokeless period to see the chronic effect of smoking on CFVR. Two days later, each subject smoked two of their usual cigarettes in a closed room within 15 minutes. Then, within 20–30 minutes, each subject underwent echocardiographic examination, including CFVR measurement, to see the acute effect of smoking on CFVR.

CFVR measurement

A transthoracic second harmonic Doppler echocardiography examination was performed on each subject using an Acuson Sequoia C256 echocardiography system (Acuson Corp, Mountain View, California, USA) equipped with a high-resolution transducer with second harmonic capability (5V2c). Visualisation of the distal left anterior descending artery (LAD) was performed using a modified, foreshortened, two-chamber view obtained by sliding the transducer on the upper part and medially, from an apical two-chamber view, to reach the best alignment with the interventricular sulcus. Subsequently, coronary flow in the distal LAD was examined by colour Doppler flow mapping over the epicardial part of the anterior wall, with the colour Doppler velocity set in the range 8.9–24.0 cm/s. The colour gain was adjusted to provide optimal images. The acoustic window was around the mid-clavicular line, in the fourth and fifth intercostal spaces, with the subject in the left lateral decubitus position. The left ventricle was imaged on the long-axis cross section, and the ultrasound beam was then inclined laterally.

Next, coronary blood flow in the LAD (middle to distal) was searched by colour Doppler flow mapping. All subjects had Doppler recordings of the LAD with a dipyridamole infusion at a rate of 0.84 mg/kg over 6 minutes. All subjects had continuous heart rate and electrocardiographic monitoring as well as blood pressure recording at baseline, during dipyridamole infusion and at recovery. Echocardiographic images were recorded on VHS videotapes.

Two experienced echocardiographers who were unaware of the clinical data analysed the recordings. By placing the sample volume on the colour signal, spectral Doppler imaging of the LAD showed the characteristic biphasic flow pattern with larger diastolic and smaller systolic components. Coronary diastolic peak velocities (DPFVs) were measured at baseline and after dipyridamole (0.84 mg/kg over 6 minutes) by averaging the highest three Doppler signals for each measurement. CFVR was defined as the ratio of hyperaemic to baseline diastolic peak velocities.[9–11] The interobserver intraclass correlation coefficient for CFVR measurement was 0.947.

Statistical analyses

Statistical analyses were performed using SPSS 9.0 (SPSS for windows 9.0, Chicago, Illinois, USA). Numeric values are expressed as mean (SD). Power analysis showed that when a 15% change in CFVR value is considered clinically important, two tailed $\alpha = 0.05$. For 80% statistical power, adequate subject count was calculated as 19 subjects. One-way analysis of variance with post hoc Scheffé test was used to compare the data of the three groups. The amounts of cigarettes smoked (pack×year) by the two groups were compared using Student's *t* test. A before smoking–after smoking comparison analysis was made using a paired samples *t* test. To compare the before smoking and after smoking CFVR values independently from

Table 2 Before smoking and after smoking haemodynamic and coronary flow measurements of the light cigarette smokers and regular cigarette smokers

Measurements	Before smoking	After smoking	p Value
Light cigarette smokers			
SBP (mm Hg)	117.5 (12.6)	123.7 (17.0)	0.101
DBP (mm hg)	72.2 (8.0)	76.1 (10.3)	0.052
Heart rate (bpm)	68.2 (11.0)	71.5 (8.7)	0.046
Rate×pressure product	8011 (1494)	8882 (1811)	0.015
Basal DPFV (cm/s)	24.6 (5.8)	27.8 (6.1)	0.006
Hyperaemic DPFV (cm/s)	63.7 (8.0)	55.7 (10.9)	0.004
CFVR	2.68 (0.50)	2.05 (0.43)	0.001
Mitral E/A ratio	1.8 (0.3)	1.5 (0.3)	0.005
Regular cigarette smokers			
SBP (mm Hg)	119.5 (11.4)	123.7 (9.9)	0.001
DBP (mm Hg)	69.5 (9.4)	72.5 (9.2)	0.012
Heart rate (bpm)	69.8 (8.4)	74.4 (11.1)	0.014
Rate×pressure product	8350 (1324)	9203 (1551)	0.004
Basal DPFV (cm/s)	24.9 (4.7)	29.3 (8.2)	0.020
Hyperaemic DPFV (cm/s)	64.5 (12.1)	61.7 (12.3)	0.137
CFVR	2.65 (0.61)	2.18 (0.48)	0.001
Mitral E/A ratio	1.6 (0.3)	1.4 (0.3)	0.012

CFVR, coronary flow velocity reserve; DBP, diastolic blood pressure; DPFV, diastolic peak flow velocity; SBP, systolic blood pressure.
Results are shown as mean (SD).

rate×pressure product, analysis of covariance was performed. Pearson's correlation analysis was used. A p value <0.05 was considered significant.

RESULTS

The three groups had similar age, body mass index, blood pressure, heart rate, glucose, cholesterol, and high sensitivity C reactive protein values. The cigarettes smoked (pack×year) values were similar for the light cigarette and regular cigarette smokers. A one-way analysis of variance test showed that basal DPFV and hyperaemic DPFV values were similar between the light cigarette smokers, regular cigarette smokers and controls; however, CFVR values were significantly lower in the light cigarette and regular cigarette smokers than in the controls (2.68 (0.50), 2.65 (0.61), 3.11 (0.53), $p = 0.013$; table 1). Post hoc Scheffé analysis showed that in both smoker groups, CFVR values were significantly lower than in the controls (table 1). Mitral E and mitral A velocities and mitral E/A ratios were similar among the three groups (table 1).

On day 2 of the study, each smoker smoked two of their normal cigarettes, and each subject was evaluated immediately after smoking (within 20–30 minutes after smoking). Coronary flow values and mitral flow were compared before and after smoking using the paired samples *t* test. The analysis showed that systolic blood pressure, diastolic blood pressure, heart rate, and rate×pressure product values were similarly increased both by smoking light and regular cigarettes (table 2). Coronary basal DPFV values were increased significantly by light and regular cigarette smoking. Coronary hyperaemic DPFV was decreased both by smoking light and regular cigarettes (table 2). Smoking two light cigarettes acutely decreased CFVR from 2.68 (0.50) to 2.05 (0.43) ($p = 0.001$), independently of the change in rate×pressure product by light cigarettes ($F = 14.11$, $p = 0.001$). Smoking two regular cigarette acutely decreased CFVR from 2.65 (0.61) to 2.18 (0.48) ($p = 0.001$), independently of the change in rate×pressure product by regular cigarettes ($F = 14.11$, $p = 0.001$). Student's *t* test showed that the acutely decreased CFVR values obtained by smoking two light or two regular cigarettes were similar to each other (2.05 (0.43) vs 2.18 (0.48), $p = 0.274$). Correlation analysis showed that the amount of cigarettes smoked (pack×year) correlated significantly with the CFVR after a 12 hour cigarette-free period ($r = -0.365$, $p = 0.020$), and with the CFVR immediately after smoking ($r = -0.443$, $p = 0.004$).

DISCUSSION

This study showed that both light cigarette and regular cigarette smoking impairs coronary microvascular functions similarly and decreases the CFVR. In addition to the chronic effects of light and regular cigarettes, both kinds of cigarette acutely impair CFVR to a similar degree. As far as we know, our study is the first to investigate the hazardous effects of chronically smoking light and regular cigarettes on coronary microvascular functions.

Kozlowski *et al* have shown that many cigarette smokers are smoking light cigarettes to reduce the risks of smoking or as a step toward quitting.[12] However, these smokers are unaware that one light cigarette will give them the same amount of noxious ingredients. In Kozlowski's study, the light cigarette smokers stated that they would be likely to stop smoking if they knew this information.[12] Borland *et al*[13] have reported that mistaken beliefs about the possible benefits of light cigarettes are still widespread in Australia, Canada, the UK and America.[13] This remains so even in countries where there has been considerable effort to educate the population about the "light and mild" deception.[13]

Nicotine, which has vasoconstricting effects and which has been demonstrated to reduce hyperaemic coronary blood flow velocity, may directly or indirectly cause coronary flow reduction.[14–16] Tanaka *et al* have investigated the acute effects of low nicotine (<1 mg nicotine) and high nicotine (>1 mg nicotine) cigarette smoking on CFVR in eight and six non-smokers (mean age 55 (13)).[14] They found no difference in the baseline coronary flow velocity before and after smoking in any group. After injection of papaverine, CFVR was reduced after smoking in the high nicotine cigarette group. There was no marked change in CFVR after smoking in low nicotine cigarette group. They measured coronary flow velocity 5 minutes after the index smoking, and it is possible that 5 minutes might not be sufficient for the full results of cigarette smoking to become apparent.[17]

Neunteufl *et al* have suggested that nicotine causes acute endothelial dysfunction in long-term smokers,[18] and they suggested that some ingredients of cigarette smoke might

contribute to this adverse effect. However, the precise mechanism responsible for this negative effect of nicotine on endothelial function remains unclear. They suggested that nicotine replacement therapy by nasal spray is less harmful for the endothelium than cigarette smoking but fails to preserve the integrity of the endothelial function.[18]

Papamichael *et al*[19] investigated acute effects of light and regular cigarette smoking on endothelial function. They found that smoking a regular or light cigarette caused a significant increase in the heart rate immediately after smoking, which was not present 30 minutes after smoking. No significant differences were observed for blood pressure and heart rate between light and regular cigarette smoking. In our study, we found that smoking light and regular cigaretts has similar effects on heart rate and blood pressure. Papamichael *et al* found that smoking low-tar, low-nicotine cigarettes is associated with impairment of endothelium-dependent vasodilatation immediately after smoking, which lasts for less than 60 minutes.[19] Smoking a cigarette with a higher content of tar and nicotine leads to vasomotor dysfunction lasting at least 60 minutes.[19]

In our study, we have found that smokers of both light and regular cigarettes have similarly impaired CFVR. This means that whether or not the effects of light cigarette smoking on endothelial functions disappear more quickly than the effects on those smoking regular cigarettes, light cigarettes are as harmful as regular cigarettes to the coronary microvascular functions in the long term. In our study, the impairment of CFVR values by both light and regular cigarettes was statistically significant, but not clinically disabling. Considering the fact that the subjects taking part in this study were mostly very young (mean age about 24–25), and their smoking history short (about 7–9 pack×year), our results should not be misinterpreted as showing that smoking significantly impairs CFVR but is not significantly clinically disabling. If we consider that smokers usually smoke for several decades of their life, the disabling nature of smoking is easily understood. It is generally believed that smokers of light cigarettes smoke more cigarettes a day than smokers of regular cigarettes,[19] and therefore the chronic effect on the endothelium may be not be less than for regular cigarette smokers. In our study, the two groups smoked similar amounts of cigarettes; however, we found that light and regular cigarette smokers have similarly impaired coronary microvascular functions.

CONCLUSION

Our study suggest that reducing the nicotine and tar yield is not sufficient for a cigarette to be called less hazardous, and other noxious compounds in cigarettes continue to compromise human health. Smoking low-tar, low-nicotine cigarettes seems to have the same unfavourable effect on the coronary microvascular functions as smoking regular cigarettes. Action should be taken to prohibit misleading terminology such as ''light''.

Authors' affiliations

Hakan Gullu, Mustafa Caliskan, Ozgur Ciftci, Dogan Erdogan, Semra Topcu, Aylin Yildirir, Haldun Muderrisoglu, Baskent University, Faculty of Medicine, Cardiology Department, Ankara, Turkey
Erkan Yildirim, Baskent University, Faculty of Medicine, Radiology Department, Ankara, Turkey

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