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RESEARCH ARTICLE

The Effects of Cigarette Smoking on Venous Flow Volume of Lower Extremity

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ABSTRACT

Aims: The purpose of this study was comparing flow volume rates, velocities and diameters of lower extremity arteries and veins of smokers and non-smokers with peripheral arterial disease.

Patients and methods: The study consisted of 58 patients, 26 smokers and 32 non-smokers, who had no smoked for at least 5 years prior to the investigation. Colour Duplex Ultrasonography measurements of the common femoral artery, common femoral vein, popliteal artery, popliteal vein, anterior tibial artery, anterior tibial vein, posterior tibial artery and posterior tibial vein were obtained in the supine position. Differences in the diameters, blood flow velocities, and flow volume rates of the vessels were compared according to the sex, age and Colour Duplex Ultrasonography measurements of the patients.

Results: The diameters of the common femoral artery, popliteal vein and posterior tibial artery were statistically significantly reduced in smokers. The flow volume rate of the popliteal artery showed a significant correlation with that of crural vessels in non-smokers but not in smokers.

Conclusions: The absence of a statistically significant correlation between the measurements of the popliteal artery and crural vessels in smokers shows that cigarette smoking reduces the diameters and flow volumes of crural vessels, potentially giving rise to impaired tissue perfusion.

Keywords: Colour Duplex Ultrasound, Spectral Doppler Ultrasound, vascular, arteries, veins.

Introduction

Peripheral arterial disease (PAD) is a common circulatory disease in which narrowed arteries reduce blood flow in the limbs. The major cause of lower extremity PAD is atherosclerosis, with risk factors including cigarette smoking, diabetes, dyslipidaemia, hypertension and hyperhomocysteinemia [1-6]

Smoking is a particularly strong etiological risk factor for peripheral vascular disease, and further researches have confirmed that active smoking independently associated with peripheral vascular disease. Cigarette smoke extracts induce endothelial cell dysfunction, smooth muscle cell remodeling and macrophage phenotypic transformation via multiple molecular mechanisms. These pathological changes form the molecular basis for the occurrence and development of peripheral vascular diseases. A systematic review showed that half of PAD cases are due to smoking. Passive smoking also increases the risk of vascular injury or the diagnosis of PAD.[7-13]

Colour duplex ultrasonography (CDU) measurement of arterial-venous flow volume (FV) in the leg is a non-invasive, low-cost, easily accessible, uses no ionizing radiation and effective method to obtain quantitative information on tissue capillary perfusion of the leg in patients with PAD. Arterial and venous FV measurement with CDU is necessary to detect ischemic regions in PAD. It has a great clinical value in the diagnosis and follow-up of PAD, evaluation of arterial perfusion of muscle tissue, and monitoring of response. The venous FV values are even more useful than arterial FV values in detecting tissue perfusion. Because, the venous FV value relies on the measurement of returning blood flow from the microvascular area that can originate from multiple sources, such as the main artery or collateral vessels, or be redistributed from other limb tissues and non-nutritive pathways.[14-17]

In this study, we hypothesized that cigarette smoking has a reducing effect on the diameter, velocity and FV rates of crural vessels, potentially giving rise to impaired tissue perfusion. Venous FV values lower than homonymous arterial FV may be an indicator of impaired tissue perfusion in smokers. Our method is based on measurement of returning blood FV from the microvascular space. Due to venous capillary direct connections, venous FV is affected by the microvascular environment. Therefore, our aim is to show the decreased tissue perfusion in smokers with FV measurement, which is a reliable quantitative method.[16,17] To the best of our knowledge, no previous study has measured FV rates of lower extremity veins to predict tissue perfusion in smokers with PAD.

Patients and Methods

Study Population

Fifty-eight patients were included in the study. The patients were classified as smokers or non-smokers. Twenty-six were current smokers (21 males and 5 females) who had smoked >1 cigarette per day ≥1 year. Thirty-two were non-smokers (24 males and 8 females) who had not smoked for at least 5 years prior to the investigation. In 2 patients, one leg had been amputated below the knee and in 11 patients, one leg of the patients do not meet the inclusion criteria. Therefore, 103 legs of the patients were examined.

The study population was consisted of the patients with PAD with mild to moderate claudication (Rutherford Stage I-II). Patients were included in this study if they had PAD with palpable distal pulses (anterior and posterior tibial artery) and a history of intermittent claudication. Exclusions were as follows: absence of PAD, asymptomatic PAD (Rutherford Stage 0), PAD with Rutherford Stage III and upper, history of surgery, arterial stenosis (50% and upper) or occlusion.

Since distal pulses were already palpable (anterior and posterior tibial artery) by hand in all patients, we did not consider ankle-brachial index test necessary for this study.

The patients were classified as smokers or non-smokers, which was defined as not smoked for at least 5 years prior to the investigation.

Written informed consent was obtained from each patient prior to the investigation.

Colour Duplex Ultrasonography

CDU was performed with Aplio XG (Toshiba Corporation, Japan) using a 7–12 MHz linear array transducer. Flow studies were performed by a single radiologist in a temperature-controlled (21±°C) environment. The patient lay for 10 min before the examination. All measurements were obtained in the supine position, with the patient's foot elevated 15 cm to neutralise central venous pressure. The inner luminal diameters, blood flow velocity and FV of the vessels were calculated for each patient. An angle of insonation of 45-60° between the transducer and vessel was used to achieve the optimum colour and spectral Doppler signal. In all patients, transverse and longitudinal images of the common femoral artery (CFA), common femoral vein (CFV), popliteal artery (PA), popliteal vein (PV), anterior tibial artery (ATA), anterior tibial vein (ATV), posterior tibial artery

(PTA) and posterior tibial vein (PTV) of the lower extremity were obtained with grey scale ultrasonography and CDU without compression. In each scan, the luminal diameter, blood flow velocity and FV rate of the vessels were measured (Figure 1). The great saphenous, superficial femoral vein and deep femoral vein were also imaged routinely. The CFA and PA were examined 2 cm above the bifurcation. The CFV and PV were examined 2 cm above the sapheno-femoral and sapheno-popliteal junction, respectively, and the ATA, ATV, PTA and PTV were examined 2 cm proximal to the ankle, wherever the clearest US image was obtained. The method and reproducibility of the arterial and venous haemodynamic CDU evaluation have been described.[16,17] A radiologist with 10 years of experience analysed all the CDU images.

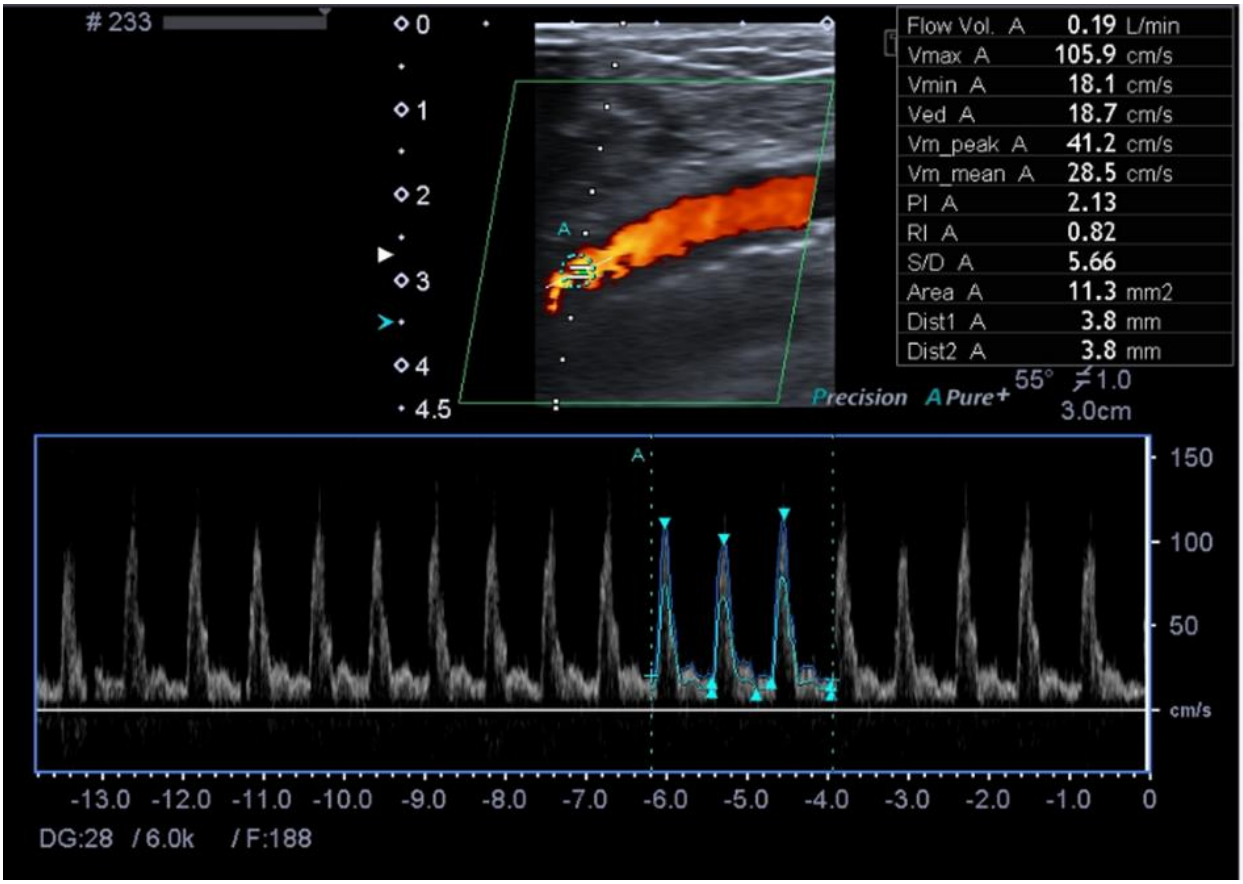

Figure. Colour duplex scan of the right common femoral artery. Flow volume rate was obtained 2 cm above the bifurcation. The luminal narrowing by atherosclerotic plaques were seen. The cross-sectional area of lumen was measuredas 11.3 mm^2 and the flow volume rate was calculated as 190 mL/min.

Statistical Analysis

The data obtained were compared according to the patient's sex, age and CDU measurements. Descriptive statistics are expressed as the mean ± standard deviation. Statistical analysis was performed with the SPSS 12.0 software package for Windows (SPSS software, version 12.0.1 for Windows, SPSS Inc., Chicago, IL). The Mann–Whitney *U* test and Pearson and Spearman's correlation coefficient were used to compare all the parameters with each other. Statistical significance was inferred at $p < 0.05$.

Human rights statements and informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study.

The study protocol was approved by the institutional ethical committee.

Results

58 patients (26 smokers and 32 non-smokers) aged 30 to 84 years, with a mean age of 57.89±13.75 years, were evaluated in the study (Table 1).

26 patients were current smokers (21 males and 5 females aged 34 to 78 years, with a mean age of 55.50±13.01 years).

32 patients were non-smokers (24 males and 8 females aged 31 to 84 years, with a mean age of 59.96±14.25 years).

We did not find statistically significant difference in terms of mean age and gender between the groups (Table 2).

There was no significant difference in the characteristics of the patients (gender, hypertension, hyperlipidaemia, diabetes mellitus and family history of cardiovascular disease).

There was no significant stenosis (50% or more) and occlusion (CFA, PA, ATA, PTA) of the patients, therefore the negative effect of stenosis was not detected on the flow volume rate of the arteries.

The mean CFA, CFV, PA, PV, ATA, ATV, PTA and PTV FV values of the smokers and non-smokers are summarised in Table 3.

Table 1. Baseline characteristics of the patients.

Characteristics	**Non smokers (n=32)**	**Smokers (n=26)**	**p**
Female/male	8/24	5/21	0.83*
Diabetes mellitus	12	8	0.79*
Hypertension	16	8	0.23*
Family history of CVD	4	2	0.68**
Hyperlipidemia	5	4	0.99**

CVD: Cardiovascular disease

*: Yates' correctedchi-square test; **: Fisher'sExact Test

Table 2. The distribution of mean age of cases according to the groups and genders.

		GROUPS				***p***
		Non smokers		**Smokers**		
		n	%	**n**	%	
Gender	**M**	24	75,0	21	80,8	0,600
	F	8	25,0	5	19,2	
Age		**n**	**Mean age**	**n**	**Mean age**	0,561
		32	59,97±14,25	26	55,50±13,02	

α:0,05; independent samples t test

Table 3. Comparison of the mean flow volume values of the lower extremity arteries and veins for current smokers (n:26) and non-smokers (n:32).

	CFA	**CFV**	**PA**	**PV**	**ATA**	**ATV**	**PTA**	**PTV**
MFVR for smokers (ml/min±SD)	314±185	259±116	110±60	94±46	24±10	11±6	14±10	13±6
MFVR for non-smokers (ml/min±SD)	268±156	239±123	89±67	83±35	20±14	15±12	18±14	15±10
***p* value**	0.322	0.516	0.253	0.367	0.407	0.407	0.387	0.757

*MFVR: Mean flow volume rate, CFA: Common femoral artery, CFV: Common femoral vein, PA: Popliteal artery, PV: Popliteal vein, ATA: Anterior tibial artery, ATV: Anterior tibial vein, PTA: Posterior tibial artery, PTV: Posterior tibial vein.

**Independent *t* test, 0.05 significance level.

According to the results of duplex ultrasound, no patient had venous thrombosis.

There was a significant correlation between FV rates of the CFA and CFV (p=0.000), PV and PA (p=0.005), PTA and PTV (p<0.05) in both the smokers and the non-smokers. No correlation was found between FV rates of ATA and ATV in the both groups.

There was a significant correlation between FV rates of the CFA and PV, CFA and ATA, PV and ATV, PV and PTA in both the smokers and the non-smokers (p<0.05).

There was a significant correlation between the mean FV rates of CFA and PTA (p=0.01), CFV and PA (p=0.002), ATA and PTA (p=0.002), ATA and PTV (p=0.002), PTA and ATV (p=0.004), PA and ATA (p=0.001), PA and ATV (p=0.004), PA and PTA (p=0.03), PA and PTV (p=0.005) in the non-smokers but not in the smokers.

There were statistically significant differences of FV rates of PA and crural vessels in the smokers (p<0.05). The inner diameters of the CFA, PV and PTA were statistically significantly reduced in the smokers (p< 0.05) (Table 4).

Table 4. Comparison of diameters of CFA, PV, PTA for smokers (n:26) and non-smokers (n:32).

Doppler measurements	**Smokers**	**Non-smokers**	***p****
	mean± SD	**mean± SD**	
Diameter of CFA (mm)	6.59±1.21	7.29±1.33	0.048**
Diameter of PV (mm)	5.5±1.35	6.54±1.38	0.010**
Diameter of PTA (mm)	2.13±0.69	2.58±0.80	0.037**

CFA: Common femoral artery, PV: Popliteal vein, PTA: Posterior tibial artery.
*Independent *t* test, 0.05 significance level.
**The differences are statistically significant between the groups.

Discussion

This study showed that cigarette smoking reduces the diameters and FV rates of the artery and veins of the leg, leading to impaired tissue perfusion, especially at the calf level. Although there was a statistical correlation between the FV rates of the common femoral and popliteal vessels among the smokers, there was no statistical correlation between the FV rates of the PA and crural arteries and veins. This indicates that crural vessels at the calf level are more sensitive to the harmful effects of smoking than the vessels in the thigh region of the leg.

Measurement of arterial and venous FV with CDU is a new and effective method and is very useful in evaluating tissue perfusion. In a study published by Kalayci et al. in 2015, they compared lower extremity arterial and venous flow measurements in 38 patients with PAH and showed that the amount of venous FV was decreased relative to arterial FV in patients with PAH. They considered this as a reflection of decreased perfusion in the microvascular space at the venous level.[16,17] In addition to these findings, in our study, we proved that the correlation of arterial and venous flow rate is impaired at the calf level rather than the thigh level in smokers with PAD. We also found a decrease in CFA, PV and PTA diameters in smokers. All these findings were of course secondary to the negative effects of smoking on the vascular endothelium and smooth muscle in the vessel wall. Smoking causes endothelial cell dysfunction, monocyte differentiation into macrophages and eventually foam cells, smooth muscle cell proliferation, and extracellular matrix degradation and remodeling. Endothelial dysfunction is one of the earliest abnormalities that is observed during the development of atherosclerosis, and endothelial nitric oxide synthase plays a crucial role in regulating endothelial dysfunction. Also smoking alters the function and phenotype of smooth muscle cells. Smoking induces smooth muscle cell autophagy through oxidative stress and causes smooth muscle cell proliferation and migration through multiple signaling pathways.[7-13]

Cigarette smoking is the most important, preventable risk factor in several different clinical atherosclerotic syndromes, especially PAD.[18,19] The association between smoking and PAD was first reported over 100 years ago. In research published in 2013, the authors presented data from over 50 studies on the association between PAD and smoking, reporting that smoking more than doubled an individual's risk of developing PAD.[19] Impairment of vasodilatory function is one of the earliest manifestations of atherosclerotic changes in a vessel. The inhalation of cigarette

smoke results in the rapid absorption of nicotine, with a consequent release of adrenaline and noradrenaline, which causes vasoconstriction. In non-smoking adults, this effect is counterbalanced by the release of vasodilators. However, in smokers, the production of vasodilators is often impaired.[12] In the both animal and human models, several studies demonstrated that active and passive cigarette smoke exposure are associated with a decrease in vasodilatory function.[20-30] In humans, cigarette smoke exposure impaired endothelium-dependent vasodilation in macrovascular beds, such as coronary and brachial arteries, and in microvascular beds.[20-25] Here, similar to previous studies, we found significant effect of cigarette smoking on the diameters and FV rates of the macrovascular structure. Nitric oxide, a free radical, is primarily responsible for vasodilatory function of the endothelium.[31] Using cigarette smoke extract or isolated components, such as nicotine, multiple in vitro studies demonstrated that smoking is associated with decreased nitric oxide availability.[26-28]

Studies also previously reported that smokers had lower calf blood velocity than non-smokers, with the smokers apparently having greater vasoconstriction in the leg musculature, even after abstaining from smoking during the morning of testing.[32,33]Afaq et al. concluded that smokers had lower calf muscle haemoglobin oxygen saturation during exercise than non-smokers because of intermittent claudication.[2] We find a significant correlation in the FV rates of the PA and crural vessels of the non-smokers but not in smokers, indicating that smoking may have a reducing effect on calf muscle perfusion as a result of suppressing the vasodilator mechanism by causing endothelial damage and smooth muscle proliferation.

In our study, there was no significant stenosis and occlusion in the arterial system of the patients, therefore the negative impact of stenosis was not detected on the flow volume rate in our study. A number of limitations should be considered for this study. First, smoking status was self-reported and not verified by biochemical analysis. Second, the study consisted of a small sample of patients. Third, a larger study population is needed to determine the cut-off values for the diameter, velocity and FV rates of the crural vessels of smokers and non-smokers.

Conclusions

In conclusion, reduced diameters of the leg vessels and the absence of a statistically significant correlation between the FV rates of the PA and crural vessels in smokers indicate that cigarette smoking decreases the diameters and FV rates of crural vessels, potentially resulting in impaired calf tissue perfusion. To the best of our knowledge, this is the first clinical study to be conducted on this subject. FV measurement with CDU is an important method to predict the capillary flow impairment. Arterial and venous FV rates and the differences in these values should be measured in cigarette smokers with PAD.

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Conflict of Interest Statement: The authors declared no conflict of interest, including specific financial interests, relationships and affiliations relevant to the subject matter or materials included.

References

1. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. *Rev Cardiovasc Med*.2004; 5:189–193.
2. Afaq A, Montgomery PS, Scott KJ, Blevins SM, Whitsett TL, Gardner AW. The effect of current cigarette smoking on calf muscle hemoglobin oxygen saturation in patients with intermittent claudication. *Vasc Med*.2007; 12:167–173.
3. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe A, Fowkes FG. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J*. 1999; 20:344–53.
4. Morotti E, Battaglia B, Fabbri R, Paradisi R, Venturoli S, Battaglia C. Cigarette smoking and cardiovascular risk in young women with polycystic ovary syndrome. *Int J FertilSteril*. 2014; 7:301–312.
5. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004; 43:1731–1737.
6. Clair C, Rigotti NA, Porneala B, Fox CS, D'Agostino RB, Pencina MJ. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA*.2013; 309:1014–1021.
7. Wang W, Zhao T, Geng K, Yuan G, Chen Y and Xu Y. Smoking and the Pathophysiology of Peripheral Artery Disease. Front. Cardiovasc. Med. 2021; 8:704106.
8. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015; 116:1509–26.
9. Creager MA. Decade in review–peripheral vascular disease: 10 years of breakthroughs in peripheral vascular disease. Nat Rev Cardiol. 2014; 11:635–6.
10. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. *BMJ*. 2018; 360:j5842.
11. Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, Boiten J, Moll FL, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. *J Vasc Surg*. 2004; 40:1158–65.
12. Aday AW, Matsushita K. Epidemiology of peripheral artery disease and polyvascular disease. *Circ Res*. 2021; 128:1818–32.
13. Ngu NL, McEvoy M. Environmental tobacco smoke and peripheral arterial disease: a review. *Atherosclerosis*. 2017; 266:113–20.
14. Dawson D, Vincent MA, Barrett EJ, et al. Vascular recruitment in skeletal muscle during exercise and hyperinsulinemia assessed by contrast ultrasound. *Am J Physiol*. 2002; 282:E714 –720.
15. Bragadeesh T, Sari I, Pascotto M, Micari A, Kaul S, Lindner JR. Detection of peripheral vascular stenosis by assessing skeletal muscle flow reserve. *J Am Coll Cardiol*. 2005; 45:780–785.
16. Kalayci TO, Sonmezgoz F, Apaydin M, et al. Venousflow volumemeasured by duplexultra-soundcan be used as an indicator of impaired tissue perfusion in patients with peripheral arterial disease. *Med Ultrason*. 2015; 17: 482-6. doi: 10.11152/mu.2013.2066.174.
17. Kalayci TO, Cakir V, Kestelli M, Apaydin M. Measure the vascular flow volume rather than vascular stenosis and pressure gradient. *Heart Lung Circ*. 2015 Jun; 24 (6): 617-20. doi:10.1016/j.hlc.2014.12.164.
18. Findlay BB, Gupta P, Szijgyarto IC, Pyke KE. Impaired brachial artery flow-mediated vasodilation in response to handgrip exercise-induced increases in shear stress in young smokers. *Vasc Med*. 2013; 18(2):63–71. doi: 10.1177/1358863X13480259.
19. Lu L, Mackay DF, Pell JD. Meta-analysis of the association between cigarette smoking andperipheral arterial disease. *Heart*. 2014; 100:414–423.
20. 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.
21. Barua RS, Ambrose JA, Eales-Reynolds LJ, DeVoe MC, Zervas JG, Saha DC. Dysfunctional endothelial nitric oxide biosynthesis inhealthy smokers with impaired endothelium-dependent vasodilatation. *Circulation*. 2001; 104:1905–1910.
22. Celermajer DS, Adams MR, Clarkson P, et al. Passive smoking and impaired endothelium-dependent arterial dilatation in healthy youngadults. *N Engl J Med*. 1996; 334:150–154.
23. Kugiyama K, Yasue H, Ohgushi M, et al. Deficiency in nitric oxidebioactivity in epicardial coronary arteries of cigarette

smokers. *J Am Coll Cardiol*. 1996; 28:1161–1167.

24. Sumida H, Watanabe H, Kugiyama K, Ohgushi M, Matsumura T,Yasue H. Does passive smoking impair endothelium-dependentcoronary artery dilation in women? J *Am Coll Cardiol*. 1998; 31:811–815.
25. Ijzerman RG, Serne EH, van Weissenbruch MM, van WeissenbruchMM, de Jongh RT, Stehouwer CD. Cigarette smoking is associatedwith an acute impairment of microvascular function in humans. *Clin Sci (Lond)*. 2003; 104:247–252.
26. Mayhan WG, Sharpe GM. Effect of cigarette smoke extract on arteriolar dilatation in vivo. *J Appl Physiol*. 1996; 81:1996–2003.
27. Mayhan WG, Patel KP. Effect of nicotine on endotheliumdependentarteriolar dilatation in vivo. *Am J Physiol*. 1997; 272:H2337–2342.
28. Ota Y, Kugiyama K, Sugiyama S, et al. Impairment of endotheliumdependent-relaxation of rabbit aortas by cigarette smoke extract—roleof free radicals and attenuation by captopril. *Atherosclerosis*. 1997; 131:195–202.
29. Barua RS, Ambrose JA, Srivastava S, DeVoe MC, Eales-ReynoldsLJ. Reactive oxygen species are involved in smoking-induced dysfunctionof nitric oxide biosynthesis and upregulation of endothelialnitric oxide synthase: an in vitro demonstration in human coronary artery endothelial cells. *Circulation*. 2003; 107:2342–2347.
30. McVeigh GE, Lemay L, Morgan D, Cohn JN. Effects of long-termcigarette smoking on endothelium-dependent responses in humans. *Am J Cardiol*. 1996; 78:668–672.
31. Napoli C, Ignarro LJ. Nitric oxide and atherosclerosis. *Nitric Oxide*. 2001; 5:88–97.
32. Gardner AW, Sieminski DJ, Killewich LA. The effect of cigarette smoking on free living daily physical activity in older claudication patients. *Angiology*.1997; 48:947–955.
33. Gardner AW, Killewich LA, Montgomery PS, Katzel LI. Theresponse to exercise rehabilitation in smoking and non-smokingpatients with intermittent claudication. J *Vasc Surg*.2004; 39:531–538.