Published in final edited form as:

Vasc Med. 2009 April ; 15(2): 119–125. doi:10.1177/1358863X09358750.

Endothelium-dependent vasodilation is associated with exercise capacity in smokers and non-smokers

Kevin S. Heffernan, PhD^{1,2}, Richard H. Karas, MD PhD^{1,2}, Eshan A. Patvardhan, MBBS¹, and Jeffrey T. Kuvin, MD¹ From the Vascular Function Study Group

¹Department of Medicine, Division of Cardiology, Tufts Medical Center, Boston, MA

²Molecular Cardiology Research Institute, Tufts Medical Center, Boston, MA

Abstract

Objectives—Smoking is an established cardiovascular risk factor that impairs endothelial function and reduces exercise capacity. Peripheral vascular endothelial function correlates with exercise capacity, but whether this association prevails in smokers is unknown. The purpose of this investigation was to examine the association between endothelial function and exercise capacity in chronic smokers and non-smoking controls.

Methods—Brachial artery flow mediated dilation (FMD, endothelium-dependent) following 5-minutes of upper arm occlusion was compared in 26 smokers (age 58±1 yrs; 15 female; BMI = 28±1) and 39 non-smokers (age 58±1 yrs; 24 female; BMI = 28±1) using ultrasound. Exercise treadmill time (ETT) was recorded from a standard Bruce protocol during symptom limited stress testing.

Results—There was a significant positive association between FMD and ETT in smokers ($r = 0.60$, $p < 0.05$) and non-smokers ($r = 0.28$, $p < 0.05$). FMD was significantly lower in smokers vs. non-smokers (8.9 ± 0.9 vs. $12.6 \pm 0.7\%$, $p < 0.05$). ETT was significantly lower in smokers (425 ± 35 sec) versus non-smokers (522 ± 25 sec, $p < 0.05$). After adjusting for FMD, there were no longer group differences in ETT. When patients were matched according to FMD, there were no differences in ETT between smokers and non-smokers.

Conclusion—Peripheral endothelial dysfunction is a correlate of low exercise capacity in smokers and non-smokers alike. Future research is needed to examine if improving endothelial function will lead to concomitant increases in exercise capacity in chronic smokers.

Keywords

flow mediated vasodilation; exercise testing; smoking; vascular function

Smokers have lower exercise capacity when compared to their non-smoking peers and this is independent of physical activity levels and/or clustering of common cardiovascular risk factors ^{1,2}. Moreover, exercise capacity increases very shortly after smoking cessation, arguing for a direct role of smoking in the diminution of exercise capacity ³. Impaired exercise capacity is related to poor quality of life, reduced physical function, inability to complete activities of daily living and increased dependence ^{4,5}. Numerous studies have demonstrated that impaired exercise capacity is predictive of increased risk/mortality even

Corresponding Author: Kevin S. Heffernan, Ph.D., Tufts Medical Center, Molecular Cardiology Research Institute and the Department of Medicine, Division of Cardiology, 800 Washington St, Boston MA 02111, Phone: 217-621-8900, Fax: 617-636-0223, KHeffernan@tuftsmedicalcenter.org .

Disclosures: None

after controlling for standard risk factors^{6,7}. Endothelial dysfunction has been shown to correlate with exercise capacity in various populations^{8–10}. Cigarette smoking causes peripheral vascular endothelial dysfunction and as such, smokers present with impaired endothelium-dependent vasodilation^{11–14}. Whether vascular endothelial function is a correlate of exercise capacity in smokers has yet to be investigated.

Vascular responsiveness to exercise may be impaired in smokers. Gaenzer *et al.* has noted impaired femoral vascular responsiveness during exercise in smokers compared to non-smokers and this blunted exercise-induced femoral flow mediated dilation (FMD) was highly correlated with brachial artery FMD induced by 5-minutes of local occlusion (a traditional measure of conduit artery endothelium-dependent vasodilation)¹³. Moreover, the vasculature of smokers appears impervious to modulation by select therapies known to improve vascular function in other clinical cohorts (e.g. ischemic preconditioning, vitamin C, vitamin E)^{15–17}. Therefore, it is possible that resting endothelium-dependent vasodilation may not be associated with exercise capacity in this unique cohort due to the severity of vascular dysfunction.

The purpose of this study was to examine the association between vascular endothelial function and exercise capacity in smokers. We hypothesized that endothelium-dependent vasodilation would be a correlate of exercise capacity in smokers and non-smokers. To comprehensively test this hypothesis, several statistical and methodological approaches were employed. First we examined the statistical association between endothelium-dependent vasodilation and exercise capacity in smokers and non-smokers. Second, we examined whether statistically adjusting for group differences in endothelium-dependent vasodilation would abolish differences in exercise capacity between smokers and nonsmokers. Third, we matched smokers and non-smokers for endothelium-dependent vasodilation and examined whether exercise capacity would be similar between groups when this factor is held constant. Finally, we examined whether exercise capacity is higher in smokers on statin therapy, a pharmacological intervention known to improve endothelium-dependent vasodilation.

Methods

Patient Selection

Sixty-five patients reporting to the outpatient Preventive Cardiology Center at Tufts Medical Center for clinically-indicated stress testing due to chest pain were investigated in this study. All patients were community dwelling individuals residing in the greater Boston area. Exclusion criteria included patients with uncontrolled hypertension, uncontrolled diabetes mellitus, known coronary artery disease (CAD), severe valvular disease, recent myocardial infarction (within three months) or unstable cardiac symptoms, congestive heart failure or left ventricular ejection fraction <40%, renal insufficiency (serum creatinine > 2 mg/dL), active liver disease, chronic obstructive pulmonary disease, known peripheral artery disease, or Raynaud's disease.

Exercise Testing

Patients completed a symptom limited exercise treadmill test using a standard Bruce protocol with continuous 12-lead ECG assessment. Exercise test time (ETT) was recorded in seconds and taken as a measure of exercise capacity. Prior to the completion of exercise, intravenous technetium-99m sestamibi was administered for subsequent myocardial perfusion imaging via single photon emission computed tomography (SPECT). Patients were considered CAD– if no perfusion abnormalities were detected and only these patients were retrospectively selected for final data analysis. Patients with fixed or reversible

perfusion defects (CAD+) were excluded to avoid the potential confounding influence of ischemia on exercise test time.

Subjects were instructed to fast overnight (at least 12-hours) and refrain from caffeine or alcohol intake, smoking and vasoactive medications on the day of testing. All vascular measures were made with the subject in the supine position in a dimly lit, temperature-controlled room following a ten-minute acclimatization period. All vascular examinations were conducted in the morning to reduce potential influence of diurnal variation on measurement of endothelial function. All subjects gave written informed consent and this study was approved by the institutional review board at Tufts Medical Center.

Brachial artery endothelium dependent and independent vasodilation

Endothelium-dependent vasodilation of the brachial artery was assessed using high resolution ultrasonography as previously described⁹. Briefly, the brachial artery was longitudinally imaged 2-cm above the antecubital fossa using a 10mHz linear array vascular ultrasound transducer. Diameters were measured during end-diastole (gated with ECG R-waves) using ultrasonic calipers. The average of 5 evenly spaced measures (distance between the anterior and posterior intima-blood interfaces) obtained within a 5 cm segment of the vessel was used for subsequent analysis. Following baseline brachial artery diameter (BAD) measurement, reactive hyperemia was induced by an ischemic stimulus (rapid inflation of a blood pressure cuff around the upper arm to a supra-systolic pressure for 5 minutes). Immediately post cuff release, reactive hyperemia was confirmed by qualitatively assessing blood velocity for 10 seconds using spectral Doppler. Sixty seconds following release of the occlusion cuff, brachial diameter was once again measured as aforementioned. Responses were calculated as percentage change in brachial artery diameter from baseline (flow mediated dilation, FMD).

Endothelium-independent vasodilation was assessed 10-min after reactive hyperemia testing. Brachial artery diameters were assessed before and 5-min following administration of sublingual nitroglycerine (nitroglycerin-mediated dilation, NMD). Intraobserver and interobserver variability in our clinic has previously been established to be low (1.8% and 2.8% respectively)¹⁸. These methods conform to the guidelines set out for the ultrasound measurement of endothelium-dependent and -independent dilation of the brachial artery¹⁹.

Statistical analysis

All data are reported as means $\pm$ SEM. A priori significance was set at $p < 0.05$. Normality of distribution was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson's correlation coefficients were used to assess relationships between variables of interest. Stepwise multiple regression analysis was performed to examine predictors of exercise test time in our cohort. Variables entered into the model included traditional cardiovascular risk factors (age, gender, presence/absence of hypertension, diabetes, hyperlipidemia, family history of CVD, and BMI), BAD, FMD and NMD. Analysis of variance (for parametric data) was used to assess differences in continuous outcome variables between groups. Analysis of co-variance (ANCOVA) was used to statistically remove the effect of FMD on ETT. In addition, we also performed ANCOVA, adjusting for the potential influence of traditional risk factors (age, gender, presence of hypertension, presence of diabetes, hypercholesterolemia) and medication use (statins, beta-blockers, ACE-inhibitors, calcium channel blockers, aspirin) on ETT. Smokers and non-smokers were then matched for FMD using previously defined clinically relevant cut-points⁹ and compared using ANOVA. FMD and ETT in smokers/non-smokers on statin therapy were compared to smokers/non-smokers not on statin therapy using ANOVA. For all ANOVA, when a group effect was detected,

post hoc comparisons were made with t-tests. Data analysis was carried out using SPSS (SPSS, Inc., Chicago, IL).

Results

Smoking and non-smoking groups were similar in age, BMI, and prevalence of cardiovascular risk factors (Table 1). According to results from stepwise multiple regression, predictors of ETT for the group as a whole included age (standardized $\beta = -0.431$, $p < 0.05$), FMD (standardized $\beta = 0.373$, $p < 0.05$), and female gender (standardized $\beta = -0.352$, $p < 0.05$). For smokers, the regression equation for FMD as a predictor of ETT was: $y = 21.5x + 233.8$. For controls, the regression equation for FMD as a predictor of ETT was: $y = 8.43x + 416.4$. There was a significant association between FMD and ETT in smokers ($r = 0.60$, $p < 0.05$) and non-smokers ($r = 0.28$, $p < 0.05$).

FMD and ETT were significantly lower in smokers versus non-smokers (Table 1). When ANCOVA was performed with traditional risk factors entered as covariates, group differences remained (adjusted means: smokers 437 ± 29 sec vs. non-smokers 516 ± 23 sec; $p < 0.05$). When ANCOVA was performed with FMD entered as the covariate, group differences in ETT were no longer significant (adjusted means: smokers 456 ± 31 sec vs. non-smokers 502 ± 25 sec; $p > 0.05$). There were no differences in NMD between smokers ($21.3 \pm 1.6\%$) and non-smokers ($18.9 \pm 0.9\%$, $p > 0.05$). There was no association between NMD and ETT in smokers ($r = 0.21$, $p > 0.05$) and non-smokers ($r = -0.04$, $p > 0.05$).

Smokers and non-smokers with low FMD ($< 10\%$) had similar ETT (Figure 1, $p > 0.05$). Similarly, smokers and non-smokers with high FMD ($\geq 10\%$) had similar ETT (Figure 1, $p > 0.05$). Smokers and non-smokers with FMD $\geq 10\%$ had greater ETT compared to smokers and non-smokers with FMD $< 10\%$ (Figure 1, $p < 0.05$).

ETT and FMD were higher in smokers taking statins versus smokers not taking statins (Table 3, Figure 2; $p < 0.05$). ETT and FMD were higher in non-smokers taking statins versus non-smokers not taking statins (Table 3, Figure 2; $p < 0.05$). In smokers and non-smokers, there were no differences in FMD or ETT between those taking anti-hypertensives (ACE inhibitors, calcium channel blockers and β blocker) or aspirin therapy versus those not taking anti-hypertensives or aspirin therapy ($p > 0.05$).

Discussion

The findings of the present study were as follows: 1) chronic smokers have lower exercise capacity and lower endothelium-dependent vasodilation compared to non-smokers 2) a positive association was noted between endothelium-dependent vasodilation and exercise capacity in smokers and non-smokers; 3) statistically adjusting for endothelium-dependent vasodilation abolished group differences in exercise capacity; 4) when smokers and non-smokers were matched for endothelial function, exercise capacity was not different between groups; 5) smokers and non-smokers on statin therapy had higher endothelium-dependent vasodilation and higher exercise capacity than their counterparts not on statin therapy.

In healthy human and animal models devoid of clinical manifestations of CAD, limitations in exercise capacity have been historically ascribed to two factors, reduced convective properties or O_2 delivery (i.e. reduced cardiac output and blood flow) and/or reduced diffusive properties or O_2 extraction at the level of the muscle mitochondria-capillary boundary 20. Recent evidence has also implicated endothelial dysfunction as a causative factor in reducing exercise capacity 21. With aging and disease, limitations in oxygen and nutrient delivery limit contractile work and age-associated impairment in endothelium-dependent vasodilation contributes to lower exercise hyperemia 21,22. Endothelial

dysfunction will result in a state of heightened vasoconstriction and blunted vasodilation, reducing blood flow into the capillary bed and preventing efficient oxygen extraction by muscle mitochondria, ultimately reducing exercise capacity. A reduction in blood flow to working skeletal muscle (i.e. reduced perfusion) may also limit the ability to perform functional tasks²³. Peripheral vascular endothelial function has been shown to correlate with exercise capacity and physical function in various populations^{8–10,23}. Although we do not have measures of endothelial function during exercise, conduit artery FMD following 5-min of occlusion (as used in the present study) is highly correlated with exercise-induced FMD in smokers and non-smokers¹³. Therefore, reduced endothelium-dependent vasodilation may contribute to reductions in exercise capacity in both smokers and non-smokers. Given the profound level of vascular dysfunction in smokers compared to non-smokers, the impact of endothelial dysfunction on blunted exercise capacity may be more pronounced.

Exercise capacity increases very shortly (7 days) after smoking cessation, arguing for a direct role of smoking in the diminishment of exercise capacity³. Smoking cessation induces rapid reversal of endothelial dysfunction and the time course is similar to improvements noted in exercise capacity²⁴. Therapies that improve endothelial function have beneficial effects on exercise capacity in other clinical cohorts. In patients with heart failure, improving endothelial function with either atorvastatin^{25,26} or sildenafil is correlated with improvements in exercise capacity^{27–29}. Statin therapy has been shown to improve endothelial function in smokers^{30,31} and this can occur in as little as 24-hours from the initial dose³². In support of this, we noted that endothelial function was higher in smokers (and non-smokers) using statins compared their non-statin using counterparts. Smokers taking statins had endothelial function comparable to that of non-smokers. Thus it would appear that statin therapy may be able to restore endothelial function in smokers to levels rivaling non-smokers. Interestingly, exercise capacity was also higher in smokers using statins compared to smokers not using statins and levels were comparable to those witnessed in non-smokers. These findings raise the intriguing possibility that therapies that improve endothelial function may be associated with concomitant improvements in exercise capacity and this may be particularly beneficial in smokers, a cohort with established endothelial dysfunction. Additional studies are needed to demonstrate this empirically.

An alternative interpretation of the present findings is that higher exercise capacity (secondary to a more physically active lifestyle) may have a favorable effect on vascular endothelial function in smokers³³. Highly endurance trained smokers have improved peripheral blood flow³⁴. Given that smoking cessation remains a very difficult task for many, physical activity may be an important lifestyle modification to preserve peripheral endothelial function in chronic smokers. This may have important implications for overall vascular health and primary/secondary disease prevention in this cohort.

Limitations to this study should be noted. These data are cross sectional. As such, cause-and-effect cannot be directly ascertained. We do not have data pertaining to the duration and magnitude of cigarette smoking in our smokers. However there does not appear to be a dose-dependent association between number of cigarettes smoked/pack-years of exposure and cardiovascular events^{35,36}. Also, light smokers have similar impairments in endothelial function as heavy smokers¹². Therefore, the possibility that smokers with attenuated decrements in endothelial function were lighter smokers or smoked for less duration remains unlikely. Finally, we did not control for shear stress when measuring FMD and this may affect interpretation of our findings^{37,38}. We do not have measures of pulmonary function. Impaired pulmonary function in smokers may reduce exercise capacity and this may hamper the interpretation of our findings². Overall, it should be stressed that the current findings are preliminary and further research is necessary to substantiate them.

In conclusion, there is an association between endothelium-dependent vasodilation and exercise capacity in chronic smokers and non-smokers. Endothelial dysfunction may be an important, previously unrecognized determinant of exercise capacity in chronic smokers. Future research is needed to prospectively examine if interventions that specifically target endothelial dysfunction in smokers concomitantly improves exercise capacity.

References

1. Bernaards CM, Twisk JW, Van Mechelen W, Snel J, Kemper HC. A longitudinal study on smoking in relationship to fitness and heart rate response. *Med Sci Sports Exerc* 2003;35(5):793–800. [PubMed: 12750589]
2. Kobayashi Y, Takeuchi T, Hosoi T, Loeppky JA. Effects of habitual smoking on cardiorespiratory responses to sub-maximal exercise. *J Physiol Anthropol Appl Human Sci* 2004;23(5):163–169.
3. Hashizume K, Yamaji K, Kusaka Y, Kawahara K. Effects of abstinence from cigarette smoking on the cardiorespiratory capacity. *Med Sci Sports Exerc* 2000;32(2):386–391. [PubMed: 10694121]
4. Arena R, Myers J, Williams MA, Gulati M, Kligfield P, Balady GJ, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007;116(3):329–343. [PubMed: 17576872]
5. Paterson DH, Govindasamy D, Vidmar M, Cunningham DA, Koval JJ. Longitudinal study of determinants of dependence in an elderly population. *J Am Geriatr Soc* 2004;52(10):1632–1638. [PubMed: 15450038]
6. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, et al. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. *JAMA* 2003;290(12):1600–1607. [PubMed: 14506119]
7. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. *Circulation* 2004;110(14):1920–1925. [PubMed: 15451778]
8. Patel AR, Kuvin JT, DeNofrio D, Kinan D, Sliney KA, Eranki KP, et al. Peripheral vascular endothelial function correlates with exercise capacity in cardiac transplant recipients. *Am J Cardiol* 2003;91(7):897–899. [PubMed: 12667585]
9. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Rand WM, Udelson JE, et al. Peripheral vascular endothelial function testing as a noninvasive indicator of coronary artery disease. *J Am Coll Cardiol* 2001;38(7):1843–1849. [PubMed: 11738283]
10. Patel AR, Kuvin JT, Sliney KA, Rand WM, Pandian NG, Karas RH. Peripheral vascular endothelial function correlates with exercise capacity in women. *Clin Cardiol* 2005;28(9):433–436. [PubMed: 16250267]
11. Barua RS, Ambrose JA, Eales-Reynolds LJ, DeVoe MC, Zervas JG, Saha DC. Dysfunctional endothelial nitric oxide biosynthesis in healthy smokers with impaired endothelium-dependent vasodilatation. *Circulation* 2001;104(16):1905–1910. [PubMed: 11602492]
12. Barua RS, Ambrose JA, Eales-Reynolds LJ, DeVoe MC, Zervas JG, Saha DC. 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(11):1758–1763. [PubMed: 12039488]
13. Gaenzer H, Neumayr G, Marschang P, Sturm W, Kirchmair R, Patsch JR. Flow-mediated vasodilation of the femoral and brachial artery induced by exercise in healthy nonsmoking and smoking men. *J Am Coll Cardiol* 2001;38(5):1313–1319. [PubMed: 11691501]
14. Wiesmann F, Petersen SE, Leeson PM, Francis JM, Robson MD, Wang Q, et al. Global impairment of brachial, carotid, and aortic vascular function in young smokers: direct quantification by high-resolution magnetic resonance imaging. *J Am Coll Cardiol* 2004;44(10):2056–2064. [PubMed: 15542292]

15. Raitakari OT, Adams MR, McCredie RJ, Griffiths KA, Stocker R, Celermajer DS. Oral vitamin C and endothelial function in smokers: short-term improvement, but no sustained beneficial effect. *J Am Coll Cardiol* 2000;35(6):1616–1621. [PubMed: 10807468]
16. Neunteufl T, Priglinger U, Heher S, Zehetgruber M, Soregi G, Lehr S, et al. Effects of vitamin E on chronic and acute endothelial dysfunction in smokers. *J Am Coll Cardiol* 2000;35(2):277–283. [PubMed: 10676670]
17. Nakamura S, Kimura M, Goto C, Noma K, Yoshizumi M, Chayama K, et al. Cigarette smoking abolishes ischemic preconditioning-induced augmentation of endothelium-dependent vasodilation. *Hypertension* 2009;53(4):674–681. [PubMed: 19237681]
18. Kuvin JT, Patel AR, Sliney KA, Pandian NG, Sheffy J, Schnall RP, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. *Am Heart J* 2003;146(1):168–174. [PubMed: 12851627]
19. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002;39(2):257–265. [PubMed: 11788217]
20. Wagner PD. New ideas on limitations to VO₂max. *Exerc Sport Sci Rev* 2000;28(1):10–14. [PubMed: 11131681]
21. Koch DW, Newcomer SC, Proctor DN. Blood flow to exercising limbs varies with age, gender, and training status. *Can J Appl Physiol* 2005;30(5):554–575. [PubMed: 16293904]
22. Schrage WG, Eisenach JH, Joyner MJ. Ageing reduces nitric-oxide- and prostaglandin-mediated vasodilatation in exercising humans. *J Physiol* 2007;579(Pt 1):227–236. [PubMed: 17138603]
23. Welsch MA, Dobrosielski DA, Arce-Esquivel AA, Wood RH, Ravussin E, Rowley C, et al. The association between flow-mediated dilation and physical function in older men. *Med Sci Sports Exerc* 2008;40(7):1237–1243. [PubMed: 18580402]
24. Kondo T, Hayashi M, Takeshita K, Numaguchi Y, Kobayashi K, Iino S, et al. Smoking cessation rapidly increases circulating progenitor cells in peripheral blood in chronic smokers. *Arterioscler Thromb Vasc Biol* 2004;24(8):1442–1447. [PubMed: 15191940]
25. Guazzi M, Tumminello G, Reina G, Vicenzi M, Guazzi MD. Atorvastatin therapy improves exercise oxygen uptake kinetics in post-myocardial infarction patients. *Eur J Clin Invest* 2007;37(6):454–462. [PubMed: 17537152]
26. Castro PF, Miranda R, Verdejo HE, Greig D, Gabrielli LA, Alcaino H, et al. Pleiotropic effects of atorvastatin in heart failure: role in oxidative stress, inflammation, endothelial function, and exercise capacity. *J Heart Lung Transplant* 2008;27(4):435–441. [PubMed: 18374881]
27. Guazzi M, Samaja M, Arena R, Vicenzi M, Guazzi MD. Long-term use of sildenafil in the therapeutic management of heart failure. *J Am Coll Cardiol* 2007;50(22):2136–2144. [PubMed: 18036451]
28. Guazzi M, Tumminello G, Di Marco F, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. *J Am Coll Cardiol* 2004;44(12):2339–2348. [PubMed: 15607396]
29. Guazzi M, Casali M, Berti F, Rossoni G, Colonna VD, Guazzi MD. Endothelium-mediated modulation of ergoreflex and improvement in exercise ventilation by acute sildenafil in heart failure patients. *Clin Pharmacol Ther* 2008;83(2):336–341. [PubMed: 17653139]
30. Beckman JA, Liao JK, Hurley S, Garrett LA, Chui D, Mitra D, et al. Atorvastatin restores endothelial function in normocholesterolemic smokers independent of changes in low-density lipoprotein. *Circ Res* 2004;95(2):217–223. [PubMed: 15178637]
31. Agewall S, Hernberg A. Atorvastatin normalizes endothelial function in healthy smokers. *Clin Sci (Lond)* 2006;111(1):87–91. [PubMed: 16608440]
32. Iida K, Goland S, Akima T, Luo H, Birnbaum Y, Siegel RJ. Effect of a single 20-mg tablet of Atorvastatin on brachial artery blood flow in normolipidemic male smokers versus nonsmokers. *Am J Cardiol* 2007;100(5):881–884. [PubMed: 17719338]

33. Lippincott MF, Carlow A, Desai A, Blum A, Rodrigo M, Patibandla S, et al. Relation of endothelial function to cardiovascular risk in women with sedentary occupations and without known cardiovascular disease. *Am J Cardiol* 2008;102(3):348–352. [PubMed: 18638600]
34. Anton MM, Cortez-Cooper MY, DeVan AE, Neidre DB, Cook JN, Tanaka H. Cigarette smoking, regular exercise, and peripheral blood flow. *Atherosclerosis* 2006;185(1):201–205. [PubMed: 16046216]
35. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004;43(10):1731–1737. [PubMed: 15145091]
36. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, 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(5):344–353. [PubMed: 10206381]
37. Padilla J, Johnson BD, Newcomer SC, Wilhite DP, Mickleborough TD, Fly AD, et al. Normalization of flow-mediated dilation to shear stress area under the curve eliminates the impact of variable hyperemic stimulus. *Cardiovasc Ultrasound* 2008;6:44. [PubMed: 18771594]
38. Padilla J, Harris RA, Rink LD, Wallace JP. Characterization of the brachial artery shear stress following walking exercise. *Vasc Med* 2008;13(2):105–111. [PubMed: 18593799]

Figure 1.

Exercise capacity in smokers and nonsmokers with low (<10%) versus high (≥10%) brachial artery flow mediated dilation (FMD).

* significantly different than smokers with FMD < 10% ($p < 0.05$).

significantly different than non-smokers with FMD < 10% ($p < 0.05$).

Figure 2.

Exercise capacity in smokers and nonsmokers taking statins versus those not taking statins.

* significantly different than smokers/statin(-) ($p < 0.05$).

significantly different than non-smokers/statin(-) ($p < 0.05$).

Table 1

Patient characteristics.

<i>variable</i>	Smokers <i>n</i> = 26	Non-Smokers <i>n</i> = 39	<i>p</i> - value
Age, yrs	58 ± 2	58 ± 2	0.843
Body mass index, kg/m ²	28 ± 1	28 ± 1	0.652
Female, %	59	62	1.000
Hypertension, %	23	44	0.116
Dyslipidemia, %	23	44	0.116
Diabetes mellitus, %	12	5	0.382
Family History CVD, %	35	54	0.204
Medications, %			
Statin	32	24	0.565
ASA	11	8	0.676
Beta blocker	8	10	1.000
Calcium channel blocker	4	10	0.640
ACE inhibitor	12	15	0.731
Ejection Fraction, %	66 ± 1	64 ± 1	0.244
BAD, mm	3.7 ± 0.1	3.7 ± 0.1	0.984
NMD, %	21.3 ± 1.6	18.9 ± 0.9	0.153
FMD, % *	8.9 ± 0.9	12.6 ± 0.7	0.004
ETT, s *	425 ± 35	522 ± 25	0.022

* significant group difference (p<0.05).

Abbreviations: CVD, cardiovascular disease; ASA, aspirin; BAD, brachial artery diameter; NMD, nitroglycerin-mediated dilation; FMD, flow mediated dilation; ETT, exercise test time.

Table 2

Patient characteristics according to FMD < 10% versus FMD ≥ 10%.

<i>variable</i>	FMD < 10 %		FMD ≥ 10%	
	Smokers <i>n</i> = 16	Non-Smokers <i>n</i> = 11	Smokers <i>n</i> = 10	Non-Smokers <i>n</i> = 28
Age, yrs	57 ± 3	59 ± 3	58 ± 3	58 ± 2
Body mass index, kg/m ²	28 ± 1	30 ± 2	26 ± 1	27 ± 1
Female, %	53	60	67	68
Hypertension, %	20	50	38	39
Dyslipidemia, %	13	40	33	46
Diabetes mellitus, %	20	10	1	4
Family History CVD, %	28	50	56	50
BAD, mm	3.9 ± 0.1	3.9 ± 0.3	3.4 ± 0.3	3.5 ± 0.1
NMD, %	17.1 ± 1.7	14.3 ± 1.5	25.6 ± 3.0 ^{*#}	21.7 ± 1.0 [#]
FMD, %	6.0 ± 0.4	7.0 ± 0.3	14.1 ± 3.2 ^{*#}	14.6 ± 3.7 ^{*#}

* significantly different than smokers with FMD < 10% (p<0.05).

[#] significantly different than non-smokers with FMD < 10% (p<0.05).

Abbreviations: CVD, cardiovascular disease; BAD, brachial artery diameter; NMD, nitroglycerin-mediated dilation; FMD, flow mediated dilation.

Table 3

Patient characteristics according to statin use.

<i>variable</i>	Statin (-)		Statin (+)	
	Smokers <i>n</i> = 18	Non-Smokers <i>n</i> = 29	Smokers <i>n</i> = 8	Non-Smokers <i>n</i> = 10
Age, yrs	58 ± 2	58 ± 2	58 ± 3	57 ± 3
Body mass index, kg/m ²	28 ± 1	28 ± 1	27 ± 2	27 ± 1
Female, %	61	62	62	44
Hypertension, %	11	48	50	33
Dyslipidemia, %	11	31	50*	89*#
Diabetes mellitus, %	17	3	1	11
Family History CVD, %	22	52	62	56
BAD, mm	3.7 ± 0.2	3.7 ± 0.1	3.5 ± 0.2	3.6 ± 0.3
NMD, %	20.9 ± 1.9	18.3 ± 1.1	22.1 ± 3.1	20.3 ± 1.3
FMD, %	7.1 ± 0.8	11.5 ± 0.7*	13.0 ± 2.1*	15.5 ± 1.9*#

* significantly different than smokers/statin(-) (p<0.05).

significantly different than non-smokers/statin(-) (p<0.05).

Abbreviations: CVD, cardiovascular disease; BAD, brachial artery diameter; NMD, nitroglycerin-mediated dilation; FMD, flow mediated dilation.