Lower Extremity Blood Flow in Healthy Men: Effect of Smoking, Cholesterol, and Physical Activity — A Doppler Study

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Tobacco smoking is one of the principal risk factors of peripheral arterial disease (PAD); cholesterol level has a lesser impact. The effect of leisure-time physical activity (LTPA) has not been studied in depth. The aim of this study was to determine the relative effects of smoking, total cholesterol, and leisure-time physical activity on blood flow parameters in the lower extremities of healthy middle-aged men with no prior symptoms or diagnosis of PAD.

The authors examined 130 men, aged 40-65 years, free of known arterial disease and hypertension. The men had either a total cholesterol concentration of < 5.7 or > 7.0 mmol/L, and were either smokers or nonsmokers. LTPA was addressed by a questionnaire. Ankle-brachial index (ABI) was calculated and Doppler examination of the femoral artery was performed before and after an exercise test.

Tobacco smoking related significantly to abnormal ABI and Doppler results (odds ratio [OR] 2.42) while the total cholesterol level did not. LTPA had a favorable effect (OR 0.51). Abnormal ABI response was greatest in smokers with high total cholesterol ($p < 0.01$).

Tobacco smoking is a significant risk factor for abnormal ABI response and blood flow abnormalities in healthy men. Regular physical activity has a measurable protective effect. An abnormal ABI suggests early atherosclerosis and indicates risk factor assessment and physician intervention.

Introduction

Peripheral arterial disease (PAD) is a common and often underdiagnosed atherosclerotic process. The prevalence of PAD among the general adult population is highly age related and has been calculated to be between 12–14% and 20% among the elderly.[1] Intermittent claudication, also strongly age related, has a reported prevalence of 3–9% for 60–70-year-old men.[2] Tobacco smoking is best recognized among the risk factors that are believed to contribute importantly to the development of PAD in the lower extremities.[3-10] The Framingham, as well as the Reykjavik Study and several other studies, have demonstrated the important risk factors related to peripheral arterial disease.[7-11]

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The diagnosis of PAD is primarily clinical and is based on subjective symptoms from the lower extremities, ie, claudication and later pain at rest, cold sensation, numbness, and other symptoms of reduced or absent arterial circulation with severe complication and morbidity.[12,13] Long before the appearance of clinical symptoms, studies of blood flow to the lower extremities can detect changes that have predictable value for the progression of atherosclerosis and the later development of PAD.[14,15]

The ankle-brachial pressure index (ABI) measured by the Doppler method has been used for the diagnosis of early atherosclerosis in the lower extremity. Normal resting ABI is 1.0–1.3. Higher ABIs may result if noncompressible vessels are present. Total arterial occlusion is often indicated by an ABI < 0.5. Resting ABI < 0.9 or exercise-induced change of ≥ 0.15 suggests a high probability of significant atherosclerosis in the lower extremity (sensitivity of ABI approximately 94–95% and specificity 99–100%).[15-17] The usefulness of ABI for the diagnosis of PAD has been confirmed by angiography.[17,18] In an epidemiologic study the diagnosis of asymptomatic PAD by ABI < 0.9 was made in 18.2% of the subjects where the prevalence of claudication was 4.5%.[19] Arterial sonography and Doppler spectral analysis are newer investigative methods that have been used to estimate blood flow and atherosclerotic process in the arterial wall.[13,20,21]

Few studies have addressed the effect of physical exercise on the progression of atherosclerosis to PAD. However standard medical advice given to patients with PAD includes augmented regular physical activity such as walking.[22]

The purpose of this study was to estimate lower extremity blood flow in men free of known arterial disease and assess the relative effect of tobacco smoking, serum cholesterol, and leisure-time physical activity on the early indicators of arterial blood flow abnormality.

Methods

This study included 130 men, aged 40–65 years, who attended the Heart Preventive Clinic (HPC), conducting the Reykjavik Study, for cardiovascular risk consultation.

We sought to include men with both low and high cholesterol levels, in this study, those with a total cholesterol value of either < 5.7 or > 7.0 mmol/L, and approximately equal number of smokers and nonsmokers. Initially 180 men were selected; 135 agreed to attend the study, but 5 men were later excluded owing to total cholesterol values outside the specified range. At entry the subjects were free of known cardiovascular disease including hypertension and peripheral arterial disease. The mean age of the participants was 52 years. The mean cholesterol values were as follows: low cholesterol group 5.0 (range 3.5–5.7) mmol/L, high-density lipoproteins (HDL) 1.28 (range 0.7–2.02); and high cholesterol group 7.8 (range 7.0–9.8) mmol/L, HDL 1.25 (range 0.80–1.92).

The subjects attended the study after an overnight fast. They all answered a questionnaire on previous health, smoking habits, current medication, and leisure-time physical activity. Leisure-time physical activity (LTPA) questions were as follows: Do you participate in regular leisure-time physical activity (sports), yes/no? If yes, how many hours per week (< 5 hours/week or > 6 hours/week; winter and/or summer) and indicated active participation in leisure-time physical activity in 10-year incremental periods from age 20 to current age.

Venous blood samples were drawn for measurements of total cholesterol, HDL, triglycerides, and blood sugar. All chemical measurements were done by the HPC, as has been previously reported.[23] The study was approved by the Ethical Committee of the University Hospital and of The Data Protection Commission. A written informed consent was obtained from all enrolled subjects.

Total cholesterol levels and smoking habits divided the subjects into 4 groups, ie, smokers and nonsmokers with high and low cholesterol levels respectively. Fasting blood sugar was normal in all participants except for 3 individuals who had elevated blood sugar concentrations, 1 of whom was a known diabetic. All subjects had blood pressure measurements within normal limits (systolic blood pressure < 160 and/or diastolic blood pressure < 95 mm Hg) on 2 occasions.[23] Smokers were defined as those who were current tobacco smokers (mean calculated pack years, 45, range 16–94) and nonsmokers as never users. Participants were also divided into 3 groups depending on their leisure-time physical activity (LTPA). Those who had indicated regular leisure-time physical activity throughout their adult life were defined as the regularly physically active group. Irregular LTPA participation formed an intermediate group while lifetime non-LTPA participants formed the sedentary group.

Hemodynamic Measurements

We used Vasculab SA from Medasonics with bidirectional Doppler (8 MHz) and spectral analyzer. Systolic blood pressure was measured in both ankles and upper arms by using cuffs (40 cm × 13 cm) and a 5 MHz Doppler listening to signals from the posterior tibial and the brachial arteries. Doppler blood flow was obtained from a spectral analyzer and a 5 MHz Doppler from the common femoral artery (CFA) before and after exercise. The same technologist (LPÁ) performed all studies. The following measurements were made at rest and repeated following exercise: Heart rate, systolic blood pressure in both arms and ankles, and Doppler spectral analysis in both common femoral arteries. ABI was calculated by using the higher measurement of the arms. An exercise test was performed using ergo-bicycle at 100 W for 5 minutes. To minimize error in the postexercise ABI, we always measured blood pressure at the right ankle first and then the brachial artery pressure and finally pressure at the left ankle. The change in ABI (Δ ABI) after stress test was calculated as well as the change in peak blood flow velocity. Since peripheral arterial disease often occurs unilaterally we used the lower value of the measured ABI.[10]

Statistical Analysis

The change in ABI between rest and exercise was categorized as critical and noncritical. To evaluate the association of this dependent variable and

Table I. Baseline values: Effect of smoking and cholesterol on blood flow indices.

Groups	Nonsmokers		Smokers	
	Low Cholesterol	High Cholesterol	Low Cholesterol	High Cholesterol
Number	37	31	32	30
Age, years (sd)	53 (5)	51 (5)	54 (5)	51 (7)
Cholesterol, mmol/L (sd)	5.04 (0.48)	7.83 (0.74)	4.94 (0.59)	7.67 (0.67)
HDL, mmol/L (sd)	1.31 (0.27)	1.33 (0.28)	1.23 (0.33)	1.17 (0.23)
Triglycerides, mmol/L (sd)	0.99 (0.75)	1.54 (0.75)	1.12 (0.50)	1.42 (0.51)
Heart rate at rest (sd)	64 (9)	62 (10)	69 (12)	68 (9)
Max heart rate (sd)	98 (16)	101 (14)	101 (16)	104 (15)
Peak blood flow at rest, m/sec (sd)	1.32 (0.26)	0.96 (0.14)	1.29 (0.41)	1.40 (0.61)
(range) median	(0.77–1.87) 1.22	(0.79–2.61) 1.24	(0.59–2.42) 1.26	(0.60–3.90) 1.30
Peak blood flow after exercise	1.87 (0.41)	1.34 (0.27)	2.32 (0.68)	2.31 (0.89)
(range) median	(1.04–2.61) 1.83	(0.84–3.06) 1.80	(1.18–3.99) 2.22	(1.18–4.80) 1.90
Δ Peak blood flow, m/sec	0.57 (0.38)	0.38 (0.24)	1.03 (0.57)	0.91 (0.59)
(range) median	(−0.12–1.37) 0.49	(−0.52–1.46) 0.63	(0.19–2.55) 0.90	(0.06–2.54) 0.78

Change in peak blood flow velocity = Δ Peak blood flow.
Results are given as mean with a calculated standard deviation (sd).

the categorical variables: smoking (yes/no), leisure time physical activity (none/moderate/considerable), and cholesterol level (high/low), we applied multiple logistic regression analysis. These 3 variables were unconditionally entered into the model to give an estimate of the effect of each of the variables, as an adjusted odds ratio (OR) with its 95% confidence interval (CI). The proportion of the "variation" explained by the model is 13.5% (Nagelkerke R2). The significance level was set at 0.05. The analysis was done with the SPSS 9.0 program package.

The risk relationship associated with lowered ABI was derived from Chi-square test for linear trend. Difference between groups was determined by Student's unpaired t test. Blood flow parameters were compared by using the Mann-Whitney test. Change in peak blood flow was calculated by using Pearson two-tailed correlation.

Results

The study included 130 healthy men with no known cardiovascular disease. Baseline characteristics and the relative effect of smoking and cholesterol on blood flow parameters may be seen in Table I. Peak blood flow velocity at rest tended to be highest in smokers with high cholesterol. Following exercise, the velocity of blood flow was higher in smokers compared to nonsmokers while cholesterol levels seemed to have lesser effect. (Resting and exercise heart rate did not differ significantly among these groups.) The mean HDL-cholesterol in nonsmokers was calculated as 1.32 (±0.27) mmol/L and as 1.20 (±0.29) mmol/L in smokers, a statistically significant difference ($p < 0.02$).

ABI was calculated for the 4 groups and the results are depicted in Figure 1. The number of subjects with abnormal response, ie, $\Delta ABI \geq 0.15$, was greatest in smokers with high total cholesterol (p for trend < 0.01).

Blood flow parameters in smokers vs nonsmokers independent of cholesterol value as well as for groups with high and low cholesterol independent of smoking habits are shown in Table II. Smoking had a significant effect on peak Doppler blood flow after exercise compared to nonsmokers, with peak blood flow velocity of 1.92 in nonsmokers and 2.32 m/sec in smokers ($p < 0.01$), while blood flow velocity was not dependent on cholesterol levels. ABI calculation for the groups in Table II is depicted in Figure 2.

The calculated exercise-induced ABI ratio difference between smokers and nonsmokers of 24% vs 44% was statistically significant ($p < 0.03$) while high vs low cholesterol values did not impact significantly on the ABI ratio.

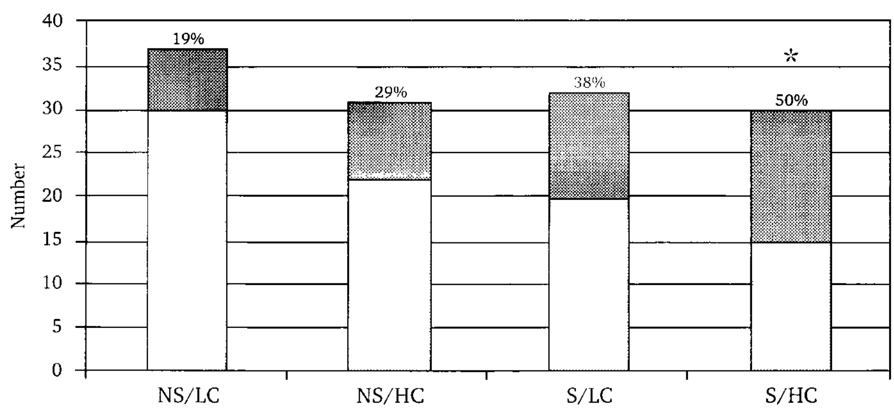

Figure 1. The ratio of abnormal response to exercise as measured by ABI in the 4 groups from Table I. Dark-shaded bars indicate $\Delta ABI \geq 0.15$ or absolute ABI < 0.9 following exercise; light-shaded bars indicate normal exercise response, ie, $\Delta ABI < 0.15$. The calculated trend in ΔABI was statistically significant; *$p < 0.01$. (NS/LC = nonsmoker/low cholesterol; NS/HC = nonsmoker/high cholesterol; S/LC = smoker/low cholesterol; S/HC = smoker/high cholesterol.)

Table II. Blood flow parameters: Smoking habits independent of cholesterol values; cholesterol levels independent of smoking habits.

	Nonsmokers LC/HC	Smokers LC/HC	Low Cholesterol NS/S	High Cholesterol NS/S
Number	68	62	69	61
Peak blood flow at rest, m/sec (sd)	1.30 (0.29)	1.35 (0.51)	1.29 (0.33)	1.36 (0.49)
(range) median	(0.76–2.61) 1.22	(0.59–3.90) 1.29	(0.59–2.42) 1.22	(0.60–3.90) 1.27
Peak blood flow after exercise	1.92 (0.47)	2.32 (0.77)*	2.08 (0.59)	2.15 (0.75)
(range) median	(0.84–3.06) 1.81	(1.18–4.80) 2.13	(1.04–3.99) 1.98	(0.84–4.80) 1.84
Δ Peak blood flow, m/sec	0.59 (0.44)	0.97 (0.58)**	0.79 (0.53)	0.75 (0.56)
(range) median	(0.86–1.46) 0.59	(0.06–2.55) 0.81	(–0.12–2.55) 0.66	(–0.86–2.54) 0.67

LC/HC = low and high cholesterol groups; NS/S = nonsmoking and smoking groups. Change in peak blood flow velocity = Δ Peak blood flow. Results are given as mean with a calculated standard deviation (sd). *$p < 0.01$; **$p < 0.01$).

Effects of differential participation in leisure-time physical activity on heart rate and blood-flow parameters are shown in Table III. Men who reportedly engaged in regular leisure-time physical activity had lower peak blood flow velocity with bicycle exercise compared to those who never exercise. Those responders who perform leisure-time physical activity irregularly formed an intermediate group with respect to blood flow parameters. The difference in peak blood flow parameters before and after exercise tended to be highest in the nonphysically active group (p for trend < 0.04). This is further illustrated in Figure 3. The number of subjects with Δ ABI ≥ 0.15 was greatest in men who do not participate in leisure-time physical activity, where 48% of men in the nonactive group showed lowering of the ABI ratio compared to 18% in the regular leisure-time physical activity group (p for trend < 0.01).

Logistic regression analyses was performed (Table IV). Tobacco smoking was found to increase the probability of an abnormal ABI response with an odds ratio of 2.42. Total cholesterol level did not have an independent adverse effect. Leisure-time physical activity was associated with a significant protective effect (odds ratio 0.51, $p = 0.023$).

Discussion

The results of this study indicate that arterial blood flow to the lower extremities, in a group of middle-aged men without known arterial disease, is greatly dependent on tobacco smoking and leisure-time physical activity. Total serum cholesterol concentration does not seem to have an independent effect on the arterial blood flow parameters as measured in our study. The data indicate, however, clear synergistic effects between high cholesterol and smoking on these parameters and, hence, on arterial blood flow, suggesting atherosclerosis and an early PAD in middle-aged smokers with a high total cholesterol level. Furthermore, bicycle exercise brings to light a clearly measurable abnormality in blood flow to the lower extremities in male smokers.

Tobacco smoking and diabetes mellitus have been found to be the 2 strongest risk factors for PAD.[7,9-11] Cigarette smoking is known to affect walking distance and exercise tolerance in subjects with PAD.[23] Epidemiologic studies have indicated a clear association of serum cholesterol concentration to claudication and PAD, whereas the magnitude of the effect has been found to be much smaller than for diabetes and tobacco

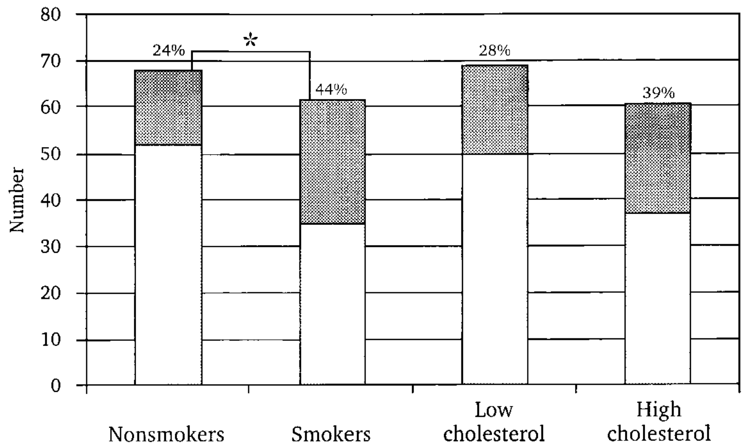

Figure 2. The effect of exercise on ABI in subjects with high versus low cholesterol values and in smokers versus nonsmokers. Dark-shaded bars indicate ΔABI ≥ 0.15 or absolute ABI < 0.9 following exercise; light-shaded bars indicate normal exercise response, ie, ΔABI < 0.15. Abnormal response was significant for smokers compared to nonsmokers, $^{*}p < 0.03$, while cholesterol levels did not have a statistically significant effect.

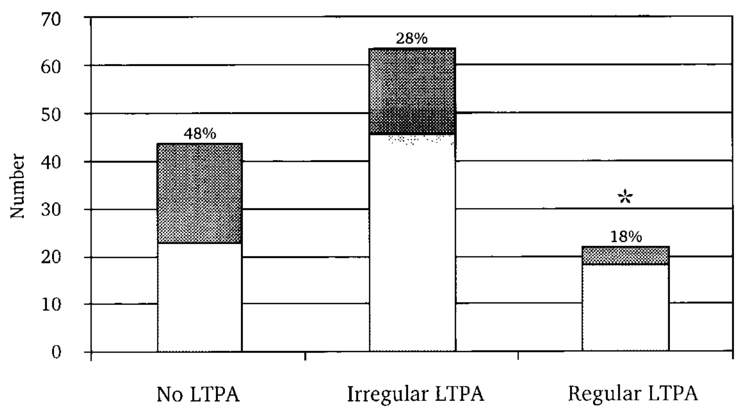

Figure 3. The response of ABI to exercise is indicated by the graph. Dark-shaded bars indicate ΔABI ≥ 0.15 or absolute ABI < 0.9 following exercise; light-shaded bars indicate normal exercise response. Calculated trend in ΔABI was statistically significant, $^{*}p < 0.01$.

smoking.[2,3,9,11] We have now extended some of these observations to the asymptomatic male smoker.

Several studies have shown the preventive effects of regular physical activity on cardiovascular diseases and stroke,[24-27] Exercise training has been shown to be an effective treatment option for subjects with PAD and symptomatic claudication.[28-30] The results of our study clearly indicate the preventive effects of regular leisure-time physical activity on blood flow parameters where an abnormal ABI was found in a significantly higher proportion of a nonactive versus an active group of middle-aged men.

Physical activity has complex physiologic effects. It has been demonstrated to affect favorable changes in the lipoprotein profile and may reduce thrombotic potential through en-

Table III. Effect of leisure-time physical activity on blood flow parameters.

	No LTPA	Irregular LTPA	Regular LTPA
Number (% of all)	44 (34)	64 (49)	22 (17)
Smokers, %	55	44	45
Heart rate at rest (sd)	67 (9)	66 (10)	63 (11)
(range) median	(48–90) 66	(44–96) 66	(46–84) 60
Max heart rate (sd)	105 (14)	101 (15)	95 (18)*
(range) median	(72–132) 108	(60–132) 96	(72–128) 90
Peak blood flow at rest, m/sec (sd)	1.47 (0.59)	1.27 (0.25)	1.30 (0.36)
(range) median	(0.59–3.90) 1.34	(0.73–1.83)1.21	(0.78–2.18) 1.34
Peak blood flow after exercise, m/sec(sd)	2.47 (0.81)	2.10 (0.53)	2.04 (0.52)
(range) median	(1.18–4.80) 2.15	(1.12–3.99) 2.08	(1.16–3.38) 1.96
Δ Peak blood flow, m/sec (sd)	1.00 (0.51)	0.83 (0.5)	0.74 (0.44)
(range) median	(0.20–2.54) 0.89	(0.06–2.55) 0.69	(0.27–1.93) 0.66

LTPA = Leisure-time physical activity; sd = standard deviation. Change in peak blood flow velocity = Δ Peak blood flow. *$p < 0.044$.

Table IV. Calculated odds ratio (OR) for PAD with 95% confidence interval (CI).

	OR	CI	p Value
Smoking	2.42	(1.12–5.26)	0.025
Cholesterol	1.49	(0.69–3.25)	0.312
LTPA	0.51	(0.28–0.91)	0.023

LTPA = Leisure-time physical activity; PAD = peripheral arterial disease.

hanced fibrinolytic activity and reduced platelet adhesiveness.[26,31]

Peripheral arterial disease is clearly associated with a reduced long-term prognosis.[2,6,9] The Edinburgh Artery Study has demonstrated an increased risk of myocardial infarction and stroke associated with asymptomatic arterial disease diagnosed by ABI; furthermore, the abnormal ABI identified a group of people at an increased risk of premature death.[32]

Hence, the identification of subjects with an asymptomatic arterial disease may have a significant health impact. Low-cost but effective treatment options such as smoking cessation; an increased regular physical activity, with at least 30 minutes of walking 3 times a week; and aspirin therapy are obviously indicated. Eventually, further treatment modalities with lipid-lowering drugs may also need to be considered.

Our study may be limited by a relatively small number of participants and may therefore underestimate the true effects of elevated cholesterol and the potentially ameliorating effect of a high HDL-cholesterol. The relative contribution of smoking and blood lipids should not, however, be biased. Extending the results to effects in women must be done with caution. The "self-reported" participation in regular physical activity may be overestimated by the study participants and, hence, would probably serve to reduce the magnitude of the actual effect of regular leisure-time exercise.

In summary, Doppler indices of abnormal arterial blood flow in middle-aged men relate more strongly to tobacco smoking than to elevated total cholesterol, while combined, these vascular risk factors further enhance blood flow abnormalities. Conversely, regular leisure-time physical activity reduced the prevalence of those abnormalities and may be associated with beneficial effects of physical exercise. Furthermore, Doppler indices of blood flow may serve as a target for aggressive risk factor management.

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