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Impaired Peripheral Circulation in Veterans with Claudication is Associated with Smoking

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Abstract

We compared the peripheral vascular function of veterans and non-veterans with peripheral artery disease (PAD) and claudication. The circulation of the lower extremities was assessed under rest and reactive hyperemia conditions in 413 veterans and in 83 non-veterans. Veterans had more severe PAD as measured by a lower ankle/brachial index ($p<0.001$). Following the occlusive test, veterans had a greater relative percentage decrease in ankle systolic blood pressure ($p=0.015$), a greater percentage decrease in calf transcutaneous oxygen tension ($p=0.035$), and a blunted percentage increase in calf blood flow ($p=0.031$). After adjustment for current smoking status, these measures were no longer statistically different between the veterans and non-veterans. We conclude that veterans with PAD and claudication have greater impairments in macrovascular and microvascular function of the lower extremities, and greater severity of PAD than compared to non-veterans, and that these factors were primarily associated with their higher prevalence of smoking. The greater compromise in peripheral vascular measures in veterans is particularly noteworthy given that the prevalence of diabetes, hypertension, and dyslipidemia were not higher.

Keywords: Claudication; Peripheral artery disease; Peripheral circulation; Veterans

Abbreviations

ABI: Ankle/Brachial Index; MVAHCS: Maryland Veterans Affairs Health Care System; PAD: Peripheral Artery Disease; PORH: Post-Occlusive Reactive Hyperemic; $Tcpo_2$: Transcutaneous Oxygen Tension; US: United States

Introduction

Peripheral artery disease (PAD) is prevalent in eight million men and women in the United States and in more than 12% of community dwelling people aged 65 years and older [1,**2**]. PAD is associated with increased prevalence of coexisting diseases in the coronary, cerebral, and renal arteries [2,3]. More than 60% of those with PAD have concomitant cardiovascular and/or cerebrovascular disease thereby contributing to their elevated rates of cardiovascular mortality [3-5]. The cost associated with PAD is comparable to, if not higher than cardiac dysrhythmias, congestive heart failure and cerebrovascular disease, averaging $3.9 billion for total Medicare paid PAD-related care annually [6]. Many of those with PAD are physically limited by ambulatory leg pain, resulting in ambulatory dysfunction, impaired physical function lower physical activity levels and even worse health-related quality of life scores than in individuals with coronary artery disease and congestive heart failure [7-13]. Furthermore, PAD patients have increased rates of functional decline and mobility loss compared to those without PAD [9,10,14].

Veterans typically have more severe PAD than non-veteran US males, and at much younger ages, requiring higher rates of medical interventions [**15**]. Veterans 45 to 64 years of age had a rate roughly 10 times higher for each of three vascular procedures (angioplasty, proximal bypass, distal bypass) as compared to the US male population [**15**]. Not only does this expose veterans to higher risk of mortality, but it also means that veterans carry a costly health care burden associated with PAD and numerous co-morbid conditions for many years. Little data is available, however, on veterans who have milder severity of PAD, such as claudication, that does not require vascular intervention. Thus, greater impairments in peripheral macrovascular and microvascular measures in veterans with claudication than in non-veterans, as well as greater comorbid burden may provide insights into why veterans progress to severe PAD at younger ages than non-veterans with claudication.

The purpose of this study was to compare the peripheral vascular function of veterans and non-veterans with PAD and claudication. We hypothesized that veterans with claudication have greater impairments in both macrovascular and microvascular function and greater severity of PAD than compared to non-veterans.

Methods

Patients

Recruitment: A total of 628 veterans and non-veterans with PAD and stable symptoms of claudication were evaluated in the Geriatrics, Research, Education, and Clinical Center at the Maryland Veterans Affairs Health Care System (MVAHCS) at Baltimore. Patients were

recruited from the Vascular Clinic at the site of the Baltimore MVAHCS, and from the Vascular Clinic at the University of Maryland at Baltimore. The Institutional Review Boards at the University of Maryland and the MVAHCS at Baltimore approved the procedures used in this study. Written informed consent was obtained from each patient prior to investigation.

Screening: Patients were included in this study if they had Fontaine stage II PAD defined by the following inclusion criteria: (a) a history of claudication, (b) ambulation during a graded treadmill test limited by claudication and (c) an ankle/brachial index (ABI) at rest <0.90 [7,16,**17**]. Patients were excluded from this study for the following conditions: (a) absence of PAD, (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD (Fontaine stage I), (d) rest pain PAD (Fontaine stage III), (e) use of medications indicated for the treatment of claudication (cilostazol and pentoxifylline) within three months prior to investigation, (f) exercise tolerance limited by any disease process other than PAD, (g) end stage renal disease defined as stage 5 chronic kidney disease, (h) abnormal liver function. A total of 496 patients were deemed eligible for this investigation, whereas 132 patients were ineligible. All patients lived independently at home.

Measurements

Medical History: Demographic information, height, weight, cardiovascular risk factors, co-morbid conditions, claudication history, and a list of current medications were obtained during a physical examination and medical history interview to begin the evaluation.

ABI: After 10 minutes of supine rest, the ankle and brachial systolic blood pressures were obtained as previously described [**18**]. The ABI was calculated as ankle systolic pressure/brachial systolic pressure. The test-retest intraclass reliability coefficient is R=0.96 for ABI [**7**].

Peripheral Vascular Test: Ankle systolic blood pressure, calf blood flow, and calf transcutaneous oxygen tension ($TcPO_2$) measures of the lower extremities were assessed under rest and reactive hyperemia conditions. The rest period consisted of the patients lying supine for 10 minutes. The reactive hyperemic test was then performed while patients were in the supine position by inflating a thigh blood pressure cuff to at least 200 mmHg to induce arterial occlusion for three minutes. Post-occlusive reactive hyperemic (PORH) peripheral hemodynamic measures were obtained within the first minute following the three-minute occlusion.

Ankle Systolic Blood Pressure: Ankle systolic pressure was measured with a Parks Medical Electronics, Inc. non-directional Doppler flow detector (Model 810-A, Aloha, OR), a pencil probe (9.3 MHZ), and standard size ankle blood pressure cuffs (10 cm width). Measurements were taken from the posterior tibial and dorsalis pedis arteries in both legs. The higher of the two arterial pressures from the more severely diseased leg was recorded as the ankle systolic pressure. Brachial blood pressures were measured from arms with a Critikon Dinamap Vital Signs Monitor (Model 1846-SX), using either a standard adult size blood pressure cuff (14 cm width) or a large adult size cuff (17 cm width). Brachial systolic pressure and diastolic pressure were recorded from the arm yielding the higher systolic pressure. From these measures, ABI was calculated as ankle systolic pressure / brachial systolic pressure.

Calf Blood Flow: Calf blood flow in the more severely diseased leg was obtained by venous occlusion strain-gauge plethysmography. A mercury strain gauge was placed around the calf at the maximal circumference, and arterial blood flow to the foot was temporarily occluded by an ankle cuff inflated to 300 mmHg. Calf blood flow was measured by inflating a thigh cuff to a venous occlusion pressure of 50 mmHg. The ankle and thigh cuffs were deflated immediately after the calf blood flow measurement was obtained. The test-retest intraclass reliability coefficient is R=0.86 for calf blood flow [**19**].

Calf TcPO: Calf $TcPO_2$ was measured on the medial portion of the calf musculature with a Clark-type polarographic heated electrode maintained at 44ºC and a Transcutaneous Oxygen Monitor (Novametrix Medical System, Model 818). These peripheral hemodynamic measurements obtained from our laboratory are highly reliable in PAD patients with claudication [7,8,20]. The test-retest intraclass reliability coefficient is R=0.87 for calf $TcPO_2$ [**21**].

Statistical Analyses

Unpaired t-tests and chi-square tests were used to assess whether differences in the clinical characteristics existed between the veterans and non-veterans with PAD. Pearson product-moment correlation coefficients were calculated to assess whether clinical characteristics were associated with peripheral vascular measures. One-factor analysis of covariance (ANCOVA) was used to compare the peripheral vascular measures in the veterans and non-veterans after adjusting for current smoking status. All analyses were performed with a two-tailed significance level of 0.05. Analyses were conducted using the SPSS statistical package version 15.0 (Chicago, IL). Measurements are presented as means ± standard deviations.

Results

The clinical characteristics of the veterans and non-veterans with PAD and claudication are displayed in Table 1. Veterans were older ($p<0.001$) and had lower values for body weight ($p<0.001$), BMI ($p<0.001$), ABI ($p<0.001$), reported walking distance to claudication ($p=0.026$), and prevalence of obesity ($p=0.023$) than the non-veterans. Additionally, veterans had a higher prevalence of smoking ($p<0.001$) and coronary artery disease ($p<0.001$), both of which may have contributed to their higher prevalence of dyspnea ($p<0.001$). The two groups were similar on the duration of being symptomatic with claudication, race, diabetes, hypertension, dyslipidemia, stroke, and chronic obstructive pulmonary disease ($p>0.05$).

Variables	Non-Veterans (n=83)	Veterans (n=413)	p Value
Age (years)	62 (11)	68 (8)	<0.001
Weight (kg)	92.8 (20.6)	84.9 (15.8)	<0.001
Body Mass Index	30.2 (5.9)	28.1 (4.7)	<0.001
Ankle/Brachial Index	0.80 (0.25)	0.64 (0.30)	<0.001
Duration of IC (years)	4.5 (6.8)	4.9 (5.8)	0.707
Walking Distance to IC (blocks)	2.9 (2.6)	2.2 (1.9)	0.026
Race (% Caucasian)	80	70	0.06
Current Smoking (% yes)	16	35	0.001
Diabetes (% yes)	19	25	0.271
Medication Use (%)	18	21	0.356

Hypertension (% yes)	59	65	0.272
Medication Use (%)	54	54	0.824
Hyperlipidemia (% yes)	41	47	0.298
Medication Use (% yes)	37	43	0.406
Obesity (% yes)	41	29	0.023
Lower Extremity Revascularization (% yes)	11	12	0.702
Coronary Artery Disease (% yes)	24	49	0.001
Cerebrovascular Accident (% yes)	8	13	0.287
Chronic Obstructive Pulmonary Disease (% yes)	16	13	0.49
Dyspnea (% yes)	29	48	0.001
IC: Intermittent claudication. Obesity was defined as having a body mass index >30 kg/m^2			

Table 1: Clinical characteristics of veterans and non-veterans with peripheral artery disease and claudication. Values are means (SD) and percentages.

We assessed whether the clinical characteristics were related to the peripheral vascular parameters, and found that smoking was the strongest correlate with the percentage increase in calf blood flow with hyperemia (r=-0.29, p<0.001), and the percentage decreases in ankle systolic pressure (r=-0.25, p<0.001) and in calf TcPO2 (r=-0.31, p<0.001). Thus, current smoking status was selected as a covariate in subsequent analyses on the peripheral vascular measurements.

The ankle systolic blood pressure measurements in veterans and non-veterans with PAD and claudication are shown in Table 2. The ankle systolic pressure was lower in the veterans at rest (p<0.001), and during hyperemic conditions (p<0.001). Furthermore, the veterans had a greater decrease in ankle systolic blood pressure following the occlusive test, expressed as an absolute decrease in ankle systolic pressure (p=0.027) and a relative percentage decrease (p=0.015). After adjustment for smoking, the group difference in ankle systolic pressure during hyperemic conditions remained (p=0.042), but the other measures were no longer significantly different between the veterans and non-veterans.

The calf blood flow measurements in veterans and non-veterans with PAD and claudication are shown in Table 3. The calf blood flow was not different between the two groups at rest (p=0.487) or during hyperemic conditions (p=0.155). However, the veterans had a blunted increase in calf blood flow following the occlusive test, expressed as an absolute increase in calf blood flow (p=0.043) and a relative percentage increase (p=0.031). After adjustment for smoking, these measures were no longer statistically different between the veterans and non-veterans.

Variables	Non-Veterans (n=83)	Veterans (n=413)	Unadjusted P Value	Adjusted P Value*
Ankle SBP at Rest (mmHg)	133 (35)	115 (43)	<0.001	0.054
Ankle SBP during Hyperemia (mmHg)	130 (41)	108 (49)	<0.001	0.042
Absolute Change in Ankle SBP from Rest to Hyperemia (mmHg)	-2.4 (15.9)	-6.6 (15.7)	0.027	0.154
Relative Change in Ankle SBP from Rest to Hyperemia (%)	-3.0 (14.0)	-8.2 (18.2)	0.015	0.145
SBP: Systolic blood pressure. *Adjusted for current smoking.				

Table 2: Ankle systolic blood pressure measurements in veteran and non-veterans with peripheral artery disease and claudication. Values are means (SD).

Variables	Non-Veterans (n=83)	Veterans (n=413)	Unadjusted P Value	Adjusted P Value*
Calf Blood Flow at Rest (%/min)	3.65 (1.59)	3.52 (1.53)	0.487	0.906
Calf Blood Flow during Hyperemia (%/min)	9.56 (6.58)	7.58 (5.01)	0.155	0.37
Absolute Change in Calf Blood Flow from Rest to Hyperemia (%/min)	5.91 (5.84)	4.06 (4.58)	0.043	0.343
Relative Change in Calf Blood Flow from Rest to Hyperemia (%)	166 (156)	115 (144)	0.031	0.807

*Adjusted for current smoking

Table 3: Calf blood flow measurements in veteran and non-veterans with peripheral artery disease and claudication. Values are means (SD).

The calf $TcPO_2$ measurement in veterans and non-veterans with PAD and claudication are shown in Table 4. The calf $TcPO_2$ was not different between the two groups at rest (p=0.977) or during hyperemic conditions (p=0.114). However, the veterans had a greater decrease in calf $TcPO_2$ following the occlusive test, expressed as an absolute decrease in calf $TcPO_2$ (p=0.044) and a relative percentage decrease (p=0.035). After adjustment for smoking, these measures were no longer statistically different between the veterans and non-veterans.

Variables	Non-Veterans (n=83)	Veterans (n=413)	Unadjusted P Value	Adjusted P Value*
Calf $TcPO_2$ at Rest (mmHg)	37.2 (16.0)	37.2 (17.0)	0.977	0.536
Calf $TcPO_2$ during Hyperemia (mmHg)	31.4 (19.6)	27.7 (19.6)	0.114	0.686
Absolute Change in Calf $TcPO_2$ from Rest to Hyperemia (mmHg)	-6.0 (16.1)	-9.5 (16.8)	0.044	0.333
Relative Change in Calf $TcPO_2$ from Rest to Hyperemia (%)	-7 (97)	-23 (54)	0.035	0.286
$TcPO_2$: Transcutaneous oxygen tension. *Adjusted for current smoking.				

Table 4: Calf transcutaneous oxygen tension measurements in veteran and non-veterans with peripheral artery disease and claudication. Values are means (SD).

Discussion

The novel findings of this investigation were that veterans with claudication had more severe PAD and greater impairment in both macrovascular and microvascular function of the lower extremities than non-veterans, and that this was primarily associated with their higher prevalence of smoking.

Veterans have worse PAD and macrovascular function than non-veterans

Although both groups had claudication, the veterans had more severe PAD than the non-veterans as indicated by a lower ABI. Furthermore, the veterans had greater impairments in macrovascular function, as measured by lower ankle systolic blood pressure at rest and one minute following the reactive hyperemia test. When the ankle SBP data was expressed as change scores the group differences were much larger, as the veterans had greater decrease in the change score and the percentage change of ankle systolic blood pressure than the non-veterans. The reduction in ankle systolic blood pressure following the reactive hyperemia test is due to a decrease in vascular resistance in the proximally located calf musculature, which shunts the already compromised blood flow away from cutaneous tissue and from the distally located dorsalis pedis and posterior tibial arteries [22]. The greater reductions in ankle systolic blood pressure in veterans after an occlusive vascular challenge indicates that the greater limitations in the macrovasculature becomes more evident when the lower extremities are stressed.

Veterans have more impaired microvascular function than non-veterans

Greater impairments in microvascular function were seen in the veterans, as they had lower increases in the absolute and percentage changes in calf blood flow from rest to hyperemia than the non-veterans We have previously shown that calf blood flow measures are associated with endothelial function in patients with PAD, as measured by the percentage change in brachial artery diameter [23]. Consequently, calf blood flow measures represent markers of endothelial function in patients with PAD. Our current finding that veterans have worse calf blood flow is not surprising since they also have more severe PAD, indicated by lower ABI. This supports earlier work that found endothelial function to be worse with more severe PAD [24]. Although other factors are independently related to impaired endothelial function in patients with PAD, such as systolic blood pressure, fasting glucose, and the ratio of low density to high density lipoprotein cholesterol these factors cannot explain the worse calf blood flow in veterans in the current study because these measures were not different between the two groups [25]. Rather, the current investigation demonstrates that the higher prevalence of smoking in veterans explains their greater impairment in microvascular function, thus supporting previous reports showing the detrimental influence of smoking on peripheral circulation in patients with PAD [26,27].

Further evidence that the veterans had more impaired microvascular function than the non-veterans is seen with the calf $TcPO_2$ data. The veterans had greater declines in the absolute and percentage changes in calf TcPO2 from rest to hyperemia than the non-veterans. The reduction in the calf $TcPO_2$ following the occlusion phase of the reactive hyperemic test indicates that ischemia persists in the cutanaeous tissue for several minutes during hyperemia, and supports our previous observations noted with post-occlusive reactive hyperemia tests and treadmill exercise tests [18,28,29]. The reduction in calf $TcPO_2$ is due to the vasodilation in the calf musculature, thereby compromising the oxygen delivery to the cutaneous tissue of the calf a phenomenon known as vascular steal [30]. Our data indicates that the veterans with PAD had greater compromise in the microcirculation of the cutaneous tissue in the calf compared to the non-veterans. The lower calf $TcPO_2$ in the veterans is related to their more severe PAD and their greater prevalence of smoking, as both of these factors are associated with $TcPO_2$ measures of the lower extremity [27,28]. When all of the peripheral vascular measures are considered, the veterans appear to be particularly compromised in their perfusion of their lower extremities because they have more severe PAD than the non-veterans, as well as greater impairments in both macro vascular function and microvascular function.

Limitations

There are several limitations to this study. Patients with PAD who participated in this trial were volunteers and therefore may represent those who were more interested in their health, who had better access to transportation to our research center, and who had relatively better health than patients who did not volunteer. The cross-sectional design comparing veterans and non-veterans with PAD does not allow causality be established, as it is possible that less favorable peripheral vascular measures could either be associated with or a consequence of being a veteran. The results are generalizable to patients with PAD who have claudication. Thus, the present findings cannot be generalized to patients with asymptomatic PAD, to patients with more

severe PAD who have critical limb ischemia, or to those who are limited in their exercise performance by other significant co-morbid conditions. Another limitation is that habitual alcohol and caffeine intake were not measured, and these factors may influence the peripheral vascular measures. A final limitation is that, by design, all of the participants were men. The veterans were all men, and therefore we needed to compare them with men who were not veterans. Despite study participation being limited to men, African-Americans are well represented, and typical risk factors for PAD such as smoking, diabetes, hypertension, dyslipidemia, and obesity are highly prevalent. Thus, in men with PAD and claudication, the findings of the present study are generalizable to the large proportion of men with PAD who have numerous co-morbid conditions.

Conclusion and Clinical Significance

We conclude that veterans with PAD and claudication have greater impairments in macrovascular and microvascular function of the lower extremities, and greater severity of PAD than compared to non-veterans, and that these factors were primarily associated with their higher prevalence of smoking. The greater compromise in peripheral vascular measures and more severe PAD in veterans are particularly noteworthy given that the prevalence of other key cardiovascular risk factors for PAD, such as diabetes, hypertension, and dyslipidemia were not higher than compared to non-veterans. The clinical significance is that impairments in macrovascular and microvascular function may be early markers for poor vascular outcomes in veterans with PAD and claudication.

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