

## Research Article

# Peripheral Circulation of Veterans and Non-Veterans with Peripheral Artery Disease and Claudication

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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 ( $p = 0.031$ ). 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. The greater compromise in peripheral vascular measures in veterans is particularly noteworthy given that the prevalence of diabetes, hypertension, and dyslipidemia were not higher.

## ABBREVIATIONS

ABI: Ankle/Brachial Index; MVAHCS: Maryland Veterans Affairs Health Care System; PAD: Peripheral Artery Disease; PORH: Post-Occlusive Reactive Hyperemic; TcPO<sub>2</sub>: Transcutaneous Oxygen Tension; US: United States

## INTRODUCTION

Peripheral Artery Disease (PAD) is prevalent in eight million men and women in the United States [1], and in more than 12% of community dwelling people aged 65 years and older [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 [3], thereby contributing to their elevated rates of cardiovascular mortality [4,5]. 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 [7,8], impaired physical function [9,10], lower physical activity levels [11,12], and even worse health-related quality of life scores than in individuals with coronary artery disease and congestive heart

failure [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 interventions. Greater impairments in peripheral vascular measures in veterans with claudication than in non-veterans may provide insight 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 [16] defined by the following inclusion criteria: (a) a history of claudication, (b) ambulation during a graded treadmill test limited by claudication [7], and (c) an ankle/brachial index (ABI) at rest < 0.90 [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 mm Hg 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 both 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 mm Hg. Calf blood flow was measured by inflating a thigh cuff to a venous occlusion pressure of 50 mm Hg. 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  $TcPO_2$ :** Calf  $TcPO_2$  was measured on the medial portion of the calf musculature with a Clark-type polarographic heated electrode maintained at 44 °C and a Transcutaneous Oxygen Monitor (Novamatrix Medical System, Model 818). These peripheral hemodynamic measurements obtained from our laboratory are highly reliable in PAD patients with claudication [7,19,20]. 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. 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  $\pm$  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 ( $p < 0.001$ ), coronary artery disease ( $p < 0.001$ ), and 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 ( $p > 0.05$ ).

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

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

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	0.060
Current Smoking (%)	16	35	0.001
Diabetes (%)	19	25	0.271
Hypertension (%)	59	65	0.272
Hyperlipidemia (%)	41	47	0.298
Obesity (%)	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	0.490
Dyspnea (% yes)	29	48	0.001

IC = Intermittent Claudication. Obesity was defined as having a body mass index  $\geq 30$  kg / m<sup>2</sup>.

**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)	P Value
Ankle SBP at Rest (mmHg)	133 (35)	115 (43)	< 0.001
Ankle SBP during Hyperemia (mmHg)	130 (41)	108 (49)	< 0.001
Absolute Change in Ankle SBP from Rest to Hyperemia (mmHg)	-2.4 (15.9)	-6.6 (15.7)	0.027
Relative Change in Ankle SBP from Rest to Hyperemia (%)	-3.0 (14.0)	-8.2 (18.2)	0.015

SBP = Systolic Blood Pressure

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 ( $p = 0.015$ ).

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 ( $p = 0.031$ ).

The calf TcPO<sub>2</sub> measurement in veterans and non-veterans with PAD and claudication are shown in Table 4. The calf TcPO<sub>2</sub> 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<sub>2</sub> following the occlusive test, expressed as an absolute decrease in calf TcPO<sub>2</sub> ( $p = 0.044$ ) and a relative percentage decrease ( $p = 0.035$ ).

## 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.

### 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 20% lower ABI. Furthermore, the veterans had greater impairments in macrovascular function, as measured by a 14% lower ankle systolic blood pressure at rest and a 17% lower ankle systolic blood pressure measured 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 a 175% greater decrease in the change score of ankle systolic blood pressure than the non-veterans, and a 173% greater decrease in the relative percentage change score in ankle systolic blood pressure. 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

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

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

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

Variables	Non-Veterans (n = 83)	Veterans (n = 413)	P Value
Calf TcPO <sub>2</sub> at Rest (mmHg)	37.2 (16.0)	37.2 (17.0)	0.977
Calf TcPO <sub>2</sub> during Hyperemia (mmHg)	31.4 (19.6)	27.7 (19.6)	0.114
Absolute Change in Calf TcPO <sub>2</sub> from Rest to Hyperemia (mmHg)	-6.0 (16.1)	-9.5 (16.8)	0.044
Relative Change in Calf TcPO <sub>2</sub> from Rest to Hyperemia (%)	-7 (97)	-23 (54)	0.035

TcPO<sub>2</sub> = transcutaneous oxygen tension.

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 a 46% lower increase in the absolute change in calf blood flow from rest to hyperemia than the non-veterans, and a 31% lower increase in the relative percentage change in calf blood flow from rest to hyperemia. 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]. Additionally, we have found that other factors are independently related to impaired endothelial function in patients with PAD, which include higher values of systolic blood pressure, fasting glucose, and the ratio of low density to high density lipoprotein cholesterol [25]. However, these factors cannot explain the worse calf blood flow in veterans in the current study because the two groups were not different on hypertension, diabetes, and dyslipidemia. It is possible, however, that the higher prevalence of current smoking in veterans may partially explain the greater impairment in microvascular function in the veterans.

Further evidence that the veterans had more impaired microvascular function than the non-veterans is seen with the calf TcPO<sub>2</sub> data. The veterans had a 58% greater decline in the absolute change in calf TcPO<sub>2</sub> from rest to hyperemia than the non-veterans, and a 60% greater decline in the relative percentage change in calf TcPO<sub>2</sub> from rest to hyperemia. The reduction in the

calf TcPO<sub>2</sub> following the occlusion phase of the reactive hyperemic test indicates that ischemia persists in the cutaneous tissue for several minutes during hyperemia, and supports our previous observations noted with post-occlusive reactive hyperemia tests [18] and treadmill exercise tests [26,27]. The reduction in calf TcPO<sub>2</sub> is due the vasodilation in the calf musculature, thereby compromising the oxygen delivery to the cutaneous tissue of the calf [28], a phenomenon known as vascular steal. 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. It is possible that the lower calf TcPO<sub>2</sub> 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<sub>2</sub> measures of the lower extremity [26,29]. 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 macrovascular 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 to 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, 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. The greater compromise in peripheral vascular measures and more severe PAD in veterans are particularly noteworthy given that the prevalence of 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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