Published in final edited form as:

Angiology. 2013 July ; 64(5): 364–370. doi:10.1177/0003319712446797.

CLINICAL SIGNIFICANCE OF ANKLE SYSTOLIC BLOOD PRESSURE FOLLOWING EXERCISE IN ASSESSING CALF MUSCLE TISSUE ISCHEMIA IN PERIPHERAL ARTERY DISEASE

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Abstract

Our primary objective assessed whether a decline in ankle systolic blood pressure (SBP) to less than 50 mmHg after treadmill exercise is associated with lower extremity ischemia, as measured by calf muscle hemoglobin oxygen saturation (StO₂). Eighty-four patients with PAD completed a treadmill test. Ankle SBP below 50 mmHg following exercise was observed in only 49% (Group 1), whereas 51% had ankle SBP ≥ 50 mmHg (Group 2). No group differences were observed for the decline in calf muscle StO₂ to a minimum value (Group 1: 18 ± 21%, Group 2: 20 ± 20%; p = 0.60), and for the time to reach minimum StO₂ (Group 1: 224 ± 251 sec, Group 2: 284 ± 283 sec; p = 0.30). Requirement of ankle SBP to decrease below 50 mmHg after exercise has little clinical significance for assessing ischemia in calf muscle of PAD patients limited by intermittent claudication.

Keywords

Ankle-brachial index; ankle systolic pressure; calf muscle hemoglobin oxygen saturation; intermittent claudication; peripheral artery disease.

INTRODUCTION

Peripheral artery disease (PAD) is prevalent in 16 % of the US population older than 70 years of age, and as high as 29% of a high risk population¹ while the symptom of claudication is prevalent in 5%.² Claudication leads to ambulatory dysfunction^{3–6} and a decline in daily physical activities.⁷ Patients with PAD have increased risk of cardiovascular events including myocardial infarction, stroke and death.⁸ Diagnosing PAD based on history is difficult, as the majority of patients with PAD are asymptomatic. In fact, “classic” claudication is the presenting symptoms in as low as 11% of patients with PAD.¹

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Ankle-brachial index (ABI) is a highly specific and sensitive noninvasive method for diagnosis of PAD.^{9–11} However, ABI measurement has limitations, as ABI accuracy is impaired in elderly patients and in those with diabetes and renal failure due to calcific medial sclerosis. In such settings, other noninvasive measures are helpful to determine the etiology of claudication. Among other tests, measurement of ankle systolic blood pressure (SBP) and ABI following exercise are used to determine presence and severity of PAD. Although a 20% decline in ABI after exercise is used to evaluate PAD,¹² this does not provide information regarding the magnitude of ischemia in the leg musculature during exercise. An ankle SBP value of 50 mmHg has been suggested as a cutoff for determining ischemia as etiology of ischemic-induced claudication.¹³ However, little evidence is available to validate the cutpoint that ankle SBP must decline to below 50 mmHg following exercise to confirm the etiology of ischemic-induced claudication pain.

Near Infrared Spectroscopy (NIRS) is a relatively new, non-invasive technique that measures hemoglobin oxygen saturation (StO₂) of the calf musculature during exercise,^{14–23} and provides real-time assessment of tissue perfusion in calf musculature. A continuous-wave NIRS spectrometer using specific, calibrated wavelengths of near infrared light quantifies the percentage of hemoglobin oxygen saturation in the microvasculature of the tissue below the NIRS probe, as well as a small contribution of intracellular myoglobin. The degree of light absorption is dependent on the amount of oxygen attached to hemoglobin in the arterioles, venules and capillaries. Non-absorbed light is returned as an optical signal and analyzed to produce a ratio of oxygenated hemoglobin to total hemoglobin, expressed as percentage of StO₂ saturation continuously displayed on the spectrometer interfaced to a laptop computer. Consequently, the NIRS technique is a measure of the balance between local oxygen delivery and oxygen demand, and is a valuable technique to obtain vascular measurements from the leg muscle during treadmill exercise.

Calf muscle StO₂ decreases more rapidly during exercise and recovers more slowly in patients with claudication than in controls.^{16, 21, 22, 24} Time to the minimum calf muscle StO₂ and the minimum value of StO₂ reflect underlying severity of PAD,^{17, 25} and have been shown to increase with exercise training.²⁵ Time to minimum StO₂ has also been shown to highly correlate with peak walking time (PWT),¹⁷ and this correlation is higher than the correlation coefficients obtained between PWT and ABI,¹⁷ and between PWT and blood flow at the ankle or calf.^{26, 27} Therefore, measurement of continuous StO₂ provides unique information about the microvascular status of exercising calf muscles that is not provided by non-invasive measures, such as ankle SBP and ABI, which are obtained before and after exercise.

In the present study the primary purpose was to assess whether a decline in ankle SBP to less than 50 mmHg after treadmill exercise is necessary to determine if lower extremity ischemia is present, as measured by calf muscle StO₂. The secondary objective was to estimate the association between calf muscle StO₂ and the absolute and relative percentage changes in ankle SBP and ABI following exercise. We hypothesized that calf muscle StO₂ does not differ significantly between patients with and without a decrease in ankle SBP to an absolute value of 50 mmHg or less. Secondly, we hypothesized that declines in macrovascular measures of ankle SBP and ABI obtained after exercise are correlated with the decline in the microvascular measure of calf muscle StO₂ obtained during exercise

METHODS

PATIENTS

Recruitment—Patients participated in this study at the General Clinical Research Center (GCRC), at the University of Oklahoma Health Sciences Center (OUHSC). Patients were

recruited by referrals from the HSC vascular clinic, as well as by newspaper advertisements for possible enrollment into a randomized controlled exercise rehabilitation study.²⁸ The procedures used in this study were approved by the Institutional Review Board at the OUHSC. Written informed consent was obtained from each patient prior to investigation.

Screening—Patients with intermittent claudication secondary to vascular insufficiency were included in this study if they met the following criteria: (a) a history of intermittent claudication, (b) ambulation during a graded treadmill test limited by intermittent claudication,²⁹ and, (c) an ABI ≥ 0.90 ² or an ABI ≥ 0.73 after exercise.³⁰ Patients were excluded from this study for the following conditions: (a) absence of PAD (ABI ≥ 0.90) and ABI ≥ 0.73 after exercise, (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD, (d) use of medications indicated for the treatment of intermittent claudication (cilostazol and pentoxifylline) within 3 months prior to investigation, (e) exercise tolerance limited by factors other than leg pain (e.g. severe coronary artery disease, dyspnea, poorly controlled blood pressure), (g) active cancer, kidney failure defined as stage 5 chronic kidney disease (glomerular filtration rate < 15 ml/min/1.73 m²), or abnormal liver function, (h) calf skin fold > 50 mm because of potential interference with the light path of the NIRS probe from penetrating the subcutaneous tissue, and, (i) pulse arterial oxygen saturation of the index finger $< 95\%$ because of the potential deleterious effect on calf muscle StO₂ from poor pulmonary gas exchange. A total of 139 patients were evaluated, of which 51 did not have PAD. Of the remaining 88 patients with PAD, 4 were deemed ineligible since they did not have limiting claudication and walked the full 20 min of treadmill testing, thereby yielding a sample size of 84 patients for the analyses.

Measurements

Medical History, Physical Examination and Anthropometry: Patients arrived at the GCRC in the morning fasted, but were permitted to take their usual morning medication regimen. Demographic information, height, weight, cardiovascular risk factors, co-morbid conditions, claudication history, and a list of current medications were obtained from a medical history and physical examination to begin the evaluation. During the physical examination, arterial oxygen saturation was measured from the index finger using a standard pulse oximeter. Afterwards, subcutaneous fat over the medial gastrocnemius muscle was measured from a skin fold obtained by a trained technician using a Lange skin fold caliper according to standard guidelines,³¹ and waist and hip circumferences were recorded.³¹

Gardner Treadmill Test

Claudication Times and Peak Oxygen Uptake: Patients performed a progressive, graded treadmill protocol to determine study eligibility, and then repeated the test several days later to obtain outcome measures related to peak exercise performance.²⁹ The claudication onset time (COT), defined as the walking time at which the patient first experienced pain, and the peak walking time (PWT), defined as the time at which ambulation could not continue due to maximal pain, were both recorded to quantify the severity of claudication. Peak oxygen uptake was measured by oxygen uptake obtained during the peak exercise work load with a Medical Graphics VO2000 metabolic system (Medical Graphics Inc, St. Paul, MN). Using these procedures, the test-retest intraclass reliability coefficient is $R = 0.89$ for COT,²⁹ $R = 0.93$ for PWT,²⁹ and $R = 0.88$ for peak oxygen uptake.³²

ABI: After completion of exercise to point of maximum claudication, 1 min post exercise ankle SBP was recorded. Ankle SBP and ABI measures were obtained from the more severely diseased lower extremity before, and at 1 min after the treadmill test and subsequently every 2 min up to 15 min.^{29, 33} Patients were grouped according to whether

their ankle SBP decreased below 50 mmHg 1 min following exercise (Group 1), or whether their ankle SBP was 50 mmHg or above (Group 2).

StO₂ of the Calf Musculature: Calf muscle StO₂ was measured before, during, and after exercise using a continuous-wave, NIRS spectrometer (InSpectra model 325; Hutchinson Technology, Inc, Hutchinson, MN), an optical cable attached to a 25-mm probe, InSpectra software (version 2.0), and a dedicated laptop computer as previously described.¹⁷ The probe was attached to the skin over the medial gastrocnemius muscle of the more severely affected leg using a double-sided adhesive light-excluding patch.³⁴ A baseline measure of calf muscle StO₂ was obtained at rest as patients stood on the treadmill for 2 min to allow for equilibration. From the start of treadmill exercise, the minimum StO₂ value and the time taken to reach the minimum value were obtained.

Statistical Analyses—A Pearson correlation coefficient, if bivariate normality was a reasonable assumption, or a Spearman rank correlation coefficient, if a bivariate normality assumption was not reasonable, was calculated to quantify the strength of the linear association between pairs of continuous measures. Mean continuous measures were compared between groups defined by ankle SBP values post-exercise using an independent sample t-test, and proportions were compared between groups using a Chi-square test or Fisher's exact test for low expected cell counts. All analyses were performed with a two-tailed significance level of 0.05.

RESULTS

Eighty four patients with PAD and limiting claudication were enrolled in the study. Patients were evenly distributed in regards to female sex and non Caucasian population (Table 1). Mean ABI, COT, and PWT were typical of patients with claudication, as were the reductions in ankle SBP, ABI, and calf muscle StO₂ with exercise (Table 2).

Forty one of 84 patients (49%) had ankle SBP < 50 mmHg post exercise after maximum claudication (Group 1), whereas the remaining 51% of patients had an ankle SBP value ≥ 50 mmHg (Group 2). Time to minimum calf muscle StO₂ was not different between the 2 groups ($p = 0.30$), and neither was the minimum value of calf muscle StO₂ ($p = 0.60$) (Table 3). Clinical characteristics also were not different between the 2 groups except baseline ABI, which was lower in Group 1 ($p < 0.001$).

Calf muscle StO₂ characteristics were compared to other macrovascular measures of PAD (Table 4). No significant correlation coefficient was found between the calf muscle StO₂ characteristics (time to minimum StO₂ and minimum StO₂) and all of the ankle SBP and ABI measures. When plotted graphically, time to minimum calf muscle StO₂ (Figure 1) and the minimum value of calf muscle StO₂ (Figure 2) had no correlation and wide data scatter with post exercise ankle SBP. Additionally, when post-exercise ankle SBP was compared with exercise performance measures, no correlation was found with COT ($r = 0.15$, $p = 0.18$) and PWT ($r = 0.17$, $p = 0.13$). Resting ABI was significantly correlated with COT ($r = 0.24$, $p = 0.027$) and PWT ($r = 0.27$, $p = 0.014$), but these associations were low in magnitude. In contrast, the time to minimum StO₂ was highly correlated with COT ($r = 0.62$, $p < 0.0001$) and PWT ($r = 0.77$, $p < 0.0001$).

DISCUSSION

A main finding of our study was that only 49% of our patients had ankle SBP less than 50 mmHg post exercise. On comparing the 2 ankle SBP groups, there was no difference in their calf muscle StO₂ characteristics. Time to the minimum StO₂ and the minimum value of calf

muscle StO₂ reflect underlying severity of PAD,^{17, 25} and have been shown to increase with exercise training.²⁵ Time to minimum StO₂ also has been shown to highly correlate with PWT,¹⁷ and this correlation is higher than the correlation coefficients obtained between PWT and ABI,¹⁷ and between PWT and blood flow at the ankle or calf.^{26, 27}

Calf muscle StO₂ is essentially reflective of the real time perfusion of the microvasculature of the exercising muscles. The fact that calf muscle StO₂ and ankle SBP did not correlate well is not surprising. Following exercise, a reduction in ankle SBP is due to vascular steal which occurs to maintain microvascular perfusion and oxygen delivery to the muscle. Initially, calf muscle StO₂ values may be maintained relatively well even with a reduction in ankle SBP, particularly in mildly affected patients. Eventually, vascular steal is insufficient to maintain the microvascular circulation and calf muscle StO₂, particularly in more severe PAD and with more strenuous exercise. There was wide scatter in the data between calf muscle StO₂ measures and ankle SBP. In fact, none of the measures of macrovascular assessment, including absolute ankle SBP, absolute ABI, and the relative declines in ankle SBP and ABI were well correlated with calf StO₂ characteristics. These results suggest that ischemia at tissue level in the exercising calf muscle occurs irrespective of the macrovascular blood supply measured at the ankle.

Pathophysiology of claudication in PAD and its beneficial response to exercise shows that anatomic obstruction causing diminished blood flow is not the sole reason for claudication.³⁵ Ischemia in the exercising calf muscle is thought to be influenced by many other factors rather than just due to impaired macrovascular supply. Oxidative stress, mitochondrial dysfunction, alteration of skeletal muscle metabolism, and endothelial dysfunction are possible factors that influence claudication.³⁵ Treatment of PAD and implementation of exercise training in PAD show that the pathophysiology of claudication is more complex than a simple mismatch in supply and demand of blood to the calf muscle. Even though exercise training is a well established treatment of claudication, meta-analysis of exercise studies demonstrated no change in resting ABI.³⁶ Further, many patients with improvement in ABI post revascularization continue to have poor exercise performance by objective testing.³⁷ The fact that exercise performance of PAD patients is improved even with arm ergometry exercise and strength training further strengthens the argument that other factors besides the macrocirculation influence claudication.³⁸

Although all patients reached a maximum claudication pain endpoint during exercise, only half of our patients had ankle SBP values less than 50 mmHg after exercise, whereas the remaining patients had values above 50 mmHg. This finding indicates that ischemic pain still needs to be considered even at higher post exercise ankle SBP values. Macrovascular measures, like ankle SBP and ABI, are imprecise measures to assess claudication. Consequently, they should not be used solely without assessment of microvascular function, such as calf muscle StO₂, when evaluating claudication, particularly in patients with ankle SBP greater than 50 mmHg. Ischemic claudication should not be ruled out on the basis of post exercise ankle SBP alone.

There are several limitations to this study. The correlation coefficients calculated in this cross-sectional design do not allow causality to be established. Furthermore, the analyses were not adjusted for potential modifying or confounding subject characteristics, although such adjustment is unlikely to change any of the results substantially. For example, in conditions which might increase arterial calcification and ankle SBP measures, such as chronic kidney disease and diabetes, we believe they had minimal influence because patients with severe chronic kidney disease were excluded from the study, and because there was no difference in the prevalence of diabetes between Groups 1 and 2. Another limitation is that some PAD patients with arterial calcification may have been excluded because of having an

ABI > 0.90, but we believe this is unlikely because another exclusion criterion was having an ABI > 0.73 after exercise. An exercise-mediated decline in ABI is a hallmark of PAD, with little decline indicative of absence of PAD. Additionally, this study is limited to PAD patients who have claudication, and may not be generalized to patients with less severe (i.e. asymptomatic) or more severe (i.e. rest pain) PAD. However, the patients in the current study are typical of those with claudication, as there was a good proportion of women and African-Americans, and high prevalence of cardiovascular risk factors for PAD, including smoking, diabetes, hypertension, dyslipidemia, and obesity. Resting ABI and ankle SBP were statistically different between the 2 groups, with Group 1 having lower values than Group 2. Thus, the findings of the present study appear generalizable to patients with claudication having a wide range in PAD severity, and who typically have numerous co-morbid conditions.

In summary, none of the ABI or ankle SBP values are significantly correlated with the calf muscle StO₂ values. Furthermore, there is no significant difference in the mean StO₂ measures between the groups of patients defined by ankle SBP < 50 mmHg or ankle SBP ≥ 50 mmHg 1 min post-exercise. Additionally, the confidence intervals for the difference in mean values are wide and therefore, we cannot conclude that the mean measures are equivalent. We conclude that the requirement of an ankle SBP below 50 mmHg after exercise has little clinical significance for assessing tissue ischemia in the exercising calf muscle of PAD patients limited by intermittent claudication. There is no association between calf muscle StO₂ and absolute and relative changes in ankle SBP and ABI following exercise. The clinical implication is ischemic induced claudication needs to be considered in patients even if post exercise ankle SBP is ≥ 50 mmHg. Further studies should be done to examine the microvascular status of exercising muscles. Our study further exemplifies that microvascular ischemia in the exercising calf muscle is not associated with macrovascular ankle SBP measurements.

Acknowledgments

Supported by grants from the National Institute on Aging (NIA) (R01-AG-24296; AWG), by an Oklahoma Center for the Advancement of Science and Technology grant (HR09-035; AWG), and by the OUHSC General Clinical Research Center grant (M01-RR-14467) sponsored by the National Center for Research Resources (NCRR) from the National Institutes of Health (NIH).

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Figure 1.
Time to minimum hemoglobin oxygen saturation (StO₂) during exercise vs. ankle systolic blood pressure (SBP) post exercise

Figure 2.
Minimum hemoglobin oxygen saturation (StO_2) during exercise vs. ankle systolic blood pressure (SBP) post exercise

Table 1

Clinical characteristics of patients with claudication (n = 84)

	Mean	SD
Age (years)	67	10.6
Weight (kg)	82.9	19.7
Height (cm)	167.8	9.6
Body mass index (kg/m ²)	29.5	6.8
Waist girth (cm)	102.0	15.6
Ankle Brachial Index	0.67	0.24
	Count	Percent
Sex (Men)	44	52
Race (Caucasian)	42	50
Current smoking	31	37
Diabetes	34	40
Hypertension	71	85
Dyslipidemia	74	88
Obesity	36	43
Medication for Diabetes	33	39
Medication for Hypertension	70	83
Medication for Dyslipidemia	61	73

Table 2

Treadmill test measurements of patients with claudication (n = 84)

Variables	Mean	SD
<u>Exercise Measures</u>		
Claudication Onset Time (sec) *	234.0	193.6
Peak Walking Time (sec)	427.1	272.9
Peak Oxygen Uptake (ml.kg ⁻¹ .min ⁻¹) *	12.3	3.9
<u>Ankle SBP and ABI Measures</u>		
Ankle SBP at rest (mmHg)	89.6	31.5
Ankle SBP at 1-min post-test (mmHg)	58.8	36.3
ankle SBP (post-exercise minus rest) (mmHg)	-30.8	23.4
Relative ankle SBP (/rest measure)	-0.4	0.3
ABI at rest	0.67	0.24
ABI at 1-min post-exercise	0.38	0.25
ABI (post-exercise minus rest)	-0.29	0.17
Relative ABI (/rest measure)	-0.46	0.24
<u>Calf muscleStO₂ Measures</u>		
StO ₂ at rest (% saturation)	52.6	19.1
Minimum StO ₂ (% saturation)	18.7	20.0
Time to minimum StO ₂ (sec)	255.0	267.9

ABI = ankle-brachial index, SBP = systolic blood pressure, StO₂ = hemoglobin oxygen saturation

* n = 82.

Calf muscle hemoglobin oxygen saturation (StO₂), demographic, clinical, and exercise performance characteristics of patients with an ankle systolic blood pressure (SBP) above and below 50 mmHg one minute post-exercise

Table 3

Variables	Ankle SBP < 50 mmHg 1 min post-exercise (n=41)		Ankle SBP 50 mmHg 1 min post-exercise (n=43)		p
	Mean	SD	Mean	SD	
StO ₂ at rest (% saturation)	52.4	20.0	52.8	18.4	0.93
Minimum StO ₂ (% saturation)	17.6	20.7	19.9	19.5	0.60
Time to minimum StO ₂ (sec)	224.0	250.9	284.5	282.9	0.30
Claudication Onset Time (sec)	158.0	126.3	216.4	175.6	0.09
Peak Walking Time (sec)	302.4	202.5	381.4	229.6	0.10
Rest ABI	0.53	0.17	0.81	0.15	<0.0001
Ankle SBP 1 min post-exercise (mmHg)	29.4	12.7	86.8	28.4	<0.0001
Age (years)	66	9.8	68	11.3	0.36
Weight (kg)	84.6	18.7	81.3	20.7	0.45
Height (cm)	168.1	10.4	167.6	8.9	0.79
Body mass index (kg/m ²)	30.0	6.4	29.0	7.1	0.48
Waist girth (cm)	102.7	14.5	101.3	16.8	0.70
	Percentage		Percentage		p-value
Sex (% Men)	51%		53%		0.84
Race (% Caucasian)	49%		51%		0.83
Current smoking (%)	46%		29%		0.094
Diabetes (%)	41%		40%		0.86
Hypertension (%)	80%		88%		0.32
Dyslipidemia (%)	95%		81%		0.089
Obesity (%)	49%		37%		0.28

ABI = ankle-brachial index, SBP = systolic blood pressure.

Table 4

Association between calf muscle hemoglobin oxygen saturation (StO₂) measures with ankle-brachial index (ABI) measures, ankle systolic blood pressure (SBP) measures, and exercise performance measures among patients (n = 84). are presented as the Pearson correlation coefficient (r) and corresponding p-value.

Variables	StO ₂ at rest		Minimum StO ₂		Time to Minimum StO ₂	
	R	p	r	p	R	p
Ankle SBP	0.10	0.38	0.13	0.22	0.14	0.19
Ankle SBP at 1-min post-exercise	-0.003	0.98	0.20	0.070	0.13	0.25
ankle SBP (post-exercise minus rest)	-0.14	0.22	0.13	0.25	0.0009	0.99
Relative ankle SBP (/rest measure)	-0.10	0.38	0.15	0.17	0.10	0.36
ABI at rest	0.02	0.87	0.09	0.42	0.15	0.18
ABI at 1-min post-exercise	-0.05	0.66	0.17	0.13	0.08	0.46
ABI (post-exercise minus rest)	-0.10	0.38	0.12	0.28	-0.09	0.42
Relative ABI (/rest measure)	-0.07	0.53	0.18	0.11	0.04	0.74
Claudication Onset Time	0.11	0.34	0.22	0.050	0.62	< 0.0001
Peak Walking Time	0.15	0.17	0.04	0.72	0.77	< 0.0001