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OXYGEN UPTAKE BEFORE AND AFTER THE ONSET OF CLAUDICATION DURING A 6-MINUTE WALK TEST

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Abstract

Purposes—To compare oxygen uptake before and after the onset of claudication in subjects with peripheral artery disease (PAD) during a 6-minute walk test, and to identify predictors of the change in oxygen uptake following the onset of claudication pain

Methods—Fifty subjects with PAD were studied, in which 33 experienced claudication (Pain Group) during a 6-minute walk test, and 17 were pain-free during this test (Pain-Free Group). Oxygen uptake and ambulatory cadence were primary outcomes obtained during the 6-minute walk test.

Results—The Pain Group experienced onset of claudication pain at 179 ± 45 meters (mean ± standard deviation) and continued to walk to achieve a 6-minute walk distance of 393 ± 74 meters, which was similar ($p = 0.74$) to the Pain-Free Group (401 ± 76 meters). Oxygen uptake increased ($p < 0.0001$) after the onset of pain in the Pain Group, and this change was greater ($p = 0.025$) than the increase in oxygen uptake from the second to fifth minute of walking in the Pain-Free Group. Furthermore, ambulatory cadence decreased after the onset of pain in the Pain Group ($p = 0.0003$). The change in oxygen uptake was associated with metabolic syndrome ($p = 0.0023$), 6-minute walk distance ($p = 0.0037$), age, ($p = 0.0041$), and the oxygen uptake during the second minute of the test ($p = 0.012$).

Conclusion—Claudication increases oxygen uptake of self-paced, over-ground ambulation despite a decrease in cadence. The pain-mediated increase in oxygen uptake was blunted in subjects with metabolic syndrome, suggesting that they have an impaired ability to increase oxygen uptake during ambulation. The clinical significance is that claudication increases metabolic cost of ambulation, thereby increasing the relative intensity of exercise and reducing the tolerance to sustain ambulation.

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INTRODUCTION

Peripheral artery disease (PAD) is prevalent in more than 12% of the US population 65 years of age and older,[1] and is associated with elevated rates of mortality[2–5] and morbidity,[6] as over 60% of subjects have concomitant cardiovascular and/or cerebrovascular disease.[7] In addition to having high cardiovascular risk, many of those with PAD are physically limited by ambulatory leg pain. Claudication is prevalent in more than 6% of those at least 65 years of age,[1;7] which results in impaired ambulation,[8;9] reduced physical function,[10;11] and lower daily physical activity.[12]

Less is known about how the onset of claudication acutely affects ambulation. Oxygen uptake is increased with the onset of claudication during treadmill exercise at constant load, thereby increasing the relative metabolic cost of painful ambulation and reducing exercise tolerance.[13] It is not clear whether the increase in oxygen uptake following pain onset during treadmill walking is evident during self-paced, over-ground ambulation because subjects may compensate by slowing their pace[14;15] to maintain a given metabolic cost. However, slowing freely-chosen velocity by too much results in less economical ambulation,[16–18] which may increase oxygen uptake even further during painful ambulation. The oxygen uptake of self-paced, over-ground ambulation during pain-free and painful ambulation has not been previously examined, and has important implications regarding the intensity at which ambulation is performed in the community setting.

The purposes of the study are to compare oxygen uptake before and after the onset of claudication in subjects with PAD during a 6-minute walk test, and to identify predictors of the change in oxygen uptake following the onset of claudication pain. The hypotheses are that oxygen uptake increases after the onset of claudication, and that severity of PAD and the change in ambulatory cadence and velocity are predictive of the change in oxygen uptake following the onset of claudication.

METHODS

SUBJECTS

Recruitment—Subjects were evaluated in the General Clinical Research Center at the University of Oklahoma Health Sciences Center (HSC). Subjects 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.[19] The data and analyses for this study were part of the baseline assessments obtained for the exercise study. The procedures used in this study were approved by the Institutional Review Board at the University of Oklahoma HSC. Written informed consent was obtained from each subject prior to investigation.

Screening—Subjects with claudication secondary to vascular insufficiency were included in this study if they met the following criteria: (a) a history of any type of exertional leg pain, (b) ambulation during a graded treadmill test limited by leg pain consistent with claudication,[8] and (c) an ankle-brachial index (ABI) ≤ 0.90 at rest,[1;7] or an ABI ≤ 0.73 after exercise because some PAD patients have normal values at rest which only become abnormal following an exercise test.[20] Subjects were excluded from this study for the following conditions: (a) absence of PAD (ABI > 0.90 at rest and ABI > 0.73 after exercise), (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD (Fontaine Stage I) determined from the medical history and verified during the graded treadmill test, (d) use of medications indicated for the treatment of claudication (cilostazol and pentoxifylline) initiated within three months prior to investigation, and (e) exercise tolerance during maximal treadmill exercise limited by factors other than claudication pain

(e.g., severe coronary artery disease, dyspnea, poorly controlled blood pressure), and (f) active cancer, end-stage renal disease, or liver disease, (g) discontinuing ambulation for any reason during the 6-minute walk test, and (h) for those experiencing pain during the 6-minute walk test, ambulating for less than one complete minute during pain-free or painful conditions because an insufficient amount of data was available for analyses. A total of 77 subjects were evaluated for this study, and 50 subjects were deemed eligible.

MEASUREMENTS

Primary Outcome Measures: Oxygen Uptake and Ambulatory Cadence Obtained During the 6-Minute Walk Test

Procedures: A trained technician administered the over ground, 6-minute walk test in which two cones were placed 100 feet apart in a marked corridor as previously described.[21] Subjects were instructed to walk as many laps around the cones as possible while wearing a light-weight (0.8 kg), portable oxygen uptake unit (COSMED K4 b^2, COSMED USA, Inc, Chicago, IL) which continuously measured oxygen uptake via indirect calorimetry, and while wearing a step activity monitor (Step Watch 3, Cyma Inc., Mountlake Terrace, WA) placed on their right ankle. During the test, subjects indicated if and when they experienced the onset of claudication pain. Subjects who experienced pain during the 6-minute walk test (Pain Group) were subsequently compared to those who completed the test without pain (Pain-Free Group), as described in the results section.

Outcome Measures: This test was the experimental protocol used to obtain the primary outcome measures of oxygen uptake and ambulatory cadence, as well as other measures consisting of stride length, ambulatory velocity, time and distance to onset of pain, and total 6-minute walk distance. Oxygen uptake and ambulatory cadence were obtained each minute during the test, and the technician recorded the time and distance to onset of claudication as well as the total distance walked. The walking distances were subsequently converted from feet to meters. Stride length and ambulatory velocity were then calculated during both pain-free and painful ambulation in the Pain Group. However, these calculations were not possible to determine in the Pain-Free Group for two reasons. First, the subjects did not experience claudication during the test, and therefore ambulation did not occur under painful conditions. Second, time and distance measures were not recorded at specified intervals during the test because of concerns that this additional encumbrance on the technician while the test was proceeding might affect the results of the self-paced 6-minute walk test. Therefore the calculation of stride length and ambulatory velocity at different time points during the test in the Pain-Free Group was not possible.

Oxygen uptake and ambulatory cadence obtained during the first and last minute of exercise in either group were not used for analyses because of the possibility that data was not recorded for a full 60 seconds during these time points. Additionally, oxygen uptake and ambulatory cadence obtained during the minute in which the onset of claudication occurred in the Pain Group was not used for analyses because it was not possible to precisely separate the data before and after the onset of pain within the minute. Change scores for oxygen uptake and gait parameters were calculated as the difference in average values obtained during painful ambulation minus the values obtained during pain-free ambulation in the Pain Group, and the difference between the fifth minute values minus the second minute values during exercise in the Pain-Free group

Secondary Outcome Measures

Medical History, Physical Examination, and Anthropometry: Demographic information, height, weight, body mass index (BMI), waist and hip circumferences,[22] cardiovascular risk factors, co-morbid conditions, claudication history, blood samples, and a list of current

medications were obtained from a medical history and physical examination at the beginning of the study.

Walking Impairment Questionnaire (WIQ): Self-reported ambulatory ability was obtained using a validated questionnaire for PAD subjects that assesses ability to walk at various speeds and distances, and to climb stairs.[23]

Graded Treadmill Test

Claudication Times and Peak Oxygen Uptake: Subjects performed a progressive, graded treadmill protocol to determine study eligibility, as well as to obtain outcome measures related to exercise performance.[8] The claudication onset time (COT), defined as the walking time at which the subjects first experienced pain, and the peak walking time (PWT), defined as the walking 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,[8] R = 0.93 for PWT,[8] and R = 0.88 for peak oxygen uptake.[24]

ABI and Ischemic Window: As previously described, ABI measures were obtained from the more severely diseased lower extremity before and 1, 3, 5, and 7 minutes after the treadmill test.[8;25] The reduction in ankle systolic blood pressure after treadmill exercise from the resting baseline value was quantified by calculating the area under the curve, referred to as the ischemic window.[26] Because the ischemic window is a function of both PAD severity and the amount of exercise performed, the ischemic window was normalized per meter walked.

Ambulatory Activity Monitoring: Daily ambulatory activity was assessed using a step activity monitor as previously described.[27] Ambulatory activity was measured during seven consecutive days in which subjects were instructed to wear the monitor during waking hours and to remove it before retiring to bed. The step activity monitor was attached to the right ankle above the lateral malleolus using elastic Velcro straps, and continuously recorded the number of steps taken on a minute-to-minute basis. The accuracy of the step activity monitor exceeds 99% ± 1% in subjects with claudication.[27]

STATISTICAL ANALYSES

An independent sample t-test was used to compare the means of continuous demographic and clinical measures between the Pain Group and the Pain-Free Group. A Chi-square test, or Fisher's exact test for small expected cell counts, was used to compare the distribution of categorical demographic and clinical measures between the two groups. To address the first aim, a non-parametric Wilcoxon signed rank test was used to compare the median oxygen uptake measures and the median ambulatory parameters (cadence, speed, and stride length) between pain-free and painful ambulation in the Pain Group, and between the second and fifth time points in the Pain-Free Group. Between-group comparisons of the distribution of changes in oxygen uptake and ambulatory parameters were made using an independent sample Wilcoxon rank sum test. For the pain-free time during the 6-minute walk test, between-group comparisons of mean values to a fixed reference were made using a one-sample t-test. A 2-sided 0.05 alpha level was used to define statistical significance.

To address the second aim, linear regression was used to identify clinical and exercise performance characteristics that were independently associated with oxygen uptake after adjustment for height. Clinical and exercise performance characteristics associated with

oxygen uptake univariately at a 0.05 alpha level were entered into a multiple linear regression model. Clinical and exercise performance characteristics were deleted from the multiple regression model until all terms were significant at the 0.05 alpha level. The clinical and exercise performance characteristics that were considered in the modeling were all factors listed in Tables I and II. Height was adjusted for in the regression model to adjust for the association between height and stride rate. Data were analyzed using SAS (SAS System for Windows, ver. 9.1, SAS Institute Inc., Cary, NC) and SPSS (SPSS for Windows, rel. 15.0, SPSS Chicago, IL).

RESULTS

Subjects were grouped according to whether they experienced claudication during the 6-minute walk test (Pain Group; n = 33) or did not experience claudication (Pain-Free Group; n = 17). The groups were similar on all clinical characteristics ($p > 0.05$), except that the Pain Group had higher body weight ($p = 0.038$), and a non-significant trend for higher prevalence of metabolic syndrome ($p = 0.070$) (Table I). The groups were similar on all measures of treadmill exercise performance, WIQ measures, and daily ambulatory activity ($p > 0.05$) (Table II), but the Pain Group, by definition, had shorter 6-minute walk pain-free time ($p < 0.001$) and pain-free distance ($p < 0.001$) than the Pain-Free Group (Table III).

Oxygen uptake during pain-free ambulation increased ($p < 0.0001$) after the onset of pain in the Pain Group, and this change was greater ($p = 0.025$) than the increase in oxygen uptake from the second to fifth minute of walking in the Pain-Free Group (Table IV and Figure 1). In contrast, the decrease in ambulatory cadence after pain onset in the Pain Group ($p = 0.0003$) was similar ($p = 0.79$) to the decline in cadence from the second to fifth minute of walking in the Pain-Free Group (Table IV). After pain onset, the Pain Group also experienced a shorter stride length ($p < 0.0001$), a decline in ambulatory velocity ($p < 0.0001$), and increased oxygen uptake when expressed per stride taken ($p < 0.0001$) or meter walked ($p < 0.0001$) than compared to before pain onset (Table IV).

The multiple regression model predicting the change in oxygen uptake following the onset of claudication in patients in the Pain Group is shown in Table V. Metabolic syndrome was negatively associated with the increase in oxygen uptake following pain onset, as subjects with metabolic syndrome had on average a 1.83 $ml \cdot kg^{-1} \cdot min^{-1}$ lower change in oxygen uptake than those without metabolic syndrome (Figure 2). In contrast, age, 6-minute walk distance, and the oxygen uptake during the second minute of the 6-minute walk test were positively associated with the pain-mediated increase in oxygen uptake.

DISCUSSION

Changes in Oxygen Uptake and Ambulatory Cadence During Painful Ambulation

The primary finding of this study was that oxygen uptake increased by 36% after the transition from pain-free to painful ambulation during the 6-minute walk test. This observation supports a previous report from our laboratory, which found that oxygen uptake was higher while ambulating with pain during a constant-speed, standardized treadmill test.[13] It was not clear whether the observed pain-mediated increase in oxygen uptake during treadmill exercise would occur during self-paced, over-ground ambulation because subjects can attempt to compensate by slowing their pace. We found that ambulatory cadence decreased during painful ambulation, supporting previous reports of changes in gait measures following the onset of claudication, such as reduced ambulatory velocity,[15] shortened step length,[15] and decreased ankle plantar flexor moments[14] at self-selected pace over short distances. However, the reduction in ambulatory cadence during painful ambulation in the present study did not reduce the metabolic cost of walking.

Although this study does not address mechanisms for the increase in oxygen uptake during painful ambulation, it indicates that a given exercise work rate becomes more challenging to perform than pain-free ambulation. Muscle force production decreases with claudication,[28;29] which may explain the decrease in stride length during painful ambulation in the Pain-Group. It is possible that the Pain Group had a greater decrease in their stride length during the test than the Pain-Free Group, and this may be one reason why the increase in oxygen uptake was not different between the two groups when expressed per stride taken. When muscle force production decreases with claudication, the recruitment of more motor units per muscle is needed to generate the required force to ambulate.[18] A change in muscle fiber recruitment patterns would be consistent with more challenging ambulation,[18] suggesting that more motor units, particularly more fast-twitch motor units which are less economical than slow-twitch fibers,[30] are recruited to perform painful ambulation. Furthermore, muscle denervation observed in PAD subjects[31] may impair optimal motor unit recruitment during exercise, becoming more evident during painful ambulation.

It should be noted that those who completed the 6-minute walk test pain-free also had an increase in oxygen uptake during exercise, albeit a smaller one than those who performed painful ambulation. It has been observed that a gradual increase in oxygen uptake occurs during intense exercise compared to light exercise, thus preventing oxygen uptake from reaching a steady-state plateau during exercise at a constant work load.[32] Since the Pain-Free Group ambulated at a relatively high intensity equal to 72% of their peak oxygen uptake during the second minute of exercise, it is not surprising that they experienced a gradual increase in oxygen uptake, referred to as the slow component of the increase in oxygen uptake which we have previously observed in PAD subjects walking on a treadmill at a constant work rate.[33]

Our data shows a lack of agreement between the COT and PWT measures obtained during a standardized treadmill test and the pain-free time and distance obtained during the 6-minute walk test. Although 33 subjects experienced claudication during the 6-minute walk test, and therefore had shorter pain-free walking time and distance than the 17 subjects who did not experience claudication, there were no group differences in COT and PWT values during treadmill exercise. This supports our previous finding that there is no significant correlation between the pain-free distance during the 6-minute walk test and the COT and PWT obtained during a standardized treadmill test.[21] This suggests that the two tests measure different aspects of ambulatory function in subjects with PAD and claudication. Given that the average, freely-chosen walking speed during the 6-minute walk test was higher (approximately 2.5 mph) than the 2.0 mph speed during the treadmill test, the first few minutes of the 6-minute walk test was performed at a higher exercise intensity than the treadmill test. Thus, it is not surprising that two-thirds of the subjects (i.e., Pain Group) experienced claudication sooner during the 6-minute walk test than during the treadmill test. However, it is surprising that one-third of the subjects (i.e., Pain-free Group) did not experience claudication during the 6-minute walk test, even though they walked at a faster pace than during the treadmill test. Although both groups attempted to walk as fast as they could during the 6-minute walk test, it is possible that the Pain-Free Group walked closer to their optimal speed during the 6-minute walk test, and that the walking speed during the treadmill test was relatively too slow for them. When expressed per distance travelled, walking too slow is equally inefficient as walking too fast, thereby decreasing efficiency.[17] Thus, the faster pace during the 6-minute walk test may have been more comfortable for the Pain-Free Group than the slower pace during the treadmill test, even though a 2% incline was added after the first two minutes of the treadmill test.

Predictors of the pain-mediated change in oxygen uptake

Oxygen uptake increased after the onset of claudication in subjects ambulating during a 6-minute walk test. Metabolic syndrome was a predictor of the pain-mediated change in oxygen uptake. This finding suggests that insulin resistance may play a prominent role in interfering with central and peripheral factors affecting the kinetics of oxygen uptake. For example, Type II diabetes slows whole-body oxygen uptake kinetics and heart rate kinetics during exercise,[34] slows oxidative enzyme activity,[35] increases the frequency of mitochondrial DNA deletions in skeletal muscle,[36] impairs endothelial function,[37] reduces leg blood flow during steady-state exercise,[38] and slows microvascular blood flow kinetics.[39] Data from our laboratory also support these findings, as PAD subjects with metabolic syndrome have a blunted increase in reactive hyperemic calf blood flow than those without metabolic syndrome, and they have more limited 6-minute walk performance.[40] Additional factors predictive of the change in pain-mediated oxygen uptake were age, 6-minute walk distance, and the oxygen uptake during the second minute of the test. The increase in oxygen uptake was greater in older subjects, in those who maintained a fast pace during the test even after pain onset to achieve a longer total distance, and in those who had high oxygen uptake values during the early phase of the test.

Limitations

There are several limitations to this study. The regression coefficients calculated between oxygen uptake and clinical characteristics and baseline exercise performance measures from this cross-sectional design do not allow causality to be established. The present findings are also limited by the relatively small sample sizes, particularly in the Pain-Free group. Another limitation is that potential group differences in co-morbid conditions that were not included in this study (e.g., arthritis, chronic obstructive pulmonary disease, congestive heart failure, etc) may partially explain the group difference in the change in oxygen uptake during the 6-minute walk. However, these co-morbid conditions would be of minimal importance unless the prevalence of these conditions was different between groups. Furthermore, the effect of these conditions (e.g., arthritic pain) would typically be present throughout the entire walking test, thereby not eliciting an increase in oxygen uptake at any particular point during the test like we found for the onset of claudication. Additionally, this study is limited to PAD subjects who have claudication, and may not be generalized to subjects with less severe or more severe PAD. However, the subjects 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. Thus, the findings of the present study appear generalizable to subjects with claudication who typically have numerous co-morbid conditions.

Conclusions and Clinical Significance

We conclude that claudication increases oxygen uptake of self-paced, over-ground ambulation despite a decrease in cadence. The pain-mediated increase in oxygen uptake was blunted in subjects with metabolic syndrome, suggesting that they have an impaired ability to increase oxygen uptake during ambulation. The clinical significance is that claudication increases metabolic cost of ambulation, thereby increasing the relative intensity of exercise and reducing the tolerance to sustain ambulation. This information is clinically relevant to exercise professionals who rehabilitate subjects with PAD, as the training intensity should be reduced to compensate for the expected increase in intensity during painful ambulation, thereby providing a safer and more effective exercise prescription. A long-term goal is to determine whether the efficacy of interventions designed to improve claudication translates to improved self-paced, over-ground ambulation, evident by delayed occurrence of pain and

by attenuation of the increase in oxygen uptake as subjects transition from pain-free to painful ambulation.

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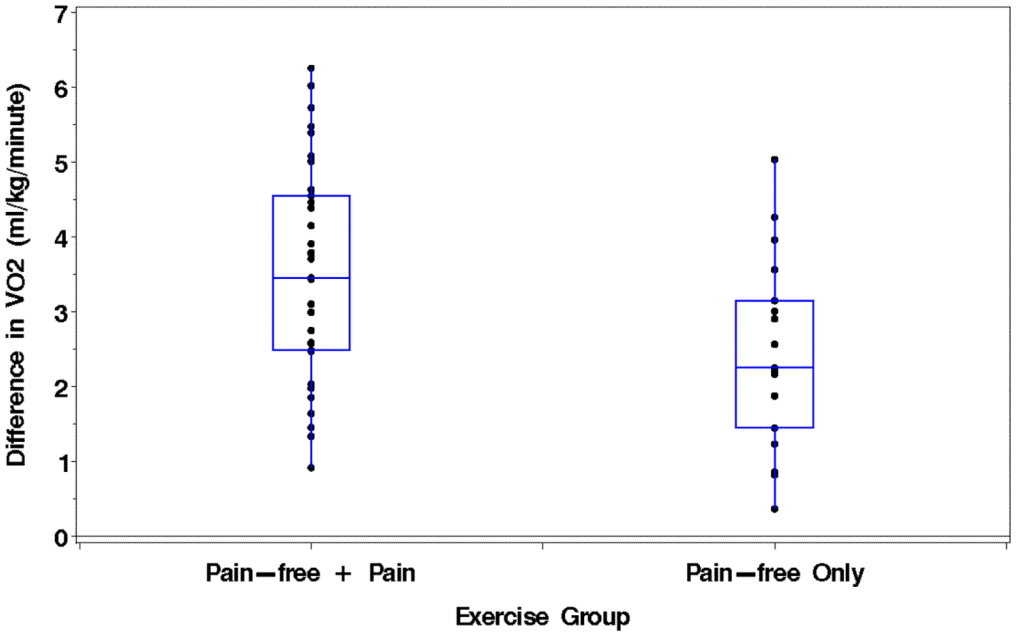

Figure 1.
Change in oxygen uptake during a 6-minute walk test in the Pain Group (n = 33) and the Pain-Free Group (n = 17). The change in the Pain Group was defined as the oxygen uptake measured during painful ambulation minus the oxygen uptake during pain-free ambulation. The change in the Pain-Free Group was defined as the oxygen uptake measured during the fifth minute minus the oxygen uptake measured during the second minute.

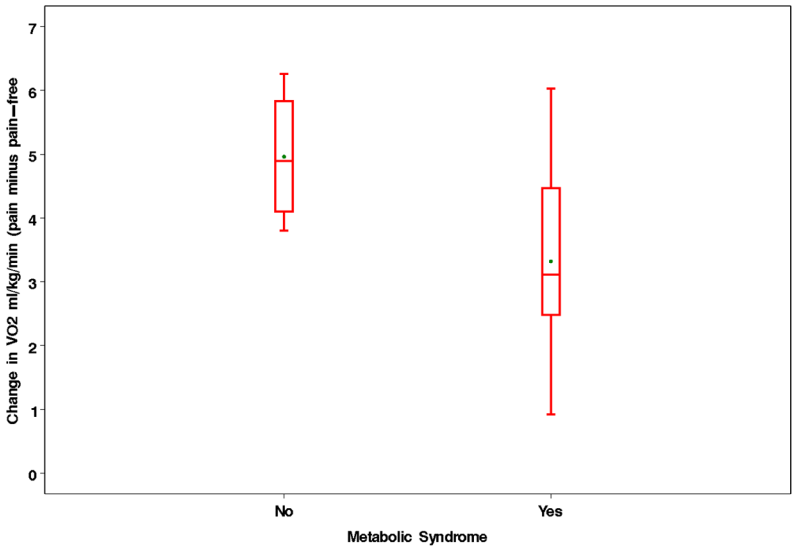

Figure 2.
Change in oxygen uptake during a 6-minute walk test in subjects with and without metabolic syndrome in the Pain Group. The change in oxygen uptake was defined as the value measured during painful ambulation minus the value obtained during pain-free ambulation.

Table I

Clinical characteristics of subjects.

	Pain Group (n=33)	Pain-Free Group (n=17)	P-value
	Mean (SD)	**Mean (SD)**	
Age (years)	65 (9)	67 (11)	0.59
Weight (kg)	89.6 (18.7)	78.0 (17.4)	0.038
Height (cm)	171.0 (9.7)	169.2 (9.1)	0.51
Body mass index (kg/m^2)	30.6 (5.8)	27.6 (7.6)	0.12
Waist girth (cm) (n=19, n=7)	105.1 (16.0)	102.6 (18.2)	0.74
Ankle/brachial index	0.72 (0.20)	0.75 (0.21)	0.61
	Percent	**Percent**	**P-value**
Sex (% Men)	67%	59%	0.58
Race (% Caucasian)	61%	47%	0.36
Current smoking (%)	36%	35%	0.94
Diabetes (%)	36%	41%	0.74
Hypertension (%)	88%	76%	0.42
Hyperlipidemia (%)	76%	82%	0.73
Abdominal obesity (%) (n=19, 7)	63%	71%	>0.99
Obesity (%)	48%	29%	0.20
Metabolic syndrome (%)	88%	65%	0.070

Table II

Treadmill exercise performance, Walking Impairment Questionnaire (WIQ) measures, and daily ambulatory activity of subjects.

	Pain Group (n=33)		Pain-Free Group (n=17)		P-value
	Mean	**SD**	**Mean**	**SD**	
Claudication Onset Time (sec)	240	178	265	214	0.68
Peak Walking Time (sec)	475	194	438	212	0.55
Peak Oxygen Uptake ($ml \cdot kg^{-1} \cdot min^{-1}$)	13.5	3.5	12.6	3.1	0.40
Ischemic Window (mmHg × min/meter)	0.52	0.45	0.47	0.62	0.74
WIQ Distance Score (%)	39	30	45	35	0.56
WIQ Speed Score (%)	35	20	42	25	0.30
WIQ Climbing Score (%)	45	29	42	31	0.73
Daily Ambulatory Activity (strides/day)	3719	1811	3688	1920	0.96

Table III

6-minute walk measurements of subjects.

	Pain Group (n=33)		Pain-Free Group (n=17)		P-value
	Mean	**SD**	**Mean**	**SD**	
6-Min Walk Pain-free Time (sec)	156	29	360	0	<0.0001*
6-Min Walk Pain-Free Distance (meters)	179	45	401	76	<0.0001
6-Min Walk Distance (meters)	393	74	401	76	0.74

*Comparison made between 6-minute walk pain-free time in the Pain group and a fixed value of 360 seconds in the Pain-Free group using a one-sample t-test.

Table IV

Oxygen uptake and gait measures during a 6-minute walk test in the Pain-Group (n = 33) and Pain-Free Group (n = 17). Data summaries are median (interquartile range: 25th to 75th percentile).

Variables	Time Point 1 *	Time Point 2 **	Δ (Time point 2 – Time point 1)	Change Score (P Value)	Difference Between Change Scores (P Value)
VO_2 per minute ($ml \cdot kg^{-1} \cdot min^{-1}$)					
Pain Group	8.4 (6.6 to 9.6)	11.4 (10.1 to 14.0)	3.5 (2.5 to 4.6)	<0.0001	0.025
Pain-Free Group	8.4 (7.5 to 10.2)	11.0 (10.2 to 12.6)	2.3 (1.5 to 3.2)	<0.0001	
VO_2 per meter walked ($ml \cdot kg^{-1} \cdot meter^{-1}$)					
Pain Group	0.10 (0.08 to 0.12)	0.14 (0.12 to 0.18)	0.05 (0.02 to 0.07)	<0.0001	-------
Pain-Free Group	-------	-------	-------	-------	
VO_2 per stride taken ($ml \cdot kg^{-1} \cdot stride^{-1}$)					
Pain Group	0.18 (0.15 to 0.20)	0.21 (0.19 to 0.26)	0.04 (0.02 to 0.06)	<0.0001	0.36
Pain-Free Group	0.17 (0.13 to 0.20)	0.21 (0.19 to 0.26)	0.05 (0.03 to 0.07)	<0.0001	
Velocity (meter/min)					
Pain Group	66.6 (61.8 to 75.5)	65.9 (53.5 to 69.2)	−4.4 (−13.3 to −1.7)	< 0.0001	-------
Pain-Free Group	-------	-------	-------	-------	
Cadence (strides/min)					
Pain Group	55.0 (52.0 to 56.0)	54.0 (50.5 to 56.0)	−1.0 (−1.5 to 0.0)	0.0003	0.79
Pain-Free Group	53.0 (50.0 to 56.0)	52.0 (50.0 to 54.0)	0.0 (−1.0 to 0.0)	0.0078	
Stride Length (meter/stride)					
Pain Group	1.25 (1.13 to 1.39)	1.17 (1.09 to 1.33)	−0.05 (−0.14 to −0.02)	< 0.0001	-------
Pain-Free Group	-------	-------	-------	-------	

* Values during Time Point 1 were obtained during pain-free ambulation in the Pain Group and during the second minute of ambulation in the Pain-Free Group.

** Values for Time Point 2 were obtained during painful ambulation in the Pain Group and during the fifth minute of ambulation in the Pain-Free Group.

Table V

Multiple regression model predicting the change in oxygen uptake following the onset of claudication in subjects in the Pain Group (n = 33).

Dependent Variables	Independent Variables	Regression Coefficient	95% Confidence Interval	P-value
Δ Oxygen Uptake ($ml \cdot kg^{-1} \cdot min^{-1}$)	Age (years)	0.064	0.022 to 0.11	0.0041
	Metabolic syndrome (no syndrome reference)	−1.83	−2.93 to −0.71	0.0023
	6-minute walk total distance (meters)	0.0093	0.0033 to 0.015	0.0037
	Minute 2 VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	0.20	0.049 to 0.36	0.012
	Height (cm)	−0.014	−0.061 to 0.033	0.54