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J Vasc Surg. Author manuscript; available in PMC 2010 July 1.

Published in final edited form as:
J Vasc Surg. 2009 July ; 50(1): 77–82. doi:10.1016/j.jvs.2008.12.065.

SEX DIFFERENCES IN CALF MUSCLE HEMOGLOBIN OXYGEN SATURATION IN PATIENTS WITH INTERMITTENT CLAUDICATION

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Abstract

Purposes—We tested the hypotheses that women have greater impairment in calf muscle hemoglobin oxygen saturation (StO_2) in response to exercise than men, and that the sex-related difference in calf muscle StO_2 would partially explain the shorter claudication distances of women.

Methods—Twenty-seven men and 24 women with peripheral arterial disease limited by intermittent claudication were studied. Patients were characterized on calf muscle StO_2 before, during, and after a graded treadmill test, as well as on demographic and cardiovascular risk factors, ankle/brachial index (ABI), ischemic window, initial claudication distance (ICD), and absolute claudication distance (ACD).

Results—Women had a 45% lower ACD than men (296 ± 268 meters vs. 539 ± 288 meters; p = 0.001) during the treadmill test. Calf muscle StO_2 declined more rapidly during exercise in women than in men, as the time to reach minimum StO_2 occurred 54% sooner in women (226 ± 241 sec vs. 491 ± 426 sec; p = 0.010). Additionally, the recovery time for calf muscle StO_2 to reach the resting value after treadmill exercise was prolonged in women (383 ± 365 sec vs. 201 ± 206 sec; p = 0.036). Predictors of ACD included the time from start of exercise to minimum calf muscle StO_2, the average rate of decline in StO_2 from rest to minimum StO_2 value, the recovery half-time of StO_2, and ABI ($R^2 = 0.70$; $p < 0.001$). The ACD of women remained lower after adjusting for ABI (mean difference = 209 meters; p = 0.003), but was no longer significantly lower (mean difference = 72 meters; p = 0.132) after further adjustment for the three calf muscle StO_2 variables.

Conclusion—In patients limited by intermittent claudication, women have lower ACD and greater impairment in calf muscle StO_2 during and following exercise than men, the exercise-mediated

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changes in calf muscle StO_2 are predictive of ACD, and women have similar ACD as men after adjusting for calf StO_2 and ABI measures.

INTRODUCTION

Intermittent claudication is a symptom of peripheral arterial disease (PAD), and is associated with elevated rates of mortality[1–4] and morbidity.[5] Intermittent claudication afflicts 5% of the US population older than 55 years of age,[6] and occurs during ambulation when the peripheral circulation is inadequate to meet the metabolic requirement of the active leg musculature. Women are less likely to report classic symptoms of intermittent claudication than men at all age groups,[7,8] and are more likely to have asymptomatic PAD.[9] The lower prevalence of intermittent claudication in women may be a consequence of lower levels of physical activity than men,[10] reporting atypical leg symptoms that are not characteristic of the classical history of intermittent claudication,[8,11] or a combination of both. Once intermittent claudication is diagnosed, women lead functionally dependent lifestyles,[9,12] and have a two-fold higher mortality rate than men.[7]

Women with intermittent claudication have shorter walking distances to the onset of claudication pain, and to maximal claudication pain during standardized treadmill exercise than men, even though their ankle/brachial index (ABI) is similar.[10] This finding suggests that women may have greater muscular ischemia during exercise than men. We have previously used the non-invasive technique of near infrared spectroscopy(NIRS) to assess hemoglobin oxygen saturation (StO_2) of the calf musculature during exercise.[13,14] This technique measures total hemoglobin content of the tissue underneath the probe, which corresponds to capillary blood volume,[15] The StO_2 measurement of the calf provides real-time information on the balance between oxygen delivery and oxygen extraction during ambulation.[13,16–22] As muscle metabolic demand increases during increasingly more intense exercise, patients with intermittent claudication deliver insufficient blood flow and oxygen to the calf musculature, resulting in a decline in StO_2. Thus, the change in calf muscle StO_2 during exercise provides clinically useful information on local ischemia in patients with intermittent claudication.

The purposes of this study were to compare the calf muscle StO_2 measured during standardized treadmill exercise between men and women with intermittent claudication, and to determine whether calf muscle StO_2 explains sex-related differences in claudication distances. Our hypotheses were that women would have greater impairment in calf muscle StO_2 in response to exercise than men, and that the sex-related difference in calf muscle StO_2 would partially explain the shorter claudication distances of women.

METHODS

SUBJECTS

Patients who were limited by intermittent claudication secondary to vascular insufficiency were recruited and screened for this study as described elsewhere.[14] The number of men and women seen in the university vascular clinics and laboratories are similar, which enhanced our ability to recruit a similar number of men and women for this investigation. 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.

MEASUREMENTS

Medical History, Physical Examination, and Anthropometry—Demographic information, height, weight, cardiovascular risk factors, co-morbid conditions, claudication history, blood samples, pulse oximeter measurement, anthropometric measures,[23] and a list of

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current medications were obtained from a medical history and physical examination to begin the evaluation.

Gardner Treadmill Test—Patients performed a progressive, graded treadmill protocol until maximal claudication pain as previously described.[24] The initial claudication distance (ICD) and the absolute claudication distance (ACD) were both recorded to quantify the severity of claudication. Exercise capacity was measured by oxygen uptake at peak exercise 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 ICD,[24] R = 0.93 for ACD[24], and R = 0.88 for peak oxygen uptake.[25] Patient who were limited by intermittent claudication on this test were included in this study, whereas those who stopped exercise for other reasons were excluded.

ABI and Ischemic Window—As previously described, ABI was obtained from the more severely diseased lower extremity by the Doppler ultrasound technique before and at 1, 3, 5, and 7 minutes after the treadmill test.[24,26] The ischemic window was determined from the reduction in ankle systolic blood pressure following treadmill exercise compared to the resting baseline value.[27]

Hemoglobin Oxygen Saturation (StO_2) of the Calf Musculature—Calf muscle StO_2 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.[14] 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.[13] A baseline measure of calf muscle StO_2 was obtained at rest as patients stood on the treadmill for two minutes to allow for equilibration. From the start of treadmill exercise, the minimum StO_2 value, the time taken to reach the minimum value, the absolute and percentage drops in calf muscle StO_2 from rest to the minimum exercise value, and the average rate of decline from rest to the minimum exercise value were obtained. The recovery times for StO_2 to reach one half of the resting StO_2 value (recovery half-time), to reach the full resting StO_2 value (recovery time), and to reach the maximum StO_2 value were calculated by subtracting the time to end of exercise from time recovery StO_2 values observed.

6-Minute Walk Test—Patients performed an over ground, 6-minute walk test and pain-free and total distance walked during the test were recorded. [28] The test-retest intraclass reliability coefficient is R = 0.75 for distance to onset of claudication pain, and R = 0.94 for total 6-minute walking distance.[28]

Walking Impairment Questionnaire (WIQ)—Self-reported ambulatory ability was assessed using a validated questionnaire for PAD patients that assesses ability to walk at various speeds and distances, and to climb stairs.[29]

Ambulatory Activity Monitoring—Daily ambulatory activity was assessed using a step activity monitor (Step Watch 3, Cyma Inc., Mountlake Terrace, WA), as previously described. [30] Ambulatory activity was measured during seven consecutive days in which patients 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 strides taken on a minute-to-minute basis. The accuracy of the step activity monitor exceeds 99% ± 1% in patients with intermittent claudication.[30]

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STATISTICAL ANALYSES

Differences in means of measurement variables in men and women were examined using the Independent Sample t-test. Chi Square procedures were used to examine differences between genders for dichotomous variables. A stepwise regression procedure with switching (probability to enter = .1 and probability to remove = .15) was used to select predictive models for ACD. Initially, measurement variables BMI, ABI, and dichotomous current smoking, and disease status variables were used as the set of possible predictors. The single variable ABI selected by the procedure was then used as a covariate in an ANCOVA analysis comparing ACD in men and women. The set of predictors was expanded to include calf muscle StO_2 variables, and a second prediction model was obtained. An ANCOVA using these model variables as covariates was used to compare ACD in men and women. All analyses were performed using the NCSS statistical package (NCSS Inc, Kaysville, UT). Statistical significance was set at $p < 0.05$. Measurements are presented as means ± standard deviations.

RESULTS

The clinical characteristics of men and women with intermittent claudication are shown in Table I. The groups were similar on all variables ($p > 0.05$), except that women were shorter ($p < 0.001$) and there was a trend for women having lower body weight ($p = 0.076$). Exercise performance measures of the men and women are shown in Table II. Women had lower ACD ($p = 0.001$), peak oxygen uptake ($p < 0.001$), WIQ speed score ($p < 0.001$), WIQ stair climbing score ($p = 0.001$), 6-minute walk pain-free distance ($p = 0.003$), and 6-minute walk total distance ($p < 0.001$). Furthermore, fewer women walked continuously during the 6-minute walk test than men ($p < 0.001$), as 64% of women stopped ambulating at some point during the test. Although not significant, there was a trend for women having lower ICD ($p = 0.094$) and WIQ distance score ($p = 0.079$). No group difference was noted for the ischemic window ($p = 0.300$).

Measures of calf muscle hemoglobin oxygen saturation (StO_2) of men and women with intermittent claudication are shown in Table III. The time to reach minimum StO_2 occurred more than four minutes sooner in women than in men ($p = 0.010$). Figure 1 illustrates the similarity of dependency of ACD on the time to minimum StO_2 in men ($R = 0.580$, $R^2 = 0.336$, $p = 0.002$), women ($R = 0.622$, $R^2 = 0.387$, $p = 0.001$), and in the total group ($R = 0.653$, $R^2 = 0.427$, $p < 0.0001$). Additionally, the recovery time for calf muscle StO_2 to reach the resting value after treadmill exercise was prolonged by more than three minutes in women ($p = 0.036$). The groups were similar on the remaining variables ($p > 0.05$).

The regression model predicting ACD of men and women with intermittent claudication is displayed in Table IV. Using a forward stepwise regression procedure, the time to minimum calf muscle StO_2, the average rate of decline in StO_2 from rest to minimum exercise value, the recovery half-time of StO_2 following treadmill exercise, and ABI entered the model predicting ACD. The R^2 of the full model was 0.70, indicating that the four predictors combined to explain 70% of the variance in ACD. The differences in unadjusted and adjusted values of ACD of the groups are displayed in Table V. Women had lower unadjusted ACD than men ($p = 0.001$), which remained lower after adjusting for ABI ($p = 0.003$), indicating that sex differences in ACD is not attributable to differences in ABI. However, after further adjustment for the three calf muscle StO_2 variables, ACD was no longer significantly lower in the women ($p = 0.132$).

DISCUSSION

The major findings of this investigation are that (1) women have lower ACD and reach minimum calf muscle StO_2 more than four minutes sooner during exercise than men, (2) the time to minimum calf muscle StO_2, the average rate of decline in StO_2 from rest to minimum

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StO_2 value, and the recovery half-time of StO_2 following treadmill exercise are predictive of ACD, and (3) women have similar ACD as men after adjusting for these calf muscle StO2 measures and ABI.

Differences in Calf Muscle StO_2 and Claudication in Women and Men

A key measure of calf muscle StO_2 during exercise is the observed time to reach the minimum StO_2 value, as this measure is positively associated with ICD and ACD, and negatively associated with ischemic window in patients with intermittent claudication.[14] In the current study, women had a shorter time to reach minimum calf muscle StO_2 than men, suggesting a greater impairment in the increase in capillary blood volume during exercise.[15] The fact that ABI was not different between men and women, and that calf muscle StO_2 was predictive of ACD after adjusting for ABI indicates that the microcirculation has an important role in exercise performance independent of the macrocirculation. The faster decline in calf muscle StO_2 in women during standardized treadmill walking is a novel finding, and provides a possible physiologic explanation for their shorter ACD noted in this study and in a previous report than compared to men.[10] Indeed, the time to minimum calf muscle StO_2 was a highly significant predictor of ACD, as well as the average rate of decline in StO_2 from rest to minimum StO_2 value, and the recovery half-time of StO_2 following exercise. The longer recovery time of calf muscle StO_2 in women is a consequence of the greater impairment in calf muscle StO_2 during exercise than compared to men. Collectively, these findings suggest that calf muscle StO_2 measured during and following exercise explain sex-related differences in ACD, even after adjusting for ABI.

In contrast to the observation that ACD was shorter in women than in men, the ICD was not significantly different between the two groups. This finding does not support our previous observation of women having a shorter ICD.[10] Upon closer examination, the discrepancy between the ICD results from this study and our previous study is most likely due to the smaller sample size of the current study. When the mean difference in ICD between women and men is compared, the results from the two studies are remarkably similar. Women reached ICD 66 meters (28%) sooner than men in this study, which is similar to our previous observation that women attained ICD 63 meters (33%) sooner.[10] The greater ischemic response during exercise in women, as measured by their shorter time to minimum calf muscle StO_2, has less impact on sex-related differences for ICD than for ACD. This is probably a reflection of the time to minimum calf muscle StO_2 during exercise having a weaker association with ICD than with ACD.[14]

Differences in Exercise Performance in Women and Men

In addition to having a shorter ACD, the peak oxygen uptake was 28% lower in women than in men. This is an expected finding, and supports our earlier observation of a lower peak oxygen uptake in women,[10] indicating that they have lower cardiopulmonary fitness than men. The impaired exercise performance of women during maximal treadmill exercise also is evident during the less intense 6-minute walk test, as the pain-free walk distance was 42% lower in women than in men, and the total distance covered during the test was 30% lower in women. Furthermore, far fewer women walked continuously for the entire six minutes, as nearly two-thirds had to stop at least once during the test. These results support another investigation which found that women with PAD had a significantly lower 6-minute walk distance than men with PAD.[8] Finally, the women in this study perceived their ambulatory function to be more impaired than men, as their scores on the WIQ walking speed and WIQ stair climbing subscales were lower, which agrees with our previous study.[10]

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Limitations

There are limitations to this study that are associated with the measurement of calf muscle StO_2 as previously described.[14] Briefly, myoglobin may partially contribute to the calf muscle StO_2 measurement, capillary and venular blood having different oxygen saturations may mix in the local tissue, and the subcutaneous fat thickness directly under the probe may interfere with the measure of calf muscle StO_2. However, we believe these limitations have minimal influence on calf muscle StO_2 as discussed earlier.[14] Another limitation is that differences in body composition between men and women may account for some of the differences seen in this study. In a previous study, we found that lean tissue mass of the legs is associated with peak VO_2 in patients with intermittent claudication,[31] but it's relationship with either ACD or calf muscle StO_2 is not known. However, we believe that group differences in leg lean tissue mass had minimal impact in the present study because no difference in ACD was found between men and women after adjustment for ABI and calf muscle StO_2 measures, suggesting that other factors did not contribute to sex-differences in exercise performance. An additional limitation is that hormonal replacement therapy may have altered results, but this is unlikely as only a couple of women were on this regimen. Finally, the results of this study are only applicable to PAD patients who are limited by intermittent claudication, and thus may not be generalizable to patients with different symptomatology.

Conclusions

We conclude that in patients limited by intermittent claudication, women have lower ACD and greater impairment in calf muscle StO_2 during and following exercise than men, the exercise-mediated changes in calf muscle StO_2 are predictive of ACD, and women have similar ACD as men after adjusting for calf StO_2 and ABI measures. These data support the hypothesis that the greater impairment in calf muscle StO_2 in women is a physiologic mechanism for their shorter ACD.

Acknowledgments

This research was supported by grants from the National Institute on Aging (NIA) (R01-AG-24296; AWG), by a Oklahoma Center for the Advancement of Science and Technology grant (HR04-113S; AWG), and by the University of Oklahoma Health Sciences Center General Clinical Research Center grant (M01-RR-14467), sponsored by the National Center for Research Resources from the National Institutes of Health. The final peer-reviewed version of this manuscript is subject to the NIH Public Access Policy, and will be submitted to PubMed Central.

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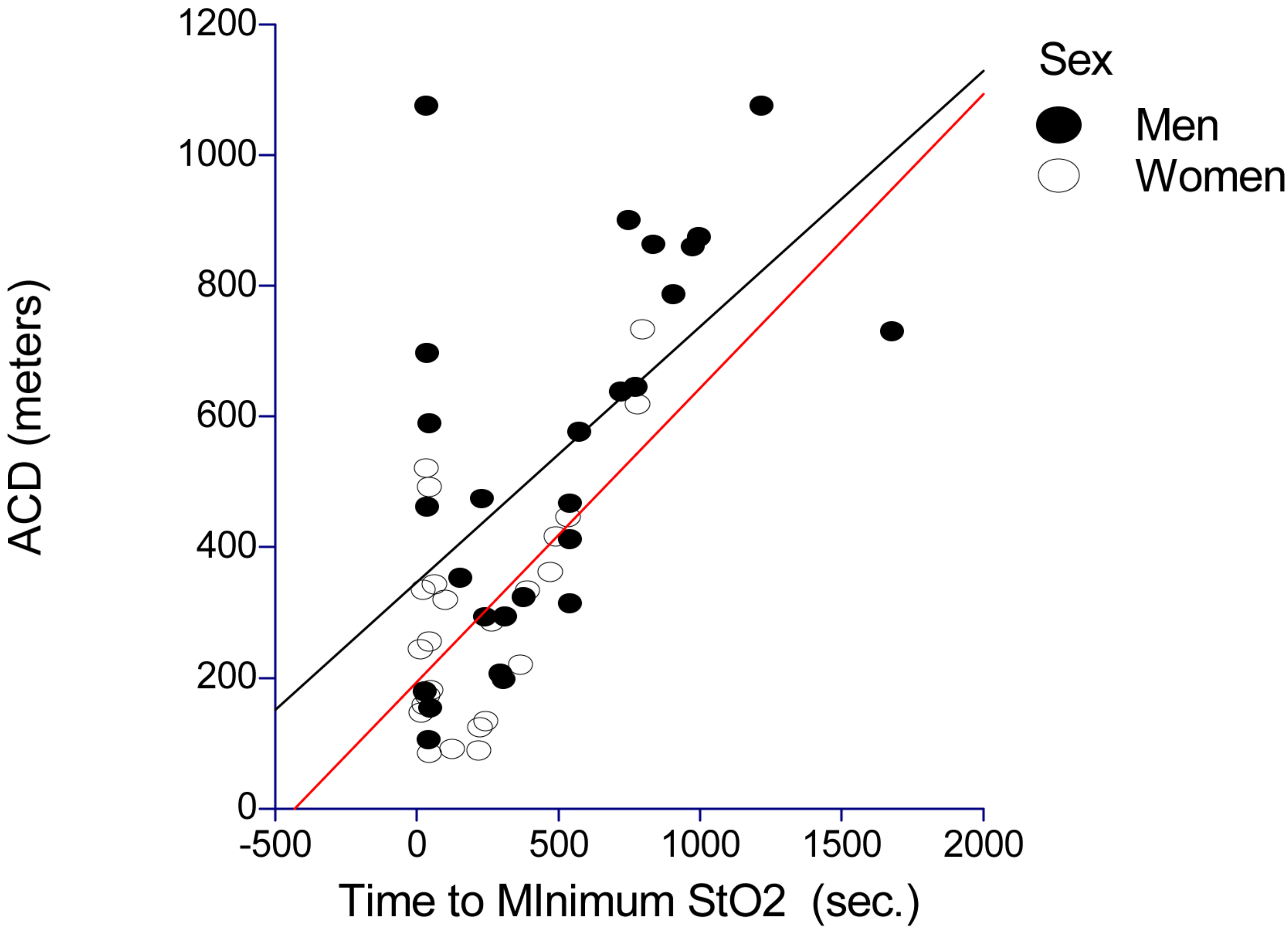

Figure 1.
Association between time to minimum calf muscle hemoglobin oxygen saturation (StO_2) and absolute claudication distance in men and women with intermittent claudication.

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Table I

Clinical characteristics of men and women with intermittent claudication. Values are means (SD) or percentage of subjects in each category.

Variables	Men (n = 27)	Women (n = 24)	P Value
Age (years)	69 (9)	67 (11)	0.522
Height (cm)	174.4 (7.4)	160.9 (6.6)	< 0.001
Weight (kg)	85.6 (19.0)	76.9 (14.7)	0.076
Body Mass Index (kg/m^2)	28.1 (6.0)	29.8 (6.0)	0.338
Ankle/Brachial Index	0.69 (0.19)	0.61 (0.19)	0.125
Race (% Caucasian)	59	38	0.121
Current Smoking (% yes)	33	48	0.297
Diabetes (% yes)	26	46	0.138
Hypertension (% yes)	89	79	0.451
Dyslipidemia (% yes)	78	88	0.473

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Table II

Exercise performance of men and women with intermittent claudication. Values are means (SD).

Variables	Men (n = 27)	Women (n = 24)	P Value
ICD (meters)	236 (151)	170 (118)	0.094
ACD (meters)	483 (258)	265 (156)	0.001
Peak Oxygen Uptake ($ml.kg^{-1} \cdot min^{-1}$)	15.0 (4.4)	10.8 (2.9)	< 0.001
Walking Economy ($ml.kg^{-1} \cdot min^{-1}$)	10.8 (1.8)	9.7 (1.6)	0.024
Ischemic Window following Graded Treadmill Test (mmHg × min/meter)	0.41 (0.48)	0.56 (0.54)	0.300
Ischemic Window following Walking Economy Test (mmHg × min/meter)	0.26 (0.45)	0.41 (0.59)	0.291
6-Minute Walk Pain-Free Distance (meters)	242 (126)	140 (89)	0.003
6-Minute Walk Distance (meters)	394 (88)	277 (78)	0.000
6-Minute Walk Rating of Perceived Exertion (score)	12.7 (2.3)	13.3 (3.5)	0.484
Walked Continuously for 6 Minutes (% of subjects)	88	36	0.001
WIQ Distance Score (%)	51 (32)	35 (30)	0.079
WIQ Speed Score (%)	46 (21)	25 (18)	0.000
WIQ Stair Climbing Score (%)	57 (25)	32 (27)	0.001
Daily Ambulatory Activity (strides/day)	3631 (2254)	3275 (2443)	0.590

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Table III

Measures of calf muscle hemoglobin oxygen saturation (StO_2) of men and women with intermittent claudication from start of exercise to maximum recovery. Values are means (SD).

Variables	Men (n = 27)	Women (n = 24)	P Value
StO_2 at rest (% saturation)	59 (18)	51 (20)	0.120
Minimum StO_2 (% saturation)	18 (20)	17 (21)	0.885
Time to minimum StO_2 (sec)	491 (426)	226 (241)	0.010
Absolute Drop in StO_2 (% saturation)	41 (20)	34 (16)	0.146
Percentage Drop in StO_2 (%)	72 (28)	72 (29)	0.972
Average Rate of Decline in StO_2 from rest to minimum exercise value (% saturation/sec)	0.40 (0.62)	0.49 (0.48)	0.553
Recovery Half-Time of StO_2 (sec)	143 (247)	183 (253)	0.575
Recovery Time of StO_2 (sec)	201 (206)	383 (365)	0.036
Recovery Time to Maximal StO_2 (sec)	618 (258)	766 (324)	0.082
Maximum recovery StO_2 (% saturation)	91 (8)	73 (21)	<0.001

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Table IV

Regression model predicting absolute claudication distance of men and women with intermittent claudication.

Variables	Regression Coefficient	Standard Error	Confidence Interval (95%)	Partial R^2 Adjusted for Other Variables	P Value
Intercept	−157.13	94.42	−347.31 to 33.04	-----	0.103
Ankle-brachial index	244.87	125.42	−7.74 to 497.47	0.078	0.057
Time to minimum calf muscle StO_2	0.56	0.12	0.31 to 0.81	0.311	< 0.001
Average Rate of Decline in calf muscle StO_2 from rest to minimum value	151.29	65.86	18.65 to 283.94	0.105	0.026
Recovery Half-Time of calf muscle StO_2	0.25	0.10	0.05 to 0.45	0.123	0.016

StO_2 = hemoglobin oxygen saturation.

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Table V

Unadjusted and adjusted absolute claudication distance of men and women with intermittent claudication. Values are means (SEM).

Variables	Men (n = 27)	Women (n = 24)	P Value
ACD unadjusted (meters)	483 (50)	265 (32)	0.001
ACD adjusted for ABI (meters)	468 (40)	281 (42)	0.003
ACD adjusted for ABI and calf muscle StO_2 variables* (meters)	401 (26)	341 (27)	0.132

*Adjusted for time to minimum StO_2, the average rate of decline in StO_2 from rest to minimum StO_2 value, and recovery half-time of StO_2. ABI = ankle/brachial index, ACD = absolute claudication distance, StO_2 = hemoglobin oxygen saturation.