

# The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication

Andrew W. Gardner, PhD,<sup>a,b</sup> Polly S. Montgomery, MS,<sup>a,b</sup> William R. Flinn, MD,<sup>c</sup> and Leslie I. Katznel, MD, PhD,<sup>b,d</sup> Oklahoma City, OK; and Baltimore Md

**Purpose:** The purpose of this randomized trial was to compare the efficacy of a low-intensity exercise rehabilitation program vs a high-intensity program in changing physical function, peripheral circulation, and health-related quality of life in peripheral arterial disease (PAD) patients limited by intermittent claudication.

**Methods:** Thirty-one patients randomized to low-intensity exercise rehabilitation and 33 patients randomized to high-intensity exercise rehabilitation completed the study. The 6-month exercise rehabilitation programs consisted of intermittent treadmill walking to near maximal claudication pain 3 days per week at either 40% (low-intensity group) or 80% (high-intensity group) of maximal exercise capacity. Total work performed in the two training regimens was similar by having the patients in the low-intensity group exercise for a longer duration than patients in the high-intensity group. Measurements of physical function, peripheral circulation, and health-related quality of life were obtained on each patient before and after the rehabilitation programs.

**Results:** After the exercise rehabilitation programs, patients in the two groups had similar improvements in these measures. Initial claudication distance increased by 109% in the low-intensity group ( $P < .01$ ) and by 109% in the high-intensity group ( $P < .01$ ), and absolute claudication distance increased by 61% ( $P < 0.01$ ) and 63% ( $P < .01$ ) in the low-intensity and high-intensity groups, respectively. Furthermore, both exercise programs elicited improvements ( $P < .05$ ) in peak oxygen uptake, ischemic window, and health-related quality of life.

**Conclusion:** The efficacy of low-intensity exercise rehabilitation is similar to high-intensity rehabilitation in improving markers of functional independence in PAD patients limited by intermittent claudication, provided that a few additional minutes of walking is accomplished to elicit a similar volume of exercise. (J Vasc Surg 2005;42:702-9.)

Peripheral arterial disease (PAD) is a leading cause of morbidity due to ambulatory dysfunction associated with intermittent claudication.<sup>1</sup> Intermittent claudication afflicts 5% of the United States population >55 years of age,<sup>2</sup> thereby limiting daily physical activities<sup>3</sup> and negatively affecting quality of life<sup>4</sup> in many older adults. A primary therapeutic goal for PAD patients with intermittent claudication is to regain lost physical function through exercise rehabilitation.<sup>5</sup> Medically supervised exercise programs are efficacious for the clinical management of intermittent clau-

dition,<sup>6</sup> as improvements are noted for initial claudication distance (ICD), absolute claudication distance (ACD), measured and perceived ambulatory function, physical activity level, quality of life, and calf blood flow in PAD patients with intermittent claudication.<sup>6-14</sup>

A meta-analysis summarizing 21 exercise trials in patients with intermittent claudication found that the optimal program to improve ICD and ACD used intermittent walking to near-maximal leg pain during a program of at least 6 months.<sup>6</sup> In addition to these factors, exercise duration of >30 minutes per training session and exercise frequency of at least three training sessions per week resulting in greater increases in ICD and ACD than exercise programs with shorter and less frequent exercise training sessions.<sup>6</sup>

One glaring omission in formulating an optimal exercise program for PAD patients with intermittent claudication is the lack of understanding of the appropriate exercise intensity to be used during the training sessions. For example, no study has examined whether intermittent walking at relatively high exercise intensity elicits more favorable adaptations in ICD and ACD than intermittent walking at lower exercise intensity. Without this fundamental understanding, it is unclear whether patients must exercise above a threshold of intensity to experience optimal improvements in their symptoms.

The purpose of this randomized trial was to compare the efficacy of a low-intensity exercise rehabilitation pro-

From the CMRI Metabolic Research Center, University of Oklahoma Health Sciences Center,<sup>a</sup> the Department of Medicine, Division of Gerontology,<sup>b</sup> and the Department of Surgery, Division of Vascular Surgery,<sup>c</sup> University of Maryland; and Maryland Veterans Affairs Health Care System.<sup>d</sup>

Competition of interest: none.

Presented at the International Society of Cardiovascular Surgery Meeting, Waimea, Hawaii, March 22-25, 2004.

Supported by grants from the National Institute on Aging (NIA) (R01-AG-16685, K01-00657; A. W. G.), by a Claude D. Pepper Older American Independence Center grant from NIA (P60-AG12583), by a Geriatric, Research, Education, and Clinical Center grant from the Veterans Affairs Administration, and by a National Institutes of Health, National Center for Research Resources, General Clinical Research Center grant (M01-RR-14467).

Reprint requests: Andrew W. Gardner, PhD, Hobbs-Recknagel Professor, CMRI Metabolic Research Center, University of Oklahoma Health Sciences Center, 1122 N.E. 13<sup>th</sup> Street, ORI-W 1400, Oklahoma City, OK 73117 (e-mail: Andrew-gardner@ouhsc.edu).

0741-5214/\$30.00

Copyright © 2005 by The Society for Vascular Surgery.

doi:10.1016/j.jvs.2005.05.049

gram vs a high-intensity program in changing physical function, peripheral circulation, and health-related quality of life in peripheral arterial disease (PAD) patients limited by intermittent claudication.

## METHODS

**Patient screening.** A total of 77 PAD patients limited by intermittent claudication were enrolled into this investigation. The patients were recruited from the vascular clinic at the Baltimore location of the Maryland Veterans Affairs Health Care System (MVAHCS) and from newspaper and radio advertisements in 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 subject before the investigation.

All patients had a physical examination and medical history during the first baseline visit and were classified as having Fontaine stage II PAD<sup>15</sup> defined by the following inclusion criteria: (1) a history of intermittent claudication, (2) exercise tolerance limited by intermittent claudication during a screening treadmill test, (3) an ankle/brachial index (ABI) at rest of  $<0.90$ ,<sup>2</sup> and (4) ability to live independently at home.

Patients were excluded from this study for (1) absence of PAD, (2) asymptomatic PAD (Fontaine stage I), (3) rest pain PAD (Fontaine stage III), (4) exercise tolerance limited by factors other than claudication (eg, coronary artery disease, dyspnea, poorly controlled blood pressure), (5) active cancer, renal disease, or liver disease, and (6) current use of pentoxifylline or cilostazol medications for the treatment of intermittent claudication.

**Procedures.** Patients were evaluated during study visits at baseline and after 6 months of exercise rehabilitation. During each study visit, patients completed tests in the following order: (1) physical examination and medical history, including a review of current medications; (2) questionnaires on quality of life, health, physical function, and physical activity; (3) peripheral hemodynamic tests; and (4) exercise and physical function tests. At the end of the final study visit, at baseline and follow-up, an activity monitor was placed on the patients and they were instructed to wear it during their waking hours. Patients returned the monitor at least 2 days later for the physical activity data to be recorded.

**Exercise rehabilitation programs.** The exercise rehabilitation programs were designed to elicit increases in distances walked to onset and to maximal claudication according to our published recommendations.<sup>6</sup> Both exercise programs consisted of 6 months of supervised, intermittent treadmill walking to near maximal claudication pain 3 days per week at a speed of approximately 2 mph, as previously described.<sup>7-10</sup>

Patients who were randomized to the low-intensity exercise program ( $n = 38$ ) walked at a constant intensity of 40% of the maximal workload (ie, grade) achieved during the baseline maximal effort treadmill test. The walking duration began at 15 minutes for the first month of the

program, and progressively increased by 5 minutes per month until a total of 40 minutes of walking was accomplished by the sixth month of the low-intensity exercise program.

Patients who were randomized to the high-intensity exercise program ( $n = 39$ ) walked at a constant intensity of 80% of the maximal workload. The walking duration was shortened in the high-intensity group so that the total caloric expenditure of each training session (ie, volume of exercise) was similar to the total caloric expenditure that they would have accomplished if they had been randomized to the low-intensity group. This was accomplished by comparing the caloric expenditure values obtained at 40% and 80% during the baseline maximal effort treadmill test. On average, the patients in the high-intensity exercise program walked for a duration of 12, 17, 21, 26, 30, and 35 minutes during the 6 respective months of exercise training to equal the total caloric expenditure that they would have accomplished in the low-intensity program while walking for 15, 20, 25, 30, 35, and 40 minutes, respectively. Five minutes of cycling on a stationary bicycle ergometer served as both warm-up and cool-down exercise during each session of the low-intensity and high-intensity exercise programs.

There were no complications during the exercise training sessions. Seven patients from the low-intensity group and 6 patients from the high-intensity group withdrew from the exercise rehabilitation programs. Of the 13 patients who dropped out, four patients were unable to continue with the exercise sessions because of lack of consistent transportation, two patients developed poorly controlled blood pressure because of noncompliance with medications, two patients moved away from the local area, two patients underwent chemotherapy for malignancies, one patient experienced limitations in gait due to a stroke, one patient developed rest pain, and one patient did not want to continue with the exercise program for an unspecified reason. The remaining 31 patients in the low-intensity group and 33 patients in the high-intensity group completed the exercise intervention and post-treatment measures and comprise the sample for the final analyses.

## Measurements

Both groups were assessed on the following measurements before and after the exercise rehabilitation programs.

**Medical history.** Demographic information, cardiovascular risk factors, comorbidities, self-reported claudication history, location of claudication, and a list of current medications were obtained during a medical history interview to begin the evaluation. The medication regimen of each patient was held constant during the study.

**Claudication distances and peak oxygen uptake.** Patients performed a progressive, graded treadmill protocol (2 mph, 0% grade with 2% increase every 2 minutes) until maximal claudication pain as previously described.<sup>16,17</sup> Maximal claudication pain was defined as the point at which patients could no longer tolerate the increase in leg pain during the treadmill test. The ICD and ACD, time to relief of claudication pain after the test, and

peak oxygen uptake were measured. These procedures result in a test-retest intraclass reliability coefficient of  $R = 0.89$  for ICD,<sup>16</sup>  $R = 0.93$  for ACD,<sup>16</sup> and  $R = 0.88$  for peak oxygen uptake.<sup>18</sup> The final grade attained during this maximal effort test during the baseline examination was used to calculate the training intensity of the low-intensity and high-intensity groups. Patients randomized to the low-intensity group trained at a treadmill grade that was 40% of the final grade attained during the maximal effort test, whereas patients randomized to the high-intensity group trained at a treadmill grade that was 80% of the final grade.

**Walking economy and fractional utilization.** Oxygen uptake was measured during a constant, submaximal work rate at a treadmill speed of 2 mph and a grade of 0% until maximal claudication pain, or for a maximum of 20 minutes.<sup>19</sup> Because the duration of submaximal exercise affects oxygen uptake, we compared the oxygen uptake of each patient at the same time point before and after the study.<sup>19</sup> Consequently, walking economy was measured as the oxygen uptake during the final minute of walking at baseline and at the same time point during the post-test. To quantify the intensity of the walking economy test as a percentage of peak capacity, fractional utilization was calculated as the walking economy oxygen uptake/peak oxygen uptake.

**6-minute walk test.** Patients performed an over ground 6-minute walk test supervised by trained exercise technicians as previously described.<sup>20</sup> The pain-free and total distance walked during the test were recorded. The test-retest intraclass reliability coefficient is  $R = 0.75$  for the distance to onset of claudication pain and  $R = 0.94$  for the total 6-minute walking distance.<sup>20</sup>

**Walking Impairment Questionnaire.** Self-reported ambulatory ability was assessed with the Walking Impairment Questionnaire (WIQ), a validated questionnaire for PAD patients that assesses the ability to walk at various speeds and distances and to climb stairs.<sup>21</sup>

**Summary performance score.** The summary performance score was calculated from the performance of the 4-meter walk, the chair stand test, and the standing balance tests as previously described.<sup>22</sup> The summary performance score ranges from 0 to 12 (0 = worst function, 12 = best function) and is predictive of mobility loss, nursing home placement, and mortality among community-dwelling elderly individuals.<sup>22</sup> The test-retest intraclass reliability coefficient is  $R = 0.93$  for the summary performance score.<sup>23</sup>

**Health Utilities Index.** The Health Utilities Index (Health Utilities Inc, Dundas, Ontario, Canada) ranging between 0 (ie, the worst imaginable health) and 100 (ie, the best imaginable health) was used to assess self-reported health as previously described.<sup>24</sup> Patients were asked to select a numeric value on the scale that best corresponded to their current overall health state.

**Daily physical activity.** Physical activity level was monitored over two consecutive weekdays by a Caltrac accelerometer (Muscle Dynamics, Torrance, Calif) attached to the belt of each subject, as previously described.<sup>25</sup> The accelerometer assessed daily physical movements by

converting vertical accelerations of the body into caloric expenditure during the 48-hour monitoring period. The accelerometer measure of physical activity has an  $R = 0.84$  test-retest intraclass reliability coefficient<sup>26</sup> and provides a valid estimate of daily physical activity assessed by the gold standard technique of doubly labeled water.<sup>25</sup>

**ABI and ischemic window.** As previously described, ABI was obtained from the more severely diseased lower extremity by the Doppler ultrasound technique before and 1, 3, 5, and 7 minutes after the progressive, graded treadmill test used to assess claudication distances and peak oxygen uptake.<sup>17</sup> The reduction in ankle systolic blood pressure after the treadmill test from the resting value was quantified by calculating the area under the curve, referred to as the ischemic window.<sup>27</sup> To assess the change in the ischemic window after exercise rehabilitation, patients performed an additional progressive, graded treadmill test at follow-up but were stopped when they achieved the same walking distance as was measured at baseline. This permitted comparison of the change in the ischemic window for a given walking distance before and after exercise rehabilitation, as described by Carter et al.<sup>28</sup>

**Calf blood flow.** Calf blood flow was obtained under resting, reactive hyperemic, and maximal hyperemic conditions in the more severely diseased leg by using venous occlusion mercury strain-gauge plethysmography as previously described.<sup>29</sup> The test-retest intraclass reliability coefficient is  $R = 0.86$  for calf blood flow.<sup>29</sup>

**Quality of life.** Health-related quality of life was assessed with the Medical Outcomes Study Short-Form 36 (MOS SF-36) General Health Survey (QualityMetric, Inc, Lincoln, RI).<sup>30</sup> The MOS SF-36 is a reliable and valid generic instrument that includes multi-item scales measuring the eight health domains of physical function, role limitations due to physical problems, general health, bodily pain, social function, role limitations due to emotional problems, mental health, and vitality. For each subscale, item scores were recorded, summed, and standardized into a scale from 0 to 100, with better health states resulting in higher scores.

**Statistical analyses.** Unpaired  $t$  tests and  $\chi^2$  tests were used to assess whether differences in baseline clinical characteristics existed between the low-intensity and high-intensity exercise groups. A series of one-factor (group; low-intensity vs high-intensity) analyses of covariance was performed to compare the changes in the functional, physiologic, and quality-of-life variables after both exercise programs. Only those patients who had both pre-test and post-test data points were used in the analyses. The dependent variable in each analysis of covariance was the within-person difference (post-test minus pre-test) in the variable being analyzed. The initial value of the dependent variable was included as an independent covariate to adjust for the difference in its initial value. Post-hoc, unpaired  $t$  tests were performed to assess group differences in the functional, physiologic, and quality-of-life variables at baseline and follow-up.

**Table I.** Baseline clinical characteristics of patients with intermittent claudication who participated in low-intensity and high-intensity rehabilitation programs

| Variables                       | Low-intensity group<br>(n = 31)* | High-intensity group<br>(n = 33)* | P    |
|---------------------------------|----------------------------------|-----------------------------------|------|
| Age (years)                     | 67 (8)                           | 68 (7)                            | .236 |
| Duration of IC (years)          | 6.6 (6.5)                        | 3.6 (4.1)                         | .020 |
| Walking distance to IC (blocks) | 1.7 (1.3)                        | 2.5 (2.2)                         | .117 |
| Location of IC                  |                                  |                                   | .767 |
| Thigh and calf (%)              | 26                               | 30                                |      |
| Calf only (%)                   | 74                               | 70                                |      |
| Sex (% Men)                     | 88                               | 88                                | .831 |
| Race (% white)                  | 56                               | 49                                | .431 |
| Smoking history                 |                                  |                                   | .001 |
| (% never)                       | 2                                | 12                                | —    |
| (% former)                      | 24                               | 58                                | —    |
| (% current)                     | 73                               | 30                                | —    |
| Diabetes (%)                    | 20                               | 37                                | .242 |
| Hypertension (%)                | 73                               | 63                                | .555 |
| Hyperlipidemia (%)              | 61                               | 58                                | .855 |
| COPD (%)                        | 12                               | 7                                 | .373 |
| Dyspnea (%)                     | 39                               | 37                                | .852 |

IC, Intermittent claudication; COPD, chronic obstructive pulmonary disease.

\*Values are means (SD) and percentages.

Results from previous studies<sup>7-10</sup> indicated that the sample sizes of the patients who completed the low-intensity (n = 31) and high-intensity (n = 33) exercise groups yielded statistical power estimates of >90% to detect exercise-mediated changes in ICD and ACD and >70% to detect changes in most of the other measurements. If none of the patients had dropped out of the study, the statistical power estimates would have >99% for the changes in ICD and ACD, and >80% for all of the other measures.

Pearson product moment correlation coefficients (*r*) were calculated to determine the bivariate relationships among the changes in variables after exercise rehabilitation. Stepwise multiple regression was performed to identify the variables independently related to the change in claudication distances. Statistical significance was set at *P* < .05. Measurements are presented as means ± SD.

## RESULTS

The randomization resulted in similar (*P* > .05) baseline clinical characteristics between the low-intensity and high-intensity exercise groups (Table I), except that the low-intensity group had a longer history of intermittent claudication (*P* = .020) and had more patients who currently smoked (*P* < .001). Furthermore, the adherence to the exercise was similar (*P* > .05) between the low-intensity group (80% ± 16% attendance) and the high-intensity group (74% ± 18% attendance).

The groups were similar (*P* < .05) at baseline on each treadmill measure described in Table II. Both groups demonstrated a significant improvement in ICD (*P* < .01), ACD (*P* < .01), peak oxygen uptake (*P* < .05), walking

economy (*P* < .01), and fractional utilization (*P* < .01) after the low-intensity and high-intensity exercise programs. The change in each measure was similar (*P* > .05) between the two groups. Neither group had a significant (*P* > .05) change in the time to relief of claudication pain after the two exercise programs.

The low-intensity and high-intensity groups were similar (*P* > .05) at baseline on physical function, self-reported health, and the physical activity measurements described in Table III. Both groups had a significant (*P* < .05) improvement in the pain-free (*P* < .01) and total walking distances (*P* < .01) during the 6-minute walk, WIQ distance score (*P* < .05), summary performance score (*P* < .05), and daily physical activity (*P* < .05) after exercise rehabilitation. The change in each measure was similar (*P* > .05) between the two groups. Neither group had a significant (*P* > .05) change in WIQ speed score, WIQ stair climbing score, and self-perceived health after the two exercise programs.

The groups were similar (*P* < .05) at baseline on each peripheral hemodynamic measure described in Table IV. Both groups demonstrated a significant improvement in ischemic window (*P* < .01) and calf blood flow while resting (*P* < .05) as well as reactive hyperemic (*P* < .01) and maximal hyperemic (*P* < .01) conditions after exercise rehabilitation. The change in each measure was similar (*P* > .05) between the two groups. Neither group had a significant (*P* > .05) change in the ABI after the two exercise programs.

The low-intensity and high-intensity groups were similar (*P* > .05) at baseline on the health-related quality-of-life measurements described in Table V. Both groups had a significant improvement (*P* < .05) in physical function and bodily pain after exercise rehabilitation. The change in each measure was similar (*P* > .05) between the two groups. Neither group had a significant (*P* > .05) change in the other health domains after the low-intensity and high-intensity exercise programs.

Because of the similar changes in ICD and ACD after exercise rehabilitation between the two groups, patients in the low-intensity and high-intensity exercise groups were pooled to assess the correlates of the changes in claudication distances. The change in ICD was correlated with the change in peak oxygen uptake (*r* = 0.25, *P* = .046), change in walking economy (*r* = -0.31, *P* = .0017), change in fractional utilization (*r* = -0.46, *P* < .001), change in calf blood flow at rest (*r* = 0.28, *P* = .024), after reactive hyperemia (*r* = 0.39, *P* < .001) and after maximal hyperemia (*r* = 0.44, *P* < .001), and change in daily physical activity (*r* = 0.26, *P* = .039). Using stepwise multiple regression, we determined that the change in fractional utilization and the change in maximal calf blood flow were the only independent predictors of the change in ICD (multiple *R* = 0.56, *R*<sup>2</sup> = 0.31, *P* < .001). The change in fractional utilization entered the model first, explaining 21% of the variance, and the change in maximal calf blood flow entered the model on the second and final steps, explaining an additional 10% of the variance.

**Table II.** Treadmill measurements in patients with intermittent claudication who participated in low-intensity (n = 31) or high-intensity (n = 33) exercise rehabilitation programs

| Variables   | Pre-test*   | Post-test*              | Change score*           |
|---|-------------|-------------------------|-------------------------|
| Initial claudication distance (meters)                          |             |                         |                         |
| Low-intensity group   | 163 (123)   | 341 (218) <sup>†</sup>  | 178 (140) <sup>†</sup>  |
| High-Intensity group  | 186 (143)   | 388 (236) <sup>†</sup>  | 202 (241) <sup>†</sup>  |
| Absolute claudication distance (meters)                         |             |                         |                         |
| Low-intensity group   | 418 (228)   | 674 (293) <sup>†</sup>  | 256 (211) <sup>†</sup>  |
| High-intensity group  | 430 (222)   | 700 (281) <sup>†</sup>  | 270 (260) <sup>†</sup>  |
| Time to relief of claudication pain (min:sec)                   |             |                         |                         |
| Low-intensity group   | 6:30 (3:22) | 5:12 (3:19)             | -1:18 (4:05)            |
| High-intensity group  | 6:22 (4:00) | 6:05 (3:48)             | -0:17 (3:30)            |
| Peak oxygen uptake (mL · kg <sup>-1</sup> · min <sup>-1</sup> ) |             |                         |                         |
| Low-intensity group   | 13.5 (4.1)  | 15.0 (3.5) <sup>†</sup> | 1.5 (2.9) <sup>†</sup>  |
| High-intensity group  | 14.1 (3.3)  | 15.4 (3.4) <sup>†</sup> | 1.3 (2.9) <sup>†</sup>  |
| Walking economy (mL · kg <sup>-1</sup> · min <sup>-1</sup> )    |             |                         |                         |
| Low-intensity group   | 11.1 (2.2)  | 10.4 (1.8) <sup>†</sup> | -0.7 (1.9) <sup>†</sup> |
| High-intensity group  | 12.1 (2.2)  | 10.6 (2.0) <sup>†</sup> | -1.5 (2.0) <sup>†</sup> |
| Fractional utilization (%)                                      |             |                         |                         |
| Low-intensity group   | 82 (22)     | 69 (18) <sup>†</sup>    | 13 (20) <sup>†</sup>    |
| High-intensity group  | 86 (17)     | 69 (17) <sup>†</sup>    | 17 (19) <sup>†</sup>    |

\*Values are means (SD).

<sup>†</sup>Significant change from the pre-test ( $P < .05$ ).

The change in ACD was correlated with the change in peak oxygen uptake ( $r = 0.55$ ,  $P = .001$ ), change in walking economy ( $r = -0.45$ ,  $P < .001$ ), change in fractional utilization ( $r = -0.58$ ,  $P < .001$ ), change in maximal calf blood flow ( $r = 0.25$ ,  $P = .046$ ), and change in daily physical activity ( $r = 0.47$ ,  $P < .001$ ). Stepwise multiple regression showed that the change in fractional utilization was the only independent predictor of the change in ACD (multiple  $R = 0.58$ ,  $R^2 = 0.34$ ,  $P < .001$ ).

## DISCUSSION

The major finding of this investigation was that PAD patients limited by intermittent claudication who completed a low-intensity exercise program had similar improvements in physical function, peripheral circulation, and health-related quality of life as those patients who completed a high-intensity exercise program. This is the first investigation to directly compare rehabilitation programs using different intensities of exercise to elicit adaptations in functional outcomes in PAD patients limited by intermittent claudication.

Adherence to the exercise rehabilitation programs was similar between the patients in the low-intensity and high-intensity exercise programs, as attendance in the two programs was 80% and 74% of the possible training sessions, respectively. This finding is similar to the exercise attendance reported in a previous randomized, controlled exercise trial from our laboratory,<sup>8,10</sup> as well as from another investigation,<sup>31</sup> and is considerably better than the 45% attendance rate reported during a 6-month exercise program in another report.<sup>32</sup> Our data indicate that the exercise intensity used during training sessions is not an influential factor in the decision of patients to attend the program. Additionally, a similar percentage of patients in the low-intensity group (18%) and patients in the high-

intensity group (15%) dropped out in the early phase of the exercise programs, and none experienced serious adverse events that caused them to discontinue the exercise program. The attrition rate of patients enrolled in this study is similar to those found in previous reports having a study duration of 3 to 6 months<sup>7,8,10,33</sup> and considerably smaller than the 40% attrition rate that we found in a long-term exercise study lasting 18 months.<sup>9</sup> Collectively, data from this study indicate that patients with intermittent claudication who perform low-intensity exercise are no more likely to attend and safely complete a supervised program of exercise than those who perform high-intensity exercise.

The patients in the high-intensity exercise group increased their ICD by 202 meters (109%) and their ACD by 270 meters (63%) after 6 months of exercise rehabilitation, supporting previous reports from our laboratory.<sup>6-10</sup> The patients in the low-intensity exercise group demonstrated similar gains in ICD (178 meters, 109%) and in ACD (256 meters, 61%) after exercise rehabilitation, suggesting that walking at a lower grade on the treadmill for several additional minutes during each rehabilitation session results in exercise-mediated improvements in claudication walking distances that are similar to walking at a higher treadmill grade. Therefore, an exercise rehabilitation program that uses intermittent walking to near-maximal claudication pain performed at a relatively low treadmill grade (ie, 40% of maximal grade) may be a good alternative for PAD patients compared with walking at a relatively high grade (ie, 80% of maximal grade), provided that a few additional minutes of walking is accomplished to elicit a similar volume of exercise.

In addition to the similar improvements in ICD and ACD after the low-intensity and high-intensity exercise programs, patients in both programs demonstrated similar exercise-mediated improvements in peak oxygen uptake,

**Table III.** Physical function, self-reported health, and physical activity level in patients with intermittent claudication who participated in low-intensity (n = 31) or high-intensity (n = 33) exercise rehabilitation programs

| Variables                                 | Pre-test* | Post-test*             | Change score*          |
|---|-----------|------------------------|------------------------|
| 6-minute walk pain-free distance (meters) |           |                        |                        |
| Low-intensity group                       | 156 (100) | 201 (121) <sup>†</sup> | 45 (131) <sup>†</sup>  |
| High-intensity group                      | 168 (211) | 211 (99) <sup>†</sup>  | 43 (104) <sup>†</sup>  |
| 6-minute walk distance (meters)           |           |                        |                        |
| Low-intensity group                       | 362 (77)  | 391 (90) <sup>†</sup>  | 29 (59) <sup>†</sup>   |
| High-intensity group                      | 377 (90)  | 402 (102) <sup>†</sup> | 25 (79) <sup>†</sup>   |
| WIQ distance score (%)                    |           |                        |                        |
| Low-intensity group                       | 32 (28)   | 46 (35) <sup>†</sup>   | 14 (33) <sup>†</sup>   |
| High-intensity group                      | 38 (35)   | 50 (38) <sup>†</sup>   | 12 (39) <sup>†</sup>   |
| WIQ speed score (%)                       |           |                        |                        |
| Low-intensity group                       | 34 (28)   | 42 (26)                | 8 (29)                 |
| High-intensity group                      | 35 (26)   | 42 (30)                | 7 (29)                 |
| WIQ stair climbing score (%)              |           |                        |                        |
| Low-intensity group                       | 42 (27)   | 53 (32)                | 11 (41)                |
| High-intensity group                      | 51 (33)   | 56 (37)                | 5 (33)                 |
| Summary performance score (units)         |           |                        |                        |
| Low-intensity group                       | 7.8 (1.3) | 8.4 (1.2) <sup>†</sup> | 0.6 (1.3) <sup>†</sup> |
| High-intensity group                      | 6.6 (2.2) | 7.3 (2.6) <sup>†</sup> | 0.7 (1.9) <sup>†</sup> |
| Self-perceived health (%)                 |           |                        |                        |
| Low-intensity group                       | 75 (18)   | 84 (8)                 | 9 (15)                 |
| High-intensity group                      | 80 (15)   | 80 (15)                | 0 (18)                 |
| Daily physical activity (kcal/day)        |           |                        |                        |
| Low-intensity group                       | 313 (249) | 451 (211) <sup>†</sup> | 138 (204) <sup>†</sup> |
| High-intensity group                      | 340 (199) | 463 (298) <sup>†</sup> | 123 (218) <sup>†</sup> |

WIQ, Walking Impairment Questionnaire.

\*Values are means (SD).

<sup>†</sup>Significant change from the pre-test ( $P < 0.05$ ).

walking economy, and fractional utilization. The improvement in fractional utilization was a result of the combined changes in peak oxygen uptake and walking economy, indicating that the patients in the low-intensity and high-intensity exercise programs were able to perform the submaximal walking test at only 69% of their peak oxygen uptake after exercise rehabilitation, compared with 82% and 86% at baseline, respectively. The similar changes in peak oxygen uptake, walking economy, and fractional utilization after the two exercise programs suggest that the exercise stimulus in the low-intensity program was sufficient to elicit favorable adaptations in cardiopulmonary function and in efficiency of walking and that exercise performed at higher intensity did not result in further adaptations

The lower fractional utilization during treadmill walking after exercise rehabilitation may have important implications in performing tasks that more closely approximate activities of daily living in the community setting. For example, patients who completed the low-intensity and high-intensity exercise programs experienced significant and similar improvements in the pain-free walking distance and total walking distance during the 6-minute walk test, in the perceived ability to ambulate at various distances, in the summary performance score, and in daily physical activity. These findings suggest that exercise performed even at low

intensity can improve these functional measures, which may lower the risk for subsequent morbidity, nursing home admission, and mortality.<sup>22</sup> Additionally, the low-intensity and high-intensity exercise programs both resulted in similar gains in health-related measures of quality of life. The exercise-mediated increase in the physical function domain is supported by previous investigations,<sup>10,13,14,34,35</sup> as is the improvement in bodily pain.<sup>10,34</sup>

Patients who completed the low-intensity and high-intensity exercise programs had significant and similar increases in perfusion of the calf musculature after exercise rehabilitation, suggesting that enhanced peripheral circulation is a potential mechanism for the improvement in claudication pain distances and ambulatory function. The change in calf blood flow obtained during maximal hyperemia independently predicted the change in ICD, suggesting that the increase in maximal calf blood flow after exercise rehabilitation is a primary physiologic mechanism by which claudication pain improves. Exercise-mediated increases in peripheral circulation, as measured by venous occlusion plethysmography, are supported by some,<sup>7-11</sup> but not, all studies.<sup>36</sup> The decrease in the ischemic window in both groups after exercise rehabilitation lends further evidence of enhanced perfusion of the lower extremities and is supported by previous investigations.<sup>7,10,27</sup> The enhanced peripheral circulation in both groups may be due to improvements in nitric oxide-mediated endothelial function seen in PAD patients after a program of exercise rehabilitation.<sup>37</sup>

Although the results of this trial support the efficacy of exercise rehabilitation for PAD patients regardless of the exercise intensity used during the program, several limitations exist:

First, patients who participated in this trial were volunteers and therefore may represent those who had more interest in exercise, who had better access to transportation to the program, and who had relatively better health than PAD patients who did not volunteer.

Second, the study participants were predominantly men. Consequently, the efficacy of exercise performed at either low-intensity or high-intensity may not generalize to women limited by intermittent claudication.

Third, some bias in the study results may exist because the analyses were limited to only those who completed the study. Although there were no differences in baseline characteristics between the 64 patients who completed the trial and the 13 patients who withdrew (data not shown), the possibility that those who withdrew from the study would have responded less favorably to exercise cannot be ruled out.

Fourth, the low-intensity group had more patients who were active smokers than the high-intensity group at baseline. However, we believe this had minimal impact on the results of the current study because a previous report from our laboratory found that smoking status of patients limited by intermittent claudication does not alter the responses to an exercise program.<sup>10</sup>

**Table IV.** Peripheral hemodynamic measurements in patients with intermittent claudication who participated in low-intensity (n = 31) or high-intensity (n = 33) exercise rehabilitation programs

| Variables                        | Pre-test     | Post-test                 | Change score             |
|----------------------------------|--------------|---------------------------|--------------------------|
| Ankle brachial index             |              |                           |                          |
| Low-intensity group              | 0.62 (0.19)  | 0.64 (0.22)               | 0.02 (0.07)              |
| High-intensity group             | 0.66 (0.21)  | 0.65 (0.22)               | 0.01 (0.13)              |
| Ischemic window (AUC)            |              |                           |                          |
| Low-intensity group              | 255 (125)    | 166 (111) <sup>†</sup>    | -89 (144) <sup>†</sup>   |
| High-intensity group             | 240 (170)    | 163 (138) <sup>†</sup>    | -77 (170) <sup>†</sup>   |
| Calf blood flow: rest (%/min)    |              |                           |                          |
| Low-intensity group              | 3.15 (1.23)  | 3.64 (1.13) <sup>†</sup>  | 0.49 (1.06) <sup>†</sup> |
| High-intensity group             | 3.27 (1.00)  | 3.53 (1.18) <sup>†</sup>  | 0.26 (0.96) <sup>†</sup> |
| Calf blood flow: PORH (%/min)    |              |                           |                          |
| Low-intensity group              | 8.27 (3.42)  | 10.29 (3.52) <sup>†</sup> | 2.02 (3.94) <sup>†</sup> |
| High-intensity group             | 8.83 (3.90)  | 11.13 (4.09) <sup>†</sup> | 2.30 (4.05) <sup>†</sup> |
| Calf blood flow: maximal (%/min) |              |                           |                          |
| Low-intensity group              | 12.21 (5.39) | 15.32 (7.41) <sup>†</sup> | 3.11 (4.44) <sup>†</sup> |
| High-intensity group             | 11.90 (4.37) | 14.87 (6.79) <sup>†</sup> | 2.97 (5.46) <sup>†</sup> |

AUC, Area under the curve; PORH, postocclusive reactive hyperemia.

\*Values are means (SD).

<sup>†</sup>Significant change from the pre-test ( $P < .05$ ).

**Table V.** Health-related quality of life in patients with intermittent claudication who participated in low-intensity (n = 31) or high-intensity (n = 33) exercise rehabilitation programs

| Variables                  | Pre-test*            | Post-test*           | Change score*        |
|----------------------------|----------------------|----------------------|----------------------|
| Physical function          |                      |                      |                      |
| Low-intensity group        | 46 (19)              | 58 (23) <sup>†</sup> | 12 (18) <sup>†</sup> |
| High-intensity group       | 49 (24)              | 59 (21) <sup>†</sup> | 10 (18) <sup>†</sup> |
| Role limitations—physical  |                      |                      |                      |
| Low-intensity group        | 54 (37)              | 63 (44)              | 9 (26)               |
| High-intensity group       | 69 (38)              | 71 (39)              | 2 (37)               |
| Bodily pain                |                      |                      |                      |
| Low-intensity group        | 48 (19)              | 61 (24) <sup>†</sup> | 13 (21) <sup>†</sup> |
| High-intensity group       | 53 (19)              | 64 (25) <sup>†</sup> | 11 (22) <sup>†</sup> |
| General health             |                      |                      |                      |
| Low-intensity group        | 44 (17) <sup>‡</sup> | 40 (20) <sup>‡</sup> | -4 (13)              |
| High-intensity group       | 61 (16)              | 61 (20)              | 0 (18)               |
| Social function            |                      |                      |                      |
| Low-intensity group        | 77 (25)              | 82 (21)              | 5 (21)               |
| High-intensity group       | 86 (21)              | 87 (19)              | 1 (15)               |
| Role limitations—emotional |                      |                      |                      |
| Low-intensity group        | 72 (44)              | 67 (30)              | -5 (61)              |
| High-intensity group       | 72 (39)              | 81 (36)              | 9 (44)               |
| Mental health              |                      |                      |                      |
| Low-intensity group        | 73 (10)              | 67 (8)               | -6 (11)              |
| High-intensity group       | 80 (16)              | 85 (13)              | 5 (10)               |
| Vitality                   |                      |                      |                      |
| Low-intensity group        | 49 (15)              | 45 (16)              | 4 (10)               |
| High-intensity group       | 63 (17)              | 65 (20)              | 2 (16)               |

\*Values are means (SD).

<sup>†</sup>Significant change from the pre-test ( $P < .05$ ).

<sup>‡</sup>Significant difference between groups ( $P < .05$ ).

Finally, patients who were on statin medications—7 (23%) of 31 patients in the low-intensity group and 7 (21%) of 33 patients in the high-intensity group—may have had a more favorable response to the exercise rehabilitation programs than those who were not.<sup>38</sup> To examine this issue

further, we performed a retrospective data analysis to compare the changes in ICD and ACD between those who were taking statins (n = 14) and those who were not (n = 50). Although both groups had significant improvements in ICD and ACD ( $P > .001$ ), the increase was similar regardless of statin use. Therefore, we believe that statins had minimal impact on the change in ICD and ACD after exercise rehabilitation.

## SUMMARY AND CONCLUSIONS

In summary, the major finding of this investigation was that PAD patients limited by intermittent claudication who completed a low-intensity exercise program had similar improvements in physical function, peripheral circulation, and health-related quality of life as those patients who completed a high-intensity exercise program. In conclusion, the efficacy of low-intensity exercise rehabilitation is similar to high-intensity rehabilitation in improving markers of functional independence in PAD patients limited by intermittent claudication, provided that a few additional minutes of walking is accomplished to elicit a similar volume of exercise.

## REFERENCES

1. Vogt MT, Wolfson SK, Kuller LH. Lower extremity arterial disease and the aging process: a review. *J Clin Epidemiol* 1992;45:529-42.
2. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996;94:3026-49.
3. Sieminski DJ, Gardner AW. The relationship between daily physical activity and the severity of peripheral arterial occlusive disease. *Vasc Med* 1997;2:286-91.
4. Feinglass J, McCarthy WJ, Slavensky R, Manheim LM, Martin GJ, and the Chicago Claudication Outcomes Research Group. Effect of lower extremity blood pressure on physical functioning in patients who have intermittent claudication. *J Vasc Surg* 1996;24:503-12.
5. Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP, and the Vascular Clinical Trialists. Clinical trials for claudication: assessment of exercise

- performance, functional status, and clinical endpoints. *Circulation* 1995;92:614-21.
6. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA* 1995;274:975-80.
  7. Gardner AW, Katzel LI, Sorkin JD, Killewich LA, Ryan A, Flinn WR, et al. Improved functional outcomes following exercise rehabilitation in patients with intermittent claudication. *J Gerontol A Biol Sci Med Sci* 2000;55A:M570-7.
  8. Gardner AW, Katzel LI, Sorkin JD, Bradham DD, Hochberg MC, Flinn WR, et al. Exercise rehabilitation improves functional outcomes and peripheral circulation in patients with intermittent claudication: a randomized controlled trial. *J Am Geriatr Soc* 2001;49:755-62.
  9. Gardner AW, Katzel LI, Sorkin JD, Goldberg AP. Effects of long-term exercise rehabilitation on claudication distances in patients with peripheral arterial disease: a randomized controlled trial. *J Cardiopulmonary Rehabil* 2002;22:192-8.
  10. Gardner AW, Killewich LA, Montgomery PS, Katzel LI. The response to exercise rehabilitation in smoking and non-smoking patients with intermittent claudication. *J Vasc Surg* 2004;39:531-8.
  11. Hiatt WR, Regensteiner JG, Hargarten ME, Wolfel EE, Brass EP. Benefit of exercise conditioning for patients with peripheral arterial disease. *Circulation* 1990;81:602-9.
  12. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise versus strength training for patients with peripheral arterial disease. *Circulation* 1994;90:1866-74.
  13. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg* 1996;23:104-15.
  14. Regensteiner JG, Meyer TJ, Krupski WC, Cranford LS, Hiatt WR. Hospital vs. home-based exercise rehabilitation for patients with peripheral arterial occlusive disease. *Angiology* 1997;48:291-300.
  15. Pentecost MJ, Criqui MH, Dorros G, Goldstone J, Johnstone KW, Martin EC, et al. Guidelines for peripheral percutaneous transluminal angioplasty of the abdominal aorta and lower extremity vessels. *Circulation* 1994;89:511-31.
  16. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs. single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc* 1991;23:402-8.
  17. Gardner AW, Skinner JS, Smith LK. Effects of handrail support on claudication and hemodynamic responses to single-stage and progressive treadmill protocols in peripheral vascular occlusive disease. *Am J Cardiol* 1991;67:99-105.
  18. Gardner AW. Reliability of transcutaneous oximeter electrode power during exercise in patients with intermittent claudication. *Angiology* 1997;48:229-35.
  19. Womack CJ, Sieminski DJ, Katzel LI, Yataco A, Gardner AW. Improved walking economy in patients with peripheral arterial occlusive disease. *Med Sci Sports Exerc* 1997;29:1286-90.
  20. Montgomery PS, Gardner AW. The clinical utility of a 6-minute walk test in peripheral arterial occlusive disease patients. *J Am Geriatr Soc* 1998;46:706-11.
  21. Regensteiner JG, Steiner JF, Panzer RL, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol* 1990;2:142-52.
  22. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;49:M85-94.
  23. Gardner AW, Montgomery PS, Killewich LA. Natural history of physical function in patients with intermittent claudication. *J Vasc Surg* 2004;40:73-8.
  24. Bartman BA, Rosen MJ, Bradham DD, Weissman J, Hochberg M, Revicki DA. Relationship between health status and utility measures in older claudicants. *Qual Life Res* 1998;7:67-73.
  25. Gardner AW, Poehlman ET. Assessment of free-living daily physical activity in older claudicants: validation against the doubly labeled water technique. *J Gerontol* 1998;53A:M275-80.
  26. Sieminski DJ, Cowell LL, Montgomery PS, Pillai SB, Gardner AW. Physical activity monitoring in patients with peripheral arterial occlusive disease. *J Cardiopulmonary Rehabil* 1997;17:43-7.
  27. Feinberg RL, Gregory RT, Wheeler JR, Snyder SO, Gayle RG, Parent FN III, et al. The ischemic window: a method for the objective quantitation of the training effect in exercise therapy for intermittent claudication. *J Vasc Surg* 1992;16:244-50.
  28. Carter SA, Hamel ER, Paterson JM, Snow CJ, Mymin D. Walking ability and ankle systolic pressures: observations in patients with intermittent claudication in a short-term walking exercise program. *J Vasc Surg* 1989;10:642-9.
  29. Gardner AW, Sieminski DJ, Killewich LA. The effect of cigarette smoking on free-living daily physical activity in older claudication patients. *Angiology* 1997;48:947-55.
  30. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). *Med Care* 1992;30:473-83.
  31. Jonason T, Ringqvist I. Effect of training on the post-exercise ankle blood pressure reaction in patients with intermittent claudication. *Clin Physiology* 1987;7:63-9.
  32. Creasy TS, McMillan PJ, Fletcher EWL, Collin J, Morris PJ. Is percutaneous transluminal angioplasty better than exercise for claudication? Preliminary results from a prospective randomised trial. *Eur J Vasc Surg* 1990;4:135-40.
  33. Williams LR, Ekers MA, Collins PS, Lee JF. Vascular rehabilitation: benefits of a structured exercise/risk modification program. *J Vasc Surg* 1991;14:320-6.
  34. Patterson RB, Pinto B, Marcus B, Colucci A, Braun T, Roberts M. Value of a supervised exercise program for the therapy of arterial claudication. *J Vasc Surg* 1997;25:312-9.
  35. Walker RD, Nawaz S, Wilkinson CH, Saxton JM, Pockley AG, Wood RFM. Influence of upper- and lower-limb exercise training on cardiovascular function and walking distances in patients with intermittent claudication. *J Vasc Surg* 2000;31:662-9.
  36. Sorlie D, Myhre K. Effects of physical training in intermittent claudication. *Scand J Clin Lab Invest* 1978;38:217-22.
  37. Brendle DC, Joseph LJO, Corretti MD, Gardner AW, Katzel LI. Effects of exercise rehabilitation on endothelial reactivity in older patients with peripheral arterial disease. *Am J Cardiol* 2001;87:324-9.
  38. Mohler ER III, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;108:481-6.

Submitted Apr 2, 2005; accepted May 30, 2005.