Propionyl-L-Carnitine Improves Exercise Performance and Functional Status in Patients with Claudication*

William R. Hiatt, MD, Judith G. Regensteiner, PhD, Mark A. Creager, MD, Alan T. Hirsch, MD, John P. Cooke, MD, PhD, Jeffrey W. Olin, DO, Georgij N. Gorbunov, MD, Jeffrey Isner, MD, Yurij V. Lukjanov, MD, Mihail Sh. Tsitsiashvili, MD, Tatyana F. Zabelskaya, MD, Antonino Amato, MD

PURPOSE: We tested the hypothesis that propionyl-L-carnitine would improve peak walking time in patients with claudication. Secondary aims of the study were to evaluate the effects of propionyl-L-carnitine on claudication onset time, functional status, and safety.

SUBJECTS AND METHODS: In this double-blind, randomized, placebo-controlled trial, 155 patients with disabling claudication from the United States (n = 72) or Russia (n = 83) received either placebo or propionyl-L-carnitine (2g/day orally) for 6 months. Subjects were evaluated at baseline and 3 and 6 months after randomization with a graded treadmill protocol at a constant speed of 2 miles per hour, beginning at 0% grade, with increments in the grade of 2% every 2 minutes until maximal symptoms of claudication forced cessation of exercise. Questionnaires were used to determine changes in functional status.

RESULTS: At baseline, peak walking time was 331 ± 171 seconds in the placebo group and 331 ± 187 seconds in the propionyl-L-carnitine group. After 6 months of treatment, subjects randomly assigned to propionyl-L-carnitine increased their peak walking time by 162 ± 222 seconds (a 54% increase) as compared with an improvement of 75 ± 191 seconds (a 25% increase) for those on placebo ($P < 0.001$). Similar improvements were observed for claudication onset time. Propionyl-L-carnitine treatment significantly improved walking distance and walking speed (by the Walking Impairment Questionnaire), and enhanced physical role functioning, reduced bodily pain, and resulted in a better health transition score (by the Medical Outcome Study SF-36 Questionnaire). The incidence of adverse events and study discontinuations were similar in the two treatment groups.

CONCLUSIONS: Propionyl-L-carnitine safely improved treadmill exercise performance and enhanced functional status in patients with claudication. **Am J Med. 2001;110:616–622.**

Peripheral arterial disease, a common manifestation of atherosclerosis, is associated with reduced arterial circulation in the lower extremities (1,2) that results in claudication, impaired peak treadmill exercise performance, and reduced ambulatory capacity during activities of daily living (3,4). There are several pharmacologic approaches to the treatment of claudication, including drugs that have metabolic actions such as carnitine, an important cofactor for skeletal muscle metabolism (5). Carnitine and propionyl-L-carnitine have been shown to improve exercise performance in patients with peripheral arterial disease (6–8).

This study was designed to test the hypothesis that treatment with propionyl-L-carnitine would improve peak walking time in patients with claudication as assessed by a graded treadmill protocol. Secondary aims of the study were to evaluate the effects of propionyl-L-carnitine on claudication onset time and functional status and to assess its safety.

METHODS

Subjects

Subjects between 40 and 80 years of age were enrolled from six centers in the United States and four centers in Russia (Appendix). Sigma-Tau Pharmaceuticals, Inc., managed the overall trial; Biomedical Research Consultants, Ltd. (Switzerland) coordinated the sites in Russia. Peripheral arterial disease was confirmed by a resting ankle/brachial index of less than 0.90 in the affected leg that decreased at least 10% after treadmill exercise. During treadmill exercise, subjects were limited by claudication pain and not by other symptoms such as chest pain, shortness of breath, or arthritis. Exclusion criteria included ischemic rest pain, ulceration, or gangrene in the lower limbs; lower extremity vascular surgery or angio-

* Access the "Journal Club" discussion of this paper at http://www.elsevier.com/locate/ajmselect/

From the Department of Medicine, Section of Vascular Medicine, Divisions of Geriatrics and Cardiology, University of Colorado Health Sciences Center, and the Colorado Prevention Center, Denver, Colorado (WRH).

Supported by a grant from Sigma Tau Pharmaceuticals, Inc. The address and institutional affiliations of the authors at the time of the study are listed in the Appendix.

Requests for reprints should be addressed to William R. Hiatt, MD, Novartis Professor of Cardiovascular Research, University of Colorado Health Sciences Center, President, Colorado Prevention Center, 789 Sherman Street, Suite 200, Denver, Colorado 80203.

Manuscript submitted September 6, 2000, and accepted in revised form February 8, 2001.

0002-9343/01/$–see front matter
PII S0002-9343(01)00704-5

Table 1. Characteristics of the Intention-to-Treat Sample at Enrollment

Characteristics	Placebo (n = 73)	Propionyl-L-carnitine (n = 82)	*P* Value
	Number (%) or Mean ± SD		
Age (years)	60 ± 10	62 ± 9	0.29
Male sex	64 (88)	67 (82)	0.33
Ankle/brachial index			
Rest	0.57 ± 0.14	0.59 ± 0.17	0.49
Postexercise	0.25 ± 0.13	0.29 ± 0.18	0.11
Constant-load exercise			
Claudication onset time (seconds)	81 ± 51	81 ± 52	0.84
Peak walking time (seconds)	185 ± 75	181 ± 74	0.64

plasty within the preceding 6 months; myocardial infarction within the past 6 months; comorbid illness such as anemia, renal insufficiency, and abnormal hepatic function; or blood pressure at rest greater than 190/100 mm Hg. Approval from the Institutional Review Board was obtained from each site, and informed consent was received from all subjects.

We estimated a sample of 150 subjects would be sufficient to detect a treatment difference of 1.5 minutes in peak walking time (assuming an SD of 3 minutes), with a power of 0.80, a type I error rate of 0.05, and allowing for a dropout rate of 15%. A total of 198 patients were screened for the study, and 37 were excluded for the following reasons: 4 subjects walked longer than 5 minutes on the screening treadmill, 15 had a peak walking time variability greater than 20%, and the remainder had medical problems including angina or ischemic electrocardiographic changes during the treadmill test, or withdrew their consent. A total of 161 subjects were enrolled in the study, but 3 subjects in each group did not have a post-baseline value for peak walking time (2 deaths and 1 loss to follow-up in the placebo group; 2 losses to follow-up and 1 withdrawal in the propionyl-L-carnitine group), leaving 155 subjects in the intention-to-treat sample.

Study Design

After a screening visit to evaluate eligibility, there was a 2-week placebo run-in period, with two visits to establish baseline treadmill performance. Patients were then randomly assigned to the placebo or propionyl-L-carnitine groups, using a computer-based algorithm, with balanced blocks of subjects. The study medication and placebo were dispensed as 500 mg tablets, which were identical in color, shape, and taste, to be taken as two pills twice a day. The number of tablets returned at each visit was used to assess medication compliance. The completer/complier subgroup included subjects who took at least 75% of the study medication and completed 6 months of treatment.

Treadmill Testing

At the screening visit, subjects performed a constant workload exercise test at 2 miles per hour, 12% grade. Those who walked between 60 and 300 seconds were eligible for inclusion. Subsequently, a graded treadmill test was administered on two occasions separated by 1 week to determine the variability of peak walking time and to establish the baseline walking time (as the mean of the two tests) (9). To qualify for randomization, the difference in peak walking time between the two tests had to be 20% or less. The graded test was conducted at a constant speed of 2 miles per hour and began at 0% grade. Every 2 minutes the grade was increased by 2% until maximal tolerated claudication pain that limited further exercise; this defined the peak walking distance. Time of the onset of claudication pain was also noted. The same treadmill methodology was used to establish efficacy of propionyl-L-carnitine during follow-up.

Assessment of Hemodynamics

The ankle/brachial index was assessed after subjects had been resting supine for 10 minutes. A sphygmomanometer cuff was placed around the ankle and inflated to suprasystolic pressure. The onset of arterial flow during cuff deflation, as detected with a continuous wave Doppler ultrasonic instrument, defined the systolic pressure. Systolic pressures were measured in both arms and in the dorsalis pedis and posterior tibial arteries at each ankle. The higher arm pressure and the higher of the dorsalis pedis or posterior tibial artery pressures were used to determine the ankle/brachial index in each extremity. The extremity with the lowest ankle/brachial index was considered the index leg. The postexercise ankle/brachial index was measured within 1 minute after treadmill exercise.

Functional Assessment

The disease-specific Walking Impairment Questionnaire (4,10) was used to assess their perceived difficulty in walking defined distances and speeds, ability to climb stairs, and degree of walking impairment due to the se-

Table 2. Effect of Propionyl-L-Carnitine on Graded Treadmill Performance in the Intention-to-Treat Sample

Performance Measure	Placebo (n = 73)	Propionyl-L-carnitine (n = 82)	*P* Value
	Number (%) or Mean ± SD		
Claudication onset time (seconds)			
Entry	120 ± 80	110 ± 81	0.44
3 Months	143 ± 107	157 ± 118	<0.001
6 Months	173 ± 144	196 ± 163	<0.01
Peak walking time (seconds)			
Entry	331 ± 171	331 ± 187	1.00
3 Months	382 ± 234	423 ± 242	<0.001
6 Months	406 ± 263	492 ± 310	<0.001

verity of claudication pain. Each domain has a score ranging from 0% (cannot perform the task) to 100% (no limitation).

The Medical Outcomes Study Short Form (SF-36) questionnaire was used to measure physical and social functioning, bodily pain (higher scores indicate less pain), general mental health, vitality, general health perceptions and health transition (lower scores indicate improved health state) (4,11,12). Each of the dimensions measured was scored on a scale of 0% (maximal impairment) to 100% (no impairment). Both questionnaires were translated into Russian, with validation by back translation into English to ensure accuracy.

Analytic Methods

Plasma L-carnitine and acylcarnitine species (acetyl-L-carnitine and propionyl-L-carnitine) levels were assessed in a subgroup of the sample (32 subjects at two of the study sites after 6 months of treatment). Carnitine and acylcarnitines were identified by a fast atom bombardment with the tandem mass spectrometry method (13,14).

Statistical Analysis

Baseline values for continuous variables in the two groups were compared using an analysis of variance model including effects for center and treatment; categorical variables were compared using a Mantel-Haenszel test with stratification by center. The primary endpoint was the change in peak walking time at 6 months. Secondary endpoints included change in the treadmill time of claudication onset, functional status by questionnaires, and safety as assessed by adverse events, laboratory tests, and vital signs.

All efficacy analyses were performed on an intention-to-treat basis, with the last observation carried forward in the case of missing data. The primary statistical analysis was the comparison of the change from baseline in peak walking time at 6 months. The intention-to-treat sample consisted of all enrolled subjects who had taken at least one dose of the study medication and who had at least one postbaseline evaluation of peak walking time. Comparisons were initially performed using an analysis of covariance (ANCOVA) model that included terms for center and treatment; a treatment-by-center interaction term was included if it was statistically significant at $P > 0.10$. The baseline peak walking times was included as a covariate in the model. If the assumptions for performing ANCOVA were not fulfilled by the observed values of peak walking time at month 6, then the protocol specified that the statistical comparisons were to be performed using the natural logarithmic transformation of the ratio of the final to baseline peak walking times. These log-transformed values were analyzed using an ANCOVA model. If the assumptions to apply an ANCOVA were not met by the log-transformed values, then a rank ANCOVA with adjustment for baseline and site was utilized. Treatment effects were tested in this final model using a generalized Cochran-Mantel-Haenszel test, carried out on within-center standardized midranks of residuals from the ANCOVA model. These transformations helped to stabilize

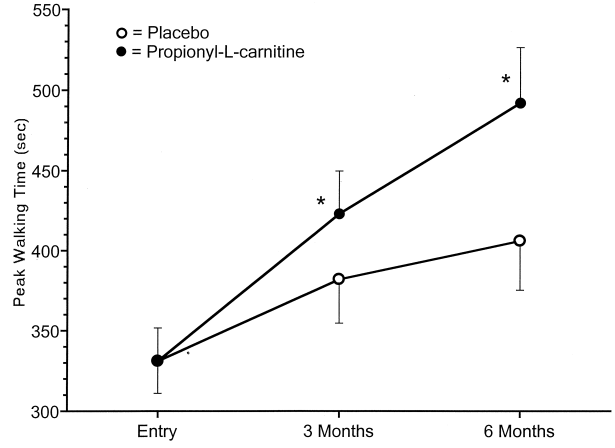

Figure. Peak treadmill walking time (seconds) is shown for patients randomized to placebo (**open circles**) or drug (**solid circles**). Data are presented as mean ± standard error of the mean. *$P < 0.001$ for the change from entry to 3 or 6 months on placebo as compared with the change on propionyl-L-carnitine.

Table 3. Effect of Treatment on Walking Impairment Questionnaire Scores and Medical Outcome Study SF-36 Questionnaire Scores

	Placebo	Propionyl-L-carnitine	*P* Value
Number of patients	73	82	
Walking Impairment Questionnaire			
Claudication pain			
Entry	79 ± 12	80 ± 12	0.39
6 Months	79 ± 11	80 ± 15	0.72
Walking distance			
Entry	29 ± 21	34 ± 24	0.10
6 Months	33 ± 27	47 ± 33	<0.01
Walking speed			
Entry	30 ± 18	32 ± 20	0.43
6 Months	31 ± 20	37 ± 26	<0.05
Stair climbing			
Entry	51 ± 29	54 ± 31	0.41
6 Months	54 ± 30	59 ± 33	0.14
Medical Outcome Study SF-36 Questionnaire			
Physical functioning			
Entry	45 ± 19	48 ± 20	0.23
6 Months	49 ± 19	55 ± 22	0.08
Role functioning-physical			
Entry	57 ± 36	63 ± 39	0.16
6 Months	50 ± 38	66 ± 41	0.01
Bodily pain*			
Entry	48 ± 16	50 ± 20	0.68
6 Months	51 ± 18	59 ± 22	<0.01
Vitality			
Entry	49 ± 18	50 ± 19	0.95
6 Months	49 ± 18	54 ± 23	0.11
Health transition			
Entry	3.0 ± 0.8	3.0 ± 0.9	0.67
6 Months	2.7 ± 0.7	2.3 ± 1.1	<0.01
General health			
Entry	43 ± 19	51 ± 20	0.01
6 Months	45 ± 19	53 ± 20	0.33
Social functioning			
Entry	78 ± 24	83 ± 20	0.17
6 Months	80 ± 21	82 ± 23	0.90
Role functioning-emotional			
Entry	80 ± 32	84 ± 30	0.31
6 Months	81 ± 34	87 ± 29	0.25
Mental health			
Entry	68 ± 17	71 ± 19	0.30
6 Months	66 ± 20	72 ± 17	0.14

* An increase in bodily pain scores indicates less pain.

the variance and produce a more symmetrical distribution. Questionnaire data were analyzed using an ANCOVA model, including effects for the baseline measurement and site. Prespecified subgroups included subjects with or without diabetes, smokers versus nonsmokers, and U.S. versus Russian sites. Risks of adverse events were compared with the chi-square test. All analyses were performed using release 6.09 of the SAS System (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Age, sex, baseline variables for ankle/brachial indexes, and screening treadmill performance were similar in the two groups (Table 1). On entry, there were no differences in age, sex, or ethnicity between the groups. Nearly all of the subjects (97%; n = 150) were white and more than 90% (n = 140) were previous or current smokers. Similar proportions of subjects in the placebo group (58%; n =

Table 4. Comparison of Characteristics at Enrollment of Subjects from the United States and Russia

Characteristics	United States (n = 72)	Russia (n = 83)	*P* Value
	Number (%) or Mean ± SD		
Age (years)	68 ± 8	57 ± 8	<0.01
Male sex	51 (71)	80 (96)	<0.01
Diabetes	23 (32)	1 (1)	<0.01
Body mass index (kg/m^2)	28 ± 4.8	24 ± 2.2	<0.01
Baseline peak walking time (seconds)	296 ± 176	361 ± 177	<0.05
Musculoskeletal disease	50 (70)	2 (2)	<0.001
Nervous system disorders	35 (48)	6 (7)	<0.001
Respiratory abnormalities	42 (58)	29 (35)	<0.01

42) and the propionyl-L-carnitine group (64%; n = 52) used nonstudy medications during the course of the study, including antiplatelet drugs, beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and nitrates.

Subjects in the placebo group completed a mean (± SD) of 187 ± 21 days of therapy and took 96% to 11% of the study medication. Those in the propionyl-L-carnitine group completed 189 ± 14 days of therapy and took 92% ± 15% of the study medication.

Effects on Exercise Performance

Subjects in each group had similar baseline graded treadmill exercise performances (Table 2). At 3 months, there was a statistically significant improvement in both claudication onset time (P <0.001) and peak walking time (P <0.001) in patients receiving propionyl-L-carnitine as compared with those in the placebo group (Table 2 and Figure 1). After 6 months of treatment, the geometric mean for log-transformed peak walking time values had improved 14% in the placebo group and 39% in the propionyl-L-carnitine group (P <0.001 for the between-group difference in the change from baseline), a net improvement of 87 seconds (95% confidence interval: 21 to 153 seconds). Because the grade of the treadmill was increased every 2 minutes, this improvement indicates an increase in walking distance and greater work performed in most patients. An analysis of changes in peak walking time of the completer/complier patients showed similar results.

Scores on the Walking Impairment Questionnaire were similar in propionyl-L-carnitine and placebo groups at enrollment (Table 3). These scores remained relatively constant in the placebo group during the study. Propionyl-L-carnitine was associated with significant improvements in subject-perceived walking distance (at 3 and 6 months) and walking speed (at 6 months), as compared with placebo (P <0.05).

Treatment with propionyl-L-carnitine was also associated with improvements in role functioning-physical, bodily pain, and transition to a better health state (P < 0.01) and perhaps better physical function at 6 months (P = 0.08; Table 5).

Subgroup Analyses

There were no significant differences in the effects of propionyl-L-carnitine among two of the prespecified subgroups (diabetes versus no diabetes, smokers versus nonsmokers). However, there was a significant treatment-by-country interaction, such that the benefits of propionyl-L-carnitine were greater at the Russian sites than at the U.S. sites (P = 0.02). However, in an ANCOVA model that included terms for country, treatment, and their interaction, a statistically significant benefit of propionyl-L-carnitine was observed (P <0.01).

Given the differences by country, we performed several posthoc analyses (Table 4). At baseline, subjects in Russia were younger, more likely to be male, and less likely to have diabetes than those from the United States. Russian subjects also had a lower body mass index and fewer musculoskeletal, nervous system, and respiratory abnormalities, and a longer baseline peak walking time.

Adverse Events

There were no notable between-group differences in adverse events (Table 5). Most of the reported adverse events were not considered to be serious (eg, flulike syndromes, pharyngitis) and were unrelated to study medication. Two subjects in the placebo group died. One subject in each treatment group withdrew from the study because of an adverse event.

Blood Carnitine Levels

Treatment with propionyl-L-carnitine produced a significant increase in the plasma concentrations of L-carnitine (from 41 to 53 nmol/mL), propionyl-L-carnitine (from 0.5 to 1.5 nmol/mL), and acylcarnitine (from 10 to 15 nmol/mL). There were no changes in these plasma levels on placebo (P <0.01 for the differences between drug and placebo for all comparisons).

Table 5. Adverse Events in the Total Sample

	Placebo (n = 76)	Propionyl-L-carnitine (n = 85)	
	Number (%)		*P* Value
Patients with at least one adverse event	29 (38)	38 (45)	0.40
Patients with at least one serious adverse event	6 (8)	5 (6)	0.61
Deaths	2 (3)	0 (0)	0.13
Medication discontinuation due to adverse events	2 (3)	1 (1)	0.50
Study discontinuation due to adverse events	1 (1)	1 (1)	0.94

DISCUSSION

We found that 6 months of treatment with propionyl-L-carnitine improved peak exercise performance as assessed by a graded treadmill protocol. This protocol was selected to minimize variability and enhance sensitivity to treatment effects (9,12). The mean difference in peak walking time between the propionyl-L-carnitine and placebo groups was 87 seconds, equivalent to 255 feet. However, because the treadmill protocol incorporated an increase in work rate every 2 minutes, a greater improvement in walking distance would have been realized on level ground. Propionyl-L-carnitine also improved subject-assessed walking distance and speed, and reported physical functioning. Subjects also perceived a reduction in bodily pain and a transition to a better state of health. This occurred with no increased risk of adverse events, indicating that propionyl-L-carnitine was both safe and effective in the treatment of claudication, as was seen in a previous 12-month study in Europe (8).

We observed greater improvements in peak walking time in the Russian subjects than in those from the United States. These differences could not be accounted for by protocol violations or unblinding of study medication, as determined by a poststudy audit by the sponsor. However, there were several between-country differences in the characteristics of the subjects. Notably, the Russian subjects had a greater peak walking time at enrollment, suggesting less severe claudication than those from the United States. Despite these differences, the treatment effect remained significant when country was included in the prespecified analytic model, indicating that significant benefits of propionyl-L-carnitine were observed in both countries.

It is not certain how propionyl-L-carnitine works. Claudication is an ischemic symptom, but it cannot be fully explained by reduced blood flow (15,16). Patients with peripheral arterial disease have alterations in skeletal muscle metabolism, such as the accumulation of acyl-CoA intermediates and acylcarnitines, that correlate with reduced exercise performance (17). Supplementation with oral propionyl-L-carnitine increases the availability of L-carnitine for skeletal muscle, which may improve muscle metabolism and vascular endothelial function (18–20).

There are several drugs that treat claudication. Pentoxifylline may provide a modest benefit (21), although a recent study showed that the drug was no more effective than placebo (22). In contrast, four published trials of cilostazol have shown consistent improvements in treadmill performance and quality of life (23–25); however, the drug cannot be used in patients with heart failure. The current study demonstrates that propionyl-L-carnitine is effective in improving treadmill exercise performance and functional status in patients with peripheral arterial disease and claudication.

ACKNOWLEDGMENTS

The authors would like to thank Aleksej Nekora, MD, Biomedical Research Consultants Ltd., Basel, for organizing the study in the Russian sites. We also thank Drs. Marco Corsi and Gaetano Marzullo for their helpful comments on the manuscript.

REFERENCES

1. Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985;71:510–515.
2. Hiatt WR, Hoag S, Hamman RF. Effect of diagnostic criteria on the prevalence of peripheral arterial disease. The San Luis Valley diabetes study. *Circulation*. 1995;91:1472–1479.
3. Hiatt WR, Nawaz D, Brass EP. Carnitine metabolism during exercise in patients with peripheral vascular disease. *J Appl Physiol*. 1987;62:2383–2387.
4. Regensteiner JG, Steiner JF, Hiatt WR. Exercise training improves functional status in patients with peripheral arterial disease. *J Vasc Surg*. 1996;23:104–115.
5. Brass EP, Hiatt WR. Carnitine metabolism during exercise. *Life Sci*. 1994;54:1383–1393.
6. Brevetti G, Chiariello M, Ferulano G, et al. Increases in walking distance in patients with peripheral vascular disease treated with L-carnitine: a double-blind, cross-over study. *Circulation*. 1988;77:767–773.
7. Brevetti G, Perna S, Sabba C, et al. Superiority of L-propionyl carnitine vs L-carnitine in improving walking capacity in patients with peripheral vascular disease. An acute, intravenous, double-blind, cross-over study. *Eur Heart J*. 1992;13:251–255.
8. Brevetti G, Diehm C, Lambert D. European multicenter study on

propionyl-L-carnitine in intermittent claudication. *J Am Coll Cardiol*. 1999;34:1618–1624.
9. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. *Med Sci Sports Exerc*. 1991;23:402–408.
10. Regensteiner JG, Steiner JF, Panzer RJ, Hiatt WR. Evaluation of walking impairment by questionnaire in patients with peripheral arterial disease. *J Vasc Med Biol*. 1990;2:142–152.
11. McHorney CA, Ware JE, Raczek AE. The MOS 36-item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993;31:247–263.
12. Hiatt WR, Hirsch AT, Regensteiner JG, et al. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. *Circulation*. 1995;92:614–621.
13. Babcock MA, Paterson DH, Cunningham DA. Effects of aerobic endurance training on gas exchange kinetics of older men. *Med Sci Sports Exerc*. 1994;26:447–452.
14. Chilibeck PD, Paterson DH, Smith WDF, Cunningham DA. Cardiorespiratory kinetics during exercize of different muscle groups and mass in old and young. *J Appl Physiol*. 1996;81:1388–1394.
15. Hiatt WR, Nawaz D, Regensteiner JG, Hossack KF. The evaluation of exercise performance in patients with peripheral vascular disease. *J Cardiopulmonary Rehabil*. 1988;12:525–532.
16. Pernow B, Zetterquist S. Metabolic evaluation of the leg blood flow in claudicating patients with arterial obstructions at different levels. *Scand J Clin Lab Invest*. 1968;21:277–287.
17. Hiatt WR, Wolfel EE, Regensteiner JG, Brass EP. Skeletal muscle carnitine metabolism in patients with unilateral peripheral arterial disease. *J Appl Physiol*. 1992;73:346–353.
18. Liedtke AJ, DeMaison L, Nellis SH. Effects of L-propionylcarnitine on mechanical recovery during reflow in intact hearts. *Am J Physiol*. 1988;255:H169–H176.
19. Paulson DJ, Traxler J, Schmidt M, et al. Protection of the ischaemic myocardium by L-propionyl carnitine: effects on the recovery of cardiac output after ischaemia and reperfusion, carnitine transport, and fatty acid oxidation. *Cardiovasc Res*. 1986;20:536–541.
20. Cipolla MJ, Nicoloff A, Rebello T, et al. Propionyl-L-carnitine dilates human subcutaneous arteries through an endothelium-dependent mechanism. *J Vasc Surg*. 1999;29:1097–1103.
21. Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Arch Intern Med*. 1999;159:337–345.
22. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med*. 2000;109:523–530.
23. Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. *Arch Intern Med*. 1999;159:2041–2050.
24. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg*. 1998;27:267–274.
25. Dawson DL, Cutler BS, Meissner MH, Strandness DEJ. Cilostazol has beneficial effects in treatment of intermittent claudication: results from a multicenter, randomized, prospective, double-blind trial. *Circulation*. 1998;98:678–686.

APPENDIX

List of Study Sites

Investigators in the United States were John P. Cooke, MD, PhD (Stanford University, Stanford, California); Mark A. Creager, MD (Brigham & Women's Hospital, Boston, Massachusetts); William R. Hiatt, MD (University of Colorado Health Sciences Center, Denver, Colorado); Alan T. Hirsch, MD (University of Minnesota, Minneapolis, Minnesota); Jeffrey W. Olin, DO (Cleveland Clinic Foundation, Cleveland, Ohio); and Jeffrey Isner, MD (St. Elizabeth's Hospital, Boston, Massachusetts). The investigators in Russia were Prof. Mihail Sh. Tsitsiashvili (State Medical University of Russia, Moscow); Dr. Tatyana F. Zabelskaya (Seventh City Clinical Hospital, Moscow); Dr. Georgij N. Gorbunov (St. Petersburg Institute of Advanced Medical Studies, St. Petersburg); and Prof. Yurij V. Lukjanov (Pavlov Medical Institute, St. Petersburg).