Effectiveness and costs of a short-course supervised training program in claudicants: proposal for a shared protocol with aerobic working load

G. M. ANDREOZZI [1], A. LEONE [2], R. MARTINI [1], R. LAUDANI [2], G. SALIMISTRARO [1], G. DEINITE [2]

[1]*Angiology Care Unit, University Hospital of Padua, Padua, Italy*
[2]*Vascular Rehabilitation Unit, Casa di Cura Carmide Rehabilitation Clinic, Catania, Italy*

Aim. **The purpose of this study was to assess the costs and effectiveness of a short-course physical training program, consisting of an aerobic protocol with clearly defined working loads in each single training session, in patients with intermittent claudication (IC).**
Methods. **Initial (ICD), absolute (ACD) claudication distance, and recovery time (RT) have been measured by maximal treadmill exercise in 74 claudicants. Ankle brachial index (ABI) has been measured too. Measurements have been repeated after 18 days of supervised physical training consisting of a daily walk reaching either a distance goal of 1-2 km or a time goal of at least 30 min. The working load of each single training session has been tailored at 60-70% of the ACD measured by a non-maximal treadmill exercise.**
Results. **ICD increased from 56.2 (± standard deviation/± standard error: 35.3/4.1) to 123.9 (66.5/7.7); ACD increased from 104.8 (49.8/5.8) to 195.1 (81.7/9.5) and RT reduced from 201.2 (98.3/11.4) to 85.8 (43.6/5.1), with P<0.0001 for all parameters. We analyzed separately patients with moderate (M-CL) and severe (S-CL) claudication, and found significant improvements in both groups. The Δs (post-training value minus pretraining value) were: ICD 89.6 (59.9/10.9) in M-CL and 50.2 (29.9/4.6) in S-CL; ACD 102.8 (66.8/11.6) in M-CL and 80.1 (41.5/6.4) in S-CL; RT -98.7 (86.9/15.1) in M-CL and -128.5 (88.1/13.7) in S-CL, with P<0.0001 for all parameters. The differences between M-CL and S-CL were significant only for ICD (P=0.0003) and ACD (P<0.05). ABI showed an increasing trend, which was statistically significant (P<0.001), but clinically irrelevant. The protocol cost was 4 179 € (average cost 46.30 € to walk one additional meter).**
Conclusion. **Supervised physical training is confirmed to be an effective tool for the treatment of IC, and the proposed short-course protocol gave the same improvements as the longer ones while reducing the costs. The proposed procedure for tailoring the working load of a single session identifies clearly the working load, near maximal pain but avoiding the risk of inflammatory activation.**

[Int Angiol 2008;27:401-7]

Key words: **Physical fitness - Rehabilitation - Peripheral vascular diseases - Intermittent claudication.**

Physical training is universally recognized as the most efficacious means for improving the walking ability in patients with intermittent claudication (IC), but in spite of being recommended by all guidelines, its application remains low and its adopted protocols unclear.

With regard to the exercise quality, power or endurance exercises have been proposed. The first kind, also indicated as strength exercise, is focused on the suffering muscles (in peripheral arterial disease muscles distal to the arterial stenosis or obstruction). This choice is based on the experience coming from the rehabilitation of neurological disease and the theory of the re-commitment of the loss function to new neurons. The second one involves all leg muscles to improve their performance.

A research done by our group in the 1980s demonstrated that the endurance exercises are more effective than power ones, because IC is not a motor neuron disease, but its pathophysiology is related to the discrepancy between the muscle oxygen demand and the oxygen arterial supply.[1, 2] These results have been confirmed in a larger series in 1994.[3]

Concerning the working load, the question is when to stop each single exercise session. The literature shows many answers and many opinions,

Fundings.—The authors did not receive specific funds for this research.

Acknowledgements.—The authors acknowledge all the patients participant to the study, and Ms. C. Andreozzi for the text revision.

Received on April 5, 2007; accepted for publication on January 14, 2008.

which can be summarized by these two sentences: utilize the aerobic load to improve the muscle performance, or reach (or overpass) the ischemic calf pain thresholds, because the hypoxia is the major vasodilating stimulus to improve the muscle perfusion by increasing the arterial inflow.

This uncertainty creates a great variety of protocols and a heterogeneous quality of training and results, with reported improvement from 70% to 230% of baseline absolute claudication distance (ACD) as shown by the largest meta-analyses.[4, 5]

The majority of papers and guidelines suggest to walk near-maximal pain,[6, 7] and the TASC 2nd Document includes the high level of claudication pain during training session as a predictor of good results.[8]

On the other hand, several data are against the concept of walking near maximal pain. First, it has never been demonstrated that physical training increases the arterial inflow, as confirmed by the Gardner series in which the walking capacity improved significantly, but the resting flow did not change.[9] Second, the maximal exercise worsens the majority of microcirculatory parameters. In our previous researches, we demonstrated that hematocrit, fibrinogen, whole blood viscosity and red cells deformability significantly worsen in well trained athletes and in healthy sedentary people, whilst the sub-maximal exercise shows the same trend without reaching statistical significance.[10, 11] These changes have been confirmed by more recent studies showing that the maximal physical exercise increases the levels of free radicals,[12] the expression of the leukocyte adhesion molecules[13] and the inflammatory activation.[14-16] Moreover, in a recent paper, we demonstrated that in patients with severe claudication the inflammatory activation increases more also during the recovery time (RT).[17] Following these recent data, physical training in claudicant patients should utilize only the aerobic exercise without really reaching the near maximal pain.

Indeed, despite the definition near maximal pain, if we look at the contents of the paper we find more cautiousness in describing the protocols. The most frequent advice suggests that the training patient records the claudication pain he experiences on an arbitrary scale (0=no pain; 1=onset of claudication; 2=mild pain; 3=moderate pain; 4=severe pain), and that during the training session he is encouraged to walk with his pain between 2 and 3 (mild and moderate intensity).[18] Hiatt *et al.* advises that during the training session the patient walks on a motor-driven treadmill until he experiences moderate claudication pain and than he steps off the treadmill and rest until pain subsides.[19, 20] The TASC 2nd Document suggests that patient should stop walking when claudication is considered moderate, and always avoid excessive fatigue or discomfort.

In 2005, Gardner did not find any difference between the results obtained with high and low intensity training program, defined as 80% and 40% of walking ability, respectively.[21]

Concerning the duration of the training period, the same uncertainties are present. The majority of papers and guidelines suggest 3 times a week for 6 months.[6-9] The costs are estimated to be less than $12 000 per life year gained in unsupervised training, whilst supervised exercise has a cost-effectiveness ratio ranging $20 000-$40 000 per life year gained.[22]

A recent study evaluated the effectiveness of a short-course (4 weeks) rehabilitation program in patients with moderate to severe claudication, producing a 132% increase in initial claudication distance (ICD) and a 87% increase of ACD. The authors concluded that the short-course training programs enhance the walking ability even in patients with moderate-to-severe IC; these programs seem to be well tolerated, supporting their widespread use in rehabilitation centers.[23]

In Italy, considering the day-hospital in-patients strategy, the cost varies from 238.12 € daily in Sicily, to 182.04 € daily for maximum 13 days, plus 138.15 for each further day in Veneto. So, the cost for a 6 months program would be 16 716.96 ? in Sicily and 10 605.15 € in Veneto. In Lombardy the cost of a 4-week long, twice a day walking exercise rehabilitation program has been estimated around 3 811.90 and 4 626.20 €.[24]

The aim of this study was to assess the effectiveness and costs of a short-course rehabilitation program in claudicants trained with a clearly established aerobic protocol.

Materials and methods

Patients and protocol

Seventy-four patients with IC have been enrolled in the Vascular Rehabilitation Unit of our clinic for the supervised training program. All subjects provided informed consent and, the day before the beginning of the rehabilitation program, they all had an echo-color Doppler of supra-aortic arteries, abdominal aorta and lower limb arteries (with ankle brachial index [ABI] measurement) to confirm the diagnosis. Following this, they had a 30 min warm-up, consisting of a bicycle exercise without any load, and then familiarized with the treadmill test device. Subsequently, they performed a maximal treadmill test (speed 3 km/h, slope 12%) to evaluate the maximal walking ability. The test was discontinued when calf pain made it impossible to continue, thus measuring the ICD (distance walked before muscular symptoms appear without impeding walking) and the ACD (distance at which the patient stops walking due to muscular cramps). The RT (time needed for the calf pain to disappear and to recover the ability to restart walking) was measured too. The patients with ACD >100 m have been classified as moderate claudicants (M-CL), and the patients with ACD <100 m have been classified as severe claudicants (S-CL).

Supervised physical training

Supervised training was 3 times weekly, for 6 weeks. The day before the starting program, 1 h after the maximal treadmill test, the patient received a lighter treadmill exercise (speed 1.5 km/h, slope 6±2%) to define the training load of the single sessions, which was tailored at 60-70% (aerobic exercise) of the walking ability measured during this non-maximal treadmill exercise. The single exercise session was repeated after a resting period so as to reach the daily distance of 1-2 km or 30 min of effective walking. To assure the wider possible muscle recovery, the resting period between two single training sessions was equal to the RT measured during the maximal treadmill test.

After 3 weeks a new non-maximal test has been realized to assess the new performance of the patients, and to modify the load of the single training session (incremental protocol of the physical training program).

After the 18th day of training (6th week) a new maximal treadmill test has been performed to assess the walking ability after training.

The costs have been calculated considering the reimbursement fees approved by the regional regulatory office of public health.

TABLE I.—*Clinic characteristics of the population study.*

	N.	Age (mean)	Min-max	Mean
Enrolled people	74	66.55	38-89	
Males	67	67	40-89	
Females	7	58	38-73	
BMI				26.57
Over-weight (N.)				43
Light obesity (N.)				7
Hypercholesterolemia	36			
Balanced	16			
Unbalanced	20			
Hypertension	42			
Smokers	56			
Ex smokers	32			
Still smokers	24			
Diabetics (type 2)	41			
Balanced	20			
Unbalanced	21			
Stroke or TIAs	6			
Myocardial infarction	15			

BMI: body mass index; TIA: transient ischemic attack.

Statistical analysis

The results of the whole population study have been evaluated calculating the average, standard deviation and standard error of ICD, ACD, RT and ABI, and comparing the differences with the Student's t-test for paired data. The same analysis has been carried out on the data of groups M-CL and S-CL.

Finally, to better assess the different effectiveness of training in M-CL and S-CL, we calculated the Δ (post-training value minus pretraining value) of ICD, ACD, RT and ABI of all patients, and compared with t test the two series of each parameter.

All the analyses were considered significant when the P value was <0.05.

Results

The mean age of the enrolled patients was 66.55 years (range: 38-89 years); 67 out of the 74 total were males (mean age: 67 years; range: 40-89 years) and 7 were women (mean age: 58 years; range: 38-73 years). All patients were able to perform the treadmill exercise.

The average of body mass index (BMI) was 26.57

TABLE II.—*Changes of walking ability after 18 days of physical training in 74 claudicant patients.*

	ICD before	ICD after	ACD before	ACD after	RT before	RT after	ABI before	ABI after
Mean	56.15	123.92	104.86	195.11	201.15	85.88	0.66	0.7
SD	35.33	66.5	49.85	81.77	98.35	43.67	0.13	0.14
SE	4.11	7.73	5.8	9.51	11.43	5.08	0.02	0.02
P	<0.0001		<0.0001		<0.0001		<0.0001	

ICD: initial claudication distance; ACD: absolute claudication distance; RT: recovery time; ABI: ankle brachial index; SD: standard deviation; SE: standard error. P values of Student's t-test between before and after values of ICD, ACD, TR and ABI.

TABLE III.—*Changes of walking ability after 18 days of physical training in 33 patients with moderate claudication.*

M-CL	ICD before	ICD after	ACD before	ACD after	RT before	RT after	ABI before	ABI after
Mean	84.85	174.48	149.36	252.18	184.55	85.76	0.63	0.68
SD	32.35	58.85	37.23	75.37	105.18	40.85	0.1	0.12
SE	5.63	10.24	6.48	13.12	18.31	7.11	0.02	0.02
P	<0.0001		<0.0001		<0.0001		<0.001	

M-CL: moderate claudication; ICD: initial claudication distance; ACD: absolute claudication distance: RT: recovery time; ABI: ankle brachial index; SD: standard deviation; SE: standard error. P values of Student's t-test between before and after values of ICD, ACD, TR and ABI.

TABLE IV.—*Changes of walking ability after 18 days of physical training in 41 patients with severe claudication.*

S-CL	ICD before	ICD after	ACD before	ACD after	RT before	RT after	ABI before	ABI after
Mean	33.05	83.22	69.05	149.17	214.51	85.98	0.68	0.72
SD	14.62	38.62	21.87	52.99	91.62	46.31	0.14	0.15
SE	2.28	6.03	3.41	8.28	14.31	7.23	0.02	0.02
P	<0.0001		<0.0001		<0.0001		<0.001	

S-CL: severe claudication; ICD: initial claudication distance; ACD: absolute claudication distance: RT: recovery time; ABI: ankle brachial index; SD: standard deviation; SE: standard error. P values of Student's t-test between before and after values of ICD, ACD, TR and ABI.

TABLE V.—*Delta between pre- and post-training values of ICD, ACD, RT, and ABI in 33 patients with moderate claudication, and 41 patients with severe claudication.*

	Δ ICD M-CL	Δ ICD S-CL	Δ ACD M-CL	Δ ACD S-CL	Δ RT M-CL	Δ RT S-CL	Δ ABI M-CL	Δ ABI S-CL
Mean	89.64	50.17	102.82	80.12	-98.79	-128.54	0.05	0.04
SD	58.96	29.99	66.82	41.51	86.92	88.12	0.04	0.05
SE	10.26	4.68	11.63	6.48	15.13	13.76	0.01	0.01
P	0.0003		0.05		NS		NS	

ICD: initial claudication distance; ACD: absolute claudication distance: RT: recovery time; ABI: ankle brachial index; M-CL: moderate claudication; S-CL: severe claudication; SD: standard deviation; SE: standard error.

(min: 19.05; max: 32.6). Forty-three patients were overweight (BMI: 25↔29.9) and 7 showed a light obesity (BMI: 30↔34.9); 36 had hypercholesterolemia, 42 were hypertensive, and 41 had type 2 diabetes. Thirty-two patients had been smokers in the past and had not smoked for at least 3 years, while 23 still smoked up to 10 cigarettes per day. Fourteen patients had a history of myocardial infarction without heart failure, and 6 had a transient ischemic attack or stroke with good clinical recovery (Table I). The mean of baseline values of considered parameters were respectively ICD 56.15 m (standard deviation [SD]: 35.33; standard error [SE]: 4.11); ACD;: 104.86 m (SD: 49.85; SE: 5.80); TR: 201.15 s (SD: 98.35-SE: 11.43); ABI: 0.66 (SD: 0.13; SE: 0.02). After 6 weeks of training, the means of the considered parameter were significantly improved, ICD 123.92 m (SD: 66.5-SE: 7.73), ACD 195.11 m (SD: 81.77; SE: 9.51), TR 85.88 s (SD: 43.67; SE: 5.08), ABI: 0.7 (SD: 0.14-SE: 0.02). All

TABLE VI.—*Arithmetic and percent Δ of ICD and ACD in 33 patients with moderate claudication, and 41 patients with severe claudication.*

	M-CL Δ	M-CL Δ (%)	S-CL Δ	S-CL Δ (%)
ICD	89.64	105.64	50.17	151.81
ACD	102.82	68.84	80.12	116.04

ICD: initial claudication distance; ACD: absolute claudication distance; M-CL: moderate claudication; S-CL: severe claudication.

the changes were highly significant (P<0.0001) (Table II).

Thirty-three patients have been classified as moderate claudicants (M-CL) because of ACD between 101 and 200 m (mean: 149.36; SD: 37.23; SE: 6.48). Within this group, ICD increased from 84.85 m (SD: 32.35; SE: 5.63) to 174.48 m (SD: 58.85; SE: 10.24); ACD increased from 149.55 m (SD: 37.23; SE: 6.48) to 252.18 m (SD: 75.37; SE: 13.12). RT decreased from 184.55 s (SD: 105.18; SE: 18.31) to 85.76 s (SD: 40.85; SE: 7.11), and ABI increased from 0.63 (SD: 0.1; SE: 0.02) to 0.68 (SD: 0.12; SE: 0.02). All the differences were highly significant with P<0.0001 for ICD, ACD and RT, and P<0.001 for ABI (Table III).

Forty-one patients have been classified as severe claudicants, because of ACD <100 m (mean: 69.05; SD: 21.87; SE: 3.41). Within the group, ICD increased from 33.05 m (SD: 14.62; SE: 2.28) to 83.22 m (SD: 38.62; SE: 6.03); ACD increased from 69.05 m (SD: 21.87; SE: 3.41) to 149.17 m (SD: 52.99; SE: 8.28). RT decreased from 214.51 s (SD: 91.62; SE: 14.31) to 85.98 s (SD: 46.31; SE: 7.23), and ABI increased from 0.68 (SD: 0.14; SE: 0.02) to 0.72 (SD: 0.15; SE: 0.02). All the differences were highly significant with P<0.0001 for ICD, ACD and RT, and P<0.001 for ABI (Table IV).

The difference of training effectiveness between M-CL and S-CL was significant only for ICD (P=0.0003) and ACD (P<0.05). The Δs of RT and ABI between M-CL and S-CL did not show significant value (Table V).

This study has been carried out in Sicily, where the cost was 4 179 €; the average cost to walk one additional meter was 46.30 € (40.64 for M-CL, and 52.16 for S-CL). In Veneto the cost of our protocol would have been 3 057 €.

Discussion

The clinical characteristics of the study population are the usual ones of the IC. Fifty-eight percent of patients were overweight and 55% were diabetics, confirming the role of the metabolic syndrome in the atherogenesis.[25] Smoking was present in the clinical history of 74% of population and 31% of enrolled people were still smokers. Hypertension and hypercholesterolemia showed a prevalence of 56% and 48%, respectively. Con-

TABLE VII.—*Increase percent of initial claudication distance and absolute claudication.*

Year	Author	Measurement	Working load	ICD (%)	ACD (%)
1985	Andreozzi *et al.*[1]	Meters	60-70% ACD	75	56
1994	Hiatt *et al.*[3]	Walking peak time	Near maximal pain	209	79
1995	Gardner *et al.*[30]	Meta-analysis		179	122
1995	Pancera *et al.*[31]	Meters	Aerobic walking	122	76
1999	Girolami *et al.*[4]	Meta-analysis		10	74
2000	Gibellini *et al.*[32]	Meters	Aerobic walking	200	200
2001	Gardner *et al.*[9]	Meters	Near maximal pain	134	77
2002	Ambrosetti *et al.*[23]	Meters (short course)	Aerobic walking	132	87
2002	Leng *et al.*[5]	Meta-analysis		10	230
2002	Tsai *et al.*[18]	Walking time	Near maximal pain	87	68
2003	Carlon *et al.*[33]	Walking peak time	Beyond pain threshold	86	50
2004	Ambrosetti *et al.*[24]	Meter (short course)	Aerobic walking	137	112
2004	McDermott *et al.*[34]*	Meters			50
2004	Menard *et al.*[35]	Meters		121	109
2005	Gardner *et al.*[21]	Meters (low intensity)	40% ACD	109	61
2005	Gardner *et al.*[21]	Meters (high intensity)	80% ACD	109	63
2007	Andreozzi (moderate claudication)	Meters (short course)	60-70% ACD	105	69
2007	Andreozzi (severe claudication)	Meters (short course)	60-70% ACD	151	116

*Pilot study on patient with peripheral arterial disease, but without symptoms of calf pain; the walking ability has been assessed measuring the meters walked during 6 min walking test. ICD: initial claudication distance; ACD: absolute claudication distance.

cerning the non-fatal cardiovascular events, myocardial infarction showed a prevalence of 19%, whilst the prevalence of cerebrovascular event was 8%.

The prevalence of unbalanced patients in each group of risk factors (Table I) confirms the inadequate cardiovascular prevention and the underuse of the guidelines' recommendations as described in a recent paper from our group.[26]

The training program realized a significant (P<0.0001) improvement of the walking ability in both ICD (from 56.15 to 123.9 m) and ACD (from 104.86 to 195.11 m). After training, patients walked longer and better than before. In fact, after the onset of calf pain (which occurred walking a longer distance than before training), the patients needed less time to recover from the discomfort and fatigue as demonstrated by the reduction of RT (from 201.15 to 85.88 s; P<0.0001) (Table II).

Significant differences between pre- and post-training values have been found not only in the walking ability, but also in ABI. An improvement of ABI is frequently described by studies on the physical and pharmacological treatment of IC, but it often remains unexplained. They are obviously very low changes, without clinical or hemodynamic relevance, but the significant difference could be explained by the improvement of the endothelial function induced by physical training.[27] In fact, a better endothelial function implies a higher arteriolar vasodilatability with a reduction of peripheral resistances, which could justify the increasing of ABI, sustained by a greater microcirculatory run-off.

The training program has been effective in both M-CL and S-CL groups, with increase of ICD, ACD, ABI, and reduction of RT (Tables III and IV).

Comparing the meters gained after training (Δs) of M-CL and in S-CL; we found significant values for ICD (P=0.0003) and ACD (P<0.05), whilst the gain of RT and ABI did not reach significant values (Table V).

These data confirm that walking ability is relatively independent from perfusion pressure and hemodynamic involvement, as demonstrated by the higher increase of walking ability after training (low ABI changes) than after endovascular procedures (high ABI changes).[28]

The Δs were obviously higher in M-CL than S-CL. But, if we consider the Δs percent (post-training value minus pretraining value, divided by pretraining value, per cent), we find the higher increase in S-CL (ICD: 151.81%; ACD: 116.04%) than M-CL (ICD: 105.64%; ACD: 68.84%) (Table VI). The Δs percent are more relevant in clinical practice, because they express the real gain related to the baseline values. The higher results obtained in S-CL agree with the suggestion to realize a supervised physical training overall in patients with S-CL.[29]

Our results also showed to be in the range of the results referred by other papers[1, 3-5, 9, 18, 21, 23, 24, 30-35] and indicate that the adopted working load is an useful method to choose the working load (Table VII). The data also indicate that the short-course protocol is as effective as the longer ones. The protocol is not only equally effective, but it is also cheaper, and that is actually one of the most important features of the medical management and health policy.

Conclusions

Supervised physical training is confirmed as an effective tool for treatment of claudicant patients, and the proposed short-course protocol showed a significant improvement of the walking ability, with lesser costs and without loss of effectiveness.

The proposed procedure to calculate the working load of the single training session (60-70% of maximal walking capacity measured during a submaximal test) is near maximal pain, yet without reaching it, and it could be a well defined method, more reliable than the self-evaluation given by the patient (individual arbitrary score, moderate pain, etc.).

A wide adoption of this suggestion could contribute to obtain more homogenous results, avoiding misunderstandings on the terms, and protocols with high inflammatory risk.

References

1. Andreozzi GM, Signorelli S. La pratica riabilitativa nell'insufficienza arteriosa periferica. Minerva Angiol 1985;10:263-74.
2. Andreozzi GM, Signorelli S, Tornetta D. The rehabilitation in angiology. In: Strano A, Novo S, editors. Advances in vascular pathology. Amsterdam: Elsevier Science Publishers B.V.; 1990.p.591-7.
3. Hiatt WR, Wolfel EE, Meier RH, Regensteiner JG. Superiority of treadmill walking exercise *versus* strength training for patients with peripheral arterial disease. Implications for the mechanism of the training response. Circulation 1994;4:1866-74.

4. Girolami B, Bernardi E, Prins MH, Ten Cate JW, Hettiarachchi R, Prandoni P *et al.* Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. Arch Intern Med 1999;159:337-45.
5. Leng GC, Fowler B, Ernst E. Exercise for intermittent claudication. In: Cochrane library, 3. Oxford: Update Software; 2002.
6. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsh AT. Exercise training for claudication. N Engl J Med 2002;347:1941-51.
7. Hirsch AT, Haskal ZJ, Hertzer NR. ACC/AHA Guidelines for the management of PAD. JACC 2006;20:1-75.
8. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group, Bell K, Caporusso J, Durand-Zaleski I, Komori K, Lammer J *et al.*; TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Eur J Vasc Endovasc Surg 2007;33 Suppl 1:S1-75.
9. 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.
10. Ferrara M, Tornetta D, Interlandi S, Lo Duca S, Monaco S, Amico-Roxas MT *et al.* Modificazioni emoreologiche indotte dallo sforzo nel soggetto sano. Rass Med Int 1984;3:137-41.
11. Signorelli S, Cottini E, Tornetta D, Aiello A, Magnano V, Andreozzi GM *et al.* Variazioni reologiche indotte dallo sforzo in due differenti gruppi di soggetti sani allenati. Minerva Angiol 1984;9:275-8.
12. Hickman P, Harrison DK, Hill A, McLaren M, Tamei H, McCollum PT *et al.* Exercise in patients with intermittent claudication results in the generation of oxygen derived free radicals and endothelial damage. Adv Exp Med Biol 1994;361:565-70.
13. Brevetti G, Martone VD, de Cristofaro T, Corrado S, Silvestro A, Di Donato AM *et al.* High levels of adhesion molecule are associated with impaired endothelium-dependent vasodilation in patients with peripheral arterial disease. Thromb Haemost 2001;85:63-6.
14. Tisi PV, Shearman CP. The evidence for exercise-induced inflammation in intermittent claudication: should we encourage patients to stop walking? Eur J Vasc Endovasc Surg 1998;15:7-17.
15. Cordova R, Martini R, D'Eri A, Salimistraro G, Mussap M, Plebani M *et al.* Flogistic arterial activity or own inflammatory attitude: what acts on PAD evolution? Int Angiol 2003;22:21-2.
16. Signorelli SS, Mazzarino MC, Di Pino L, Malaponte G, Porto C, Pennisi G *et al.* High circulating levels of cytokines (IL-6 and TNFalpha), adhesion molecules (VCAM-1 and ICAM-1) and selectins in patients with peripheral arterial disease at rest and after a treadmill test. Vasc Med 2003;8:15-9.
17. Andreozzi GM, Martini R, Cordova R, D'Eri A, Salmistraro G, Mussap M *et al.* Circulating levels of cytokines (IL-6 and IL-1beta) in patients with intermittent claudication, at rest, after maximal exercise treadmill test and during restore phase. Could they be progression markers of the disease? Int Angiol 2007;26:245-52.
18. Tsai JC, Chan P, Wang CH, Jeng C, Hsieh MH, Kao PF *et al.* The effects of exercise training on walking function and perception of health status in elderly patients with peripheral arterial occlusive disease. J Intern Med 2002;252:448-55.
19. Hiatt WR, Wolfel EE, Meier RH, Regensteiner GJ. Superiority of treadmill walking exercise *versus* strength training for patients with peripheral arterial disease. Circulation 1994;90:1866-74.
20. Hiatt WR. Medical treatment pf peripheral arterial disease and claudication. N Engl J Med 2001;344:1608-21.
21. Gardner AW, Montgomery PS, Flinn WR, Katzel LI. The effect of exercise intensity on the response to exercise rehabilitation in patients with intermittent claudication. J Vasc Surg 2005;42:702-9.
22. Lowensteyn I, Coupal L, Zowall H, Grover SA. The cost-effectiveness of exercise training for the primary and secondary prevention of cardiovascular disease. J Cardiopulm Rehabil 2000;20:147-55.
23. Ambrosetti M, Salerno M, Tramarin R, Pedretti RF. Efficacy of a short-course intensive rehabilitation program in patients with moderate-to-severe intermittent claudication. Ital Heart J 2002;8:467-72.
24. Ambrosetti M, Salerno M, Boni S, Daniele G, Tramarin R, Pedretti RF. Economic evaluation of a short-course intensive rehabilitation program in patients with intermittent claudication. Int Angiol 2004;23:108-13.
25. Ambrosetti M, Salerno M, Laporta A, Pedretti RF. Metabolic syndrome in patients with intermittent claudication referred to vascular rehabilitation. Int Angiol 2006;25:14-7.
26. Marzolo M, Verlato F, Zotta L, Guadagnin ML, Borgese L, Cravatari M *et al.* Occult atherosclerosis and physical vascular examination. A simple strategy to avoid inadequate cardiovascular prevention and under- use of diagnostic vascular guidelines in outpatients: a multicenter study in Angiology Care Units in North-Eastern Italy. Int Angiol. Submitted for publication 2008.
27. Andreozzi GM, Leone A, Laudani R, Deinite G, Martini R. Acute impairment of the endothelial function by maximal treadmill exercise in patients with intermittent claudication, and its improvement after supervised physical training. Int Angiol 2007;26 12-7.
28. Perkins JM, Collin J, Creasy TS, Fletcher EW, Morris PJ. Exercise training *versus* angioplasty for stable claudication. Long and medium term results of a prospective, randomised trial. Eur J Vasc Endovasc Surg 1996;11:409-31.
29. Consensus on Intermittent Claudication. Abano Terme (PD), Italy, 7th May 2005 (Writing Committee: Andreozzi GM, Arosio E, Martini R, Verlato F, Visonà A) Milano, Roma: Wolters Kluwer Health; 2006.
30. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain. A meta-analysis. JAMA 1995;27:975-80.
31. Pancera P, Prior M, Zannoni M, Lucchese M, De Marchi S, Arosio E. Micro- and macrocirculatory, and biohumoral changes after a month of physical exercise in patients with intermittent claudication. Scand J Rehabil Med 1995;27:73-6.
32. Gibellini R, Fanello M, Bardile AF, Salerno M, Aloi T. Exercise training in intermittent claudication. Int Angiol 2000;19:8-13.
33. Carlon R, Morlino T, Maiolino P. Beneficial effects of exercise beyond the pain threshold in intermittent claudication. Ital Heart J. 2003;4:113-20.
34. McDermott MM, Tiukinhoy S, Greenland P, Liu K, Pearce WH, Guralnik JM *et al.* A pilot exercise intervention to improve lower extremity functioning in peripheral arterial disease unaccompanied by intermittent claudication. J Cardiopulm Rehabil 2004;24:187-96.

Menard JR, Smith HE, Riebe D, Braun CM, Blissmer B, Patterson RB. Long-term results of peripheral arterial disease rehabilitation. J Vasc Surg 2004;39:1186-92.

Corresponding author: Prof. G. M. Andreozzi, Angiology Care Unit, University Hospital, Via Giustiniani 2, 35128 Padua, Italy. E-mail: gm.andreozzi@angio-pd.it