Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Extracorporeal Shock Wave Therapy Improves the Walking Ability of Patients With Peripheral Artery Disease and Intermittent Claudication

Fukashi Serizawa, MD; Kenta Ito, MD; Keiichiro Kawamura, MD; Ken Tsuchida, MD; Yo Hamada, MD; Tsutomu Zukeran, MD; Takuya Shimizu, MD; Daijiro Akamatsu, MD; Munetaka Hashimoto, MD; Hitoshi Goto, MD; Tetsuo Watanabe, MD; Akira Sato, MD; Hiroaki Shimokawa, MD; Susumu Satomi, MD

Background: Despite the recent advances in bypass surgery and catheter interventional therapy for peripheral artery disease (PAD), the long-term outcome of revascularization therapy for infrapopliteal lesions remains unsatisfactory. We have previously demonstrated that low-energy extracorporeal shock wave (SW) therapy effectively induces neovascularization through upregulation of angiogenic factors and improves myocardial ischemia in pigs and humans and in hindlimb ischemia in rabbits. In this study, we thus examined whether our SW therapy also improves the walking ability of patients with PAD and intermittent claudication.

Methods and Results: We treated 12 patients (19 limbs) in Fontaine II stage (males/females, 10/2; 60–86 years old) with low-energy SW therapy to their ischemic calf muscle 3 times/week for 3 consecutive weeks. After 24 weeks, the pain and distance subscale scores of the walking impairment questionnaire were significantly improved (33±25 vs. 64±26, 27±16 vs. 64±23, respectively, both $P<0.01$). Maximum walking distance was also significantly improved at 4 weeks (151±37% from baseline, $P<0.01$) and was maintained at 24 weeks (180±74% from baseline, $P<0.01$). Moreover, the recovery time of the tissue oxygenation index in the calf muscle during a treadmill test, which reflects local O_2 supply, was significantly shortened (295±222 s vs. 146±137 s, $P<0.01$). Importantly, no adverse effects were noted.

Conclusions: Non-invasive SW therapy improves the walking ability of PAD patients.

Key Words: Angiogenesis; Ischemia; Peripheral artery disease; Shock wave therapy

Peripheral artery disease (PAD) is caused by arterial stenosis and/or occlusion in the lower extremities, mainly because of atherosclerosis, and is associated with poor prognosis.[1] The number of patients with PAD has been recently increasing worldwide. Reduced blood supply causes tissue ischemia and subsequent various symptoms depending on its severity, including intermittent claudication, limb coldness, rest pain, and tissue necrosis. These ischemic symptoms impair exercise capacity and quality of life, together with increased risk of cardiovascular disorders.[1,2] Therapeutic strategies for PAD are several, including medication, exercise, bypass surgery, and catheter intervention. Although long-term outcomes of bypass surgery and endovascular intervention for ilio-femoral artery are acceptable,[3–6] the long-term patency rate for infrapopliteal lesions remain low,[7,8] which often requires repeated invasive procedures for these patients. New, non-invasive therapeutic strategies remain to be developed.

Editorial p????

We have previously demonstrated that low-energy extracorporeal shock wave (SW) therapy effectively induces therapeutic angiogenesis and improves myocardial ischemia in pigs and humans, and in hindlimb ischemia in rabbits, through upregu-

Received October 24, 2011; revised manuscript received January 9, 2012; accepted January 27, 2012; released online March 3, 2012
Time for primary review: 39 days

Division of Advanced Surgical Science and Technology (F.S., K.K., K.T., Y.H., T.Z., T.S., D.A., M.H., H.G., A.S., S.S.), Department of Cardiovascular Medicine (K.I., H.S.), Tohoku University Graduate School of Medicine, Sendai; and Division of Surgery, Sendai City Hospital, Sendai (T.W.), Japan

The Guest Editor for this article was Kimihiro Komori, MD.

Mailing address: Akira Sato, MD, PhD, Division of Advanced Surgical Science and Technology, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan. E-mail: attkas@med.tohoku.ac.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-11-1216

Figure 1. Shock wave therapy was performed with the guidance of an inline ultrasound device. Patients were awake and no invasive procedures were needed for this therapy.

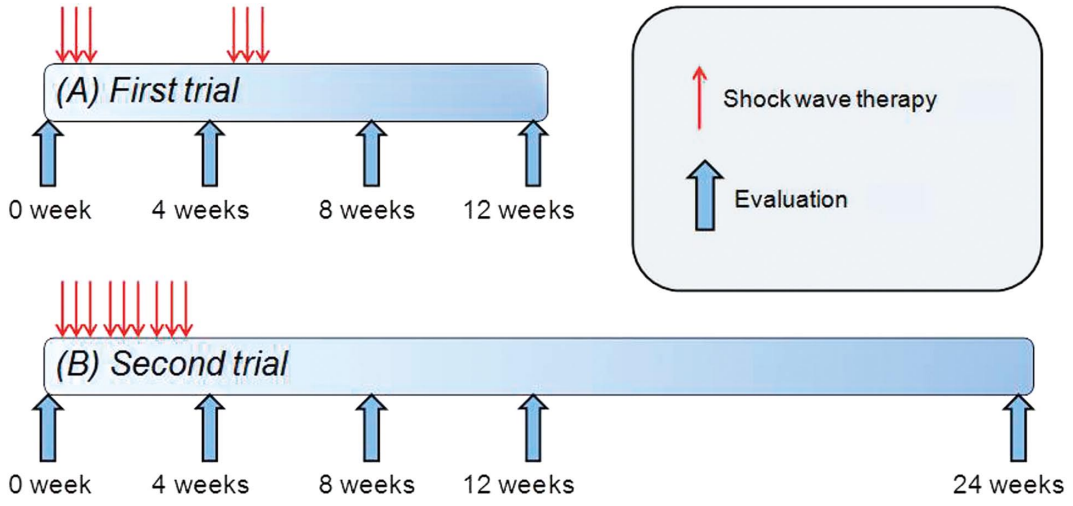

Figure 2. Treatment protocols. (**A**) First trial (pilot study) in which patients were treated in the 1st and 5th weeks. (**B**) Second trial in which patients were treated in 3 consecutive weeks.

lation of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS).[9–14] Because of its non-invasive nature, our low-energy SW therapy is applicable for both patients with complicating disorders and elderly patients, and can be repeated if needed.

In the present study, we thus examined whether our low-energy SW therapy also improves the walking ability of PAD patients with intermittent claudication.

Methods

Patients

We enrolled PAD patients who were classified as Fontaine II. In the first trial (a pilot study), we treated 6 patients from September 2007 to July 2008. After modifying the treatment protocol based on the results of the pilot study, we then treated another 12 patients in the second trial from September 2008 to

Table. Basic Characteristics of the Patients (Second Trial)

Age (years)	Sex	Primary disease	Site of lesion (CT findings)	Hypertension	Hyperlipidemia	Diabetes mellitus	Smoking history	Cilostazol	Sarpogrelate
77	M	PAD	F, IP	+	+	+	+	+	+
60	M	PAD	F, IP	+	+	+	+	−	+
75	M	BD	F, IP	−	−	−	+	−	+
86	M	PAD	I, F, IP	+	−	−	+	−	−
67	M	PAD	I, F, IP	+	+	+	+	+	−
75	M	PAD	F, IP	+	+	+	+	+	+
60	F	PN	I, IP	−	−	−	−	−	+
67	M	PAD	IP	+	−	−	+	+	−
67	M	PAD	I	−	+	−	+	+	−
70	F	PAD	I, F, IP	+	−	−	+	−	−
68	M	PAD	IP	+	−	−	+	+	−
84	M	PAD	F, IP	+	−	−	+	−	+

PAD, peripheral artery disease; Buerger, Buerger's disease; PN, polyarteritis nodosa; I, iliac region (from aortic bifurcation to external iliac artery); F, femoral region (common/superficial/deep femoral artery); IP, infra-popliteal region.

May 2011. Exclusion criteria were as follows: absence of PAD (ankle-brachial pressure index [ABI] >0.90 at rest), asymptomatic PAD, unstable coronary artery disease, current smoking, inability to perform treadmill test, active cancer, and dementia. Smoking history was obtained from the patient's self-report and non-smoking for more than 6 months was required to participate in the present study. Antiplatelet agents were administered for at least 1 year before enrolment and all antiplatelet agents were continued during the follow-up period. Both trials were approved by the ethical committees of Tohoku University, and written informed consent was given by each patient.

Low-Energy SW Therapy

Low-energy SW therapy was performed with a SW generator (Modulith® SLC, Storz Medical AG, Switzerland) (**Figure 1**). Based on our previous work, 1 SW session consisted of 200 shots in each of 40 sites on the ischemic calf muscle at 0.1 mJ/mm^2, approximately 10% of the energy level that is used for lithotripsy.[9–17] If the patient felt discomfort in the legs during the SW therapy, the energy level was reduced to a tolerable level and then the energy level was gradually increased.

First Trial (Pilot Study)

We treated 6 limbs in 6 patients (5 males/1 female, 67–82 years old; all patients had arteriosclerosis obliterans) with the low-energy SW therapy 3 times/week in the first (days 1, 3, 5) and fifth weeks (days 29, 31, 33) (**Figure 2**).

Second Trial

Based on the results of the pilot study, we modified the treatment protocol. In the second trial, the low-energy SW therapy was performed 3 times/week for 3 consecutive weeks (**Figure 2**). We treated 19 limbs in another 12 PAD patients (10 males/2 females, 60–86 years old), comprising arteriosclerosis obliterans in 10, Buerger's disease in 1 and polyarteritis nodosa in 1 (**Table**).

Evaluation of Walking Ability

Walking Impairment Questionnaire (WIQ) Subjective walking ability was evaluated in the second trial with a WIQ (Japanese version).[18] The patients answered the WIQ before and 4, 8, 12 and 24 weeks after the SW therapy.

ABI ABI was examined before and 4, 8, and 12 weeks after the SW therapy in the first trial, and before and 4, 8, 12, and 24 weeks after the SW therapy in the second trial. All measurements were performed with an ABI measurement device (VaSera VS-1500A®; Fukuda Denshi, Tokyo, Japan) at rest.

Maximum Walking Distance The treadmill test was performed under the condition of 2.4 km/h, 12% degrees in incline with treadmill device, and the maximum walking distance was measured (up to 400 m in 10 min). The maximum walking distance was evaluated before and 4, 8, and 12 weeks after the SW therapy in the first trial, and before and 4, 8, 12, and 24 weeks after the SW therapy in the second trial. Seven patients enrolled in the second trial had bilateral lesions and their maximum walking distance was measured in the more severely diseased leg.

Recovery Time of Tissue Oxygenation Index (TOI) TOI was measured with near-infrared spectroscopy (NIRO-200®; Hamamatsu Photonics, Japan) during the treadmill test in the second trial before and 4, 8, 12 and 24 weeks after the SW therapy (**Figure 3**).

$$\text{TOI} = \text{oxygenated hemoglobin } (O_2\text{Hb})/\text{concentration of hemoglobin (cHb)}$$

The near-infrared spectroscopy probes were attached to the calf muscle, and the recovery time of TOI, which reflects local O_2 supply, was obtained.

CT Angiography CT angiography was performed to evaluate collateral vascular growth before and 12 weeks after the SW therapy in the first trial, and before and 24 weeks after the SW therapy in the second trial. The angiographic images were independently evaluated by 2 radiologists in a blinded manner.

Statistical Analysis

Statistical analyses were performed by unpaired t-test using StatMate 4. The results are expressed as means±standard deviations (SD). Differences were considered statistically significant at $P<0.05$.

Results

First Trial (Pilot Study)

There were no significant changes in ABI during the follow-up period in the first trial (data not shown). After the SW therapy, the maximum walking distance was significantly increased at 4 weeks (130±27% from baseline, $P<0.05$) and 8 weeks

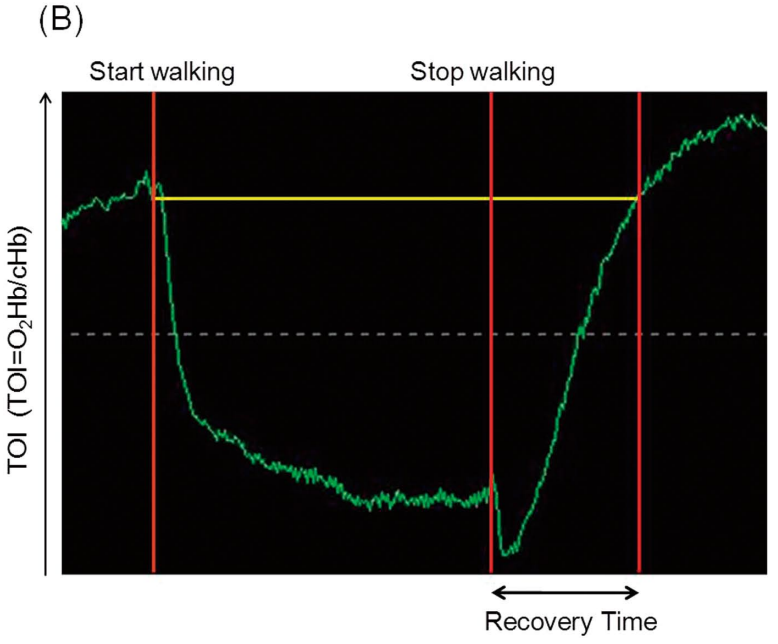

Figure 3. Treadmill test and near-infrared spectroscopy. (**A**) Treadmill test in a patient with peripheral artery disease. (**B**) The tissue oxygenation index (TOI) decreased after starting exercise and recovered to the pre-exercise level after stopping exercise.

(162±30% from baseline, P<0.05). However, the increased maximum walking distance was not sustained at 12 weeks in 3 of the 6 patients (146±63% from baseline, P=0.14). Thus, we modified the treatment protocol following our previous study of hindlimb ischemia in a rabbit model.[11] No detectable change in collateral vessels was observed with CT angiography at 12 weeks after the SW therapy.

Second Trial

WIQ The pain and distance subscale scores were significantly increased at 8, 12 and 24 weeks (**Figure 4**). The stairs subscale score was increased only at 8 weeks and no significant change was observed in the speed subscale score (**Figure 4**).

ABI There were no significant changes in ABI during the follow-up period (baseline: 0.57±0.15, 4 weeks: 0.58±0.13, 8 weeks: 0.58±0.13, 12 weeks: 0.57±0.14, 24 weeks: 0.59±0.12, all P=NS).

Maximum Walking Distance After the SW therapy, the maximum walking distance was significantly increased at 4 weeks (151±37% from baseline, P<0.01), and was maintained at 8 weeks (161±56%, P<0.01), 12 weeks (171±75%, P<0.01) and 24 weeks (180±74%, P<0.01) (**Figure 5**). One patient

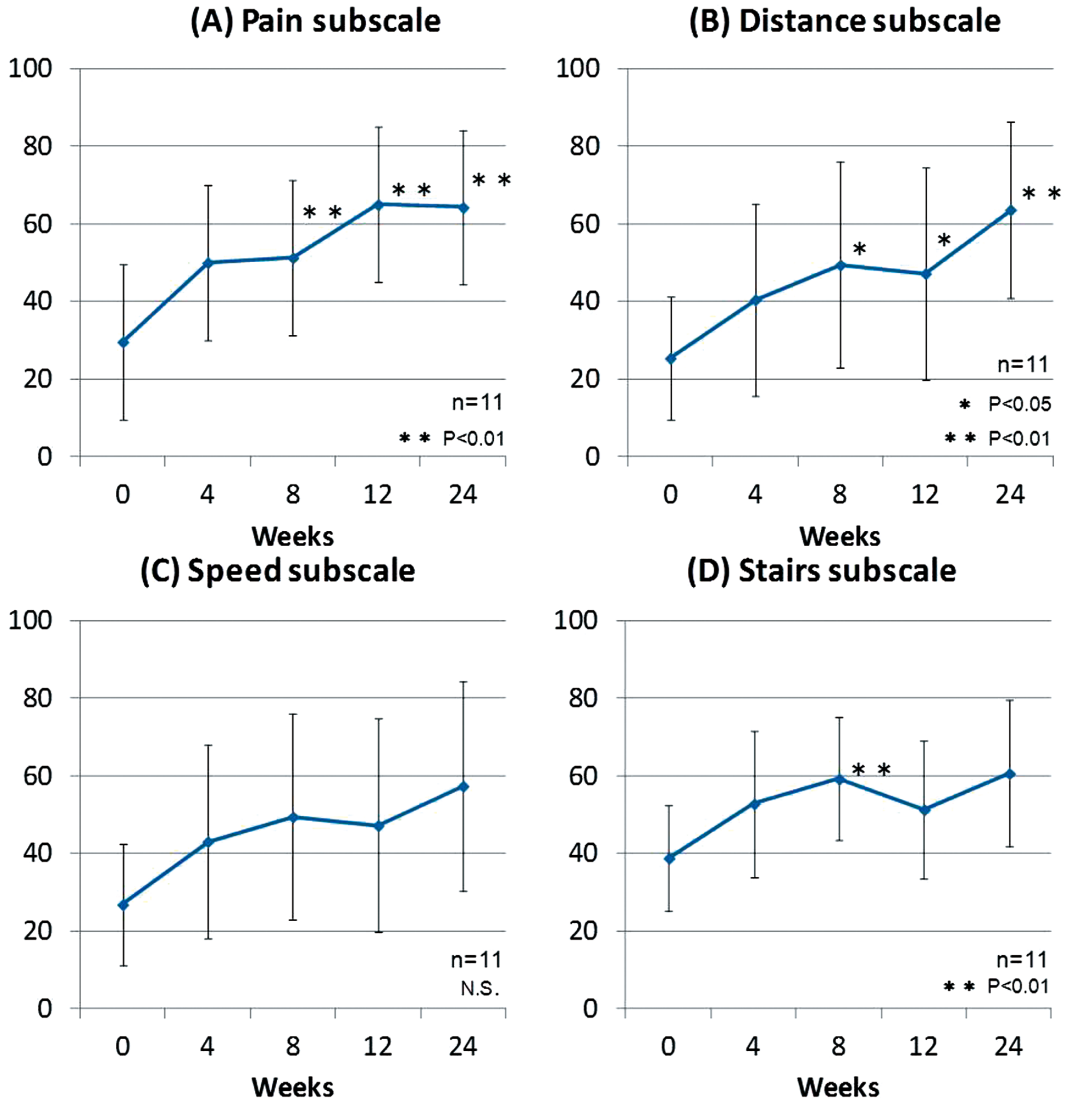

Figure 4. Scores for the walking impairment questionnaire in the second trial. (**A**) Pain subscale score, (**B**) distance subscale score, (**C**) speed subscale score, (**D**) stairs subscale score. The pain subscale and the distance subscale scores were significantly increased and were maintained for 24 weeks after the shock wave therapy.

failed to undergo the treadmill test at 4 weeks because of knee joint pain, and another patient at 24 weeks because of a respiratory disorder.

Recovery Time of TOI The recovery time of TOI was significantly shortened at 4, 8, 12 and 24 weeks compared with baseline (all P<0.01) (**Figure 6**).

CT Angiography No increase in visible collateral vessels was noted on the CT angiograms at 24 weeks after the SW therapy.

Discussion

In the present study, the low-energy SW therapy significantly improved symptoms, walking ability and peripheral perfusion without any adverse effects in PAD patients with intermittent claudication. To our knowledge, this is the first report to demonstrate the beneficial effects of low-energy SW therapy for PAD patients.

Treatment Protocol

In the first trial, although the maximum walking distance was increased at 4 weeks after the SW therapy, the beneficial effect was not sustained for a longer period. Thus, we modified the protocol by increasing the duration of the SW therapy in the second protocol, and we were able to confirm sustained beneficial effects of the therapy on the walking ability of PAD patients. In our previous studies, 1-week treatment (total 3 times) was enough for the treatment of myocardial ischemia in pigs and humans,[9,10,12–16] whereas the 3-week treatment (total 9 times) was required for the treatment of hindlimb ischemia

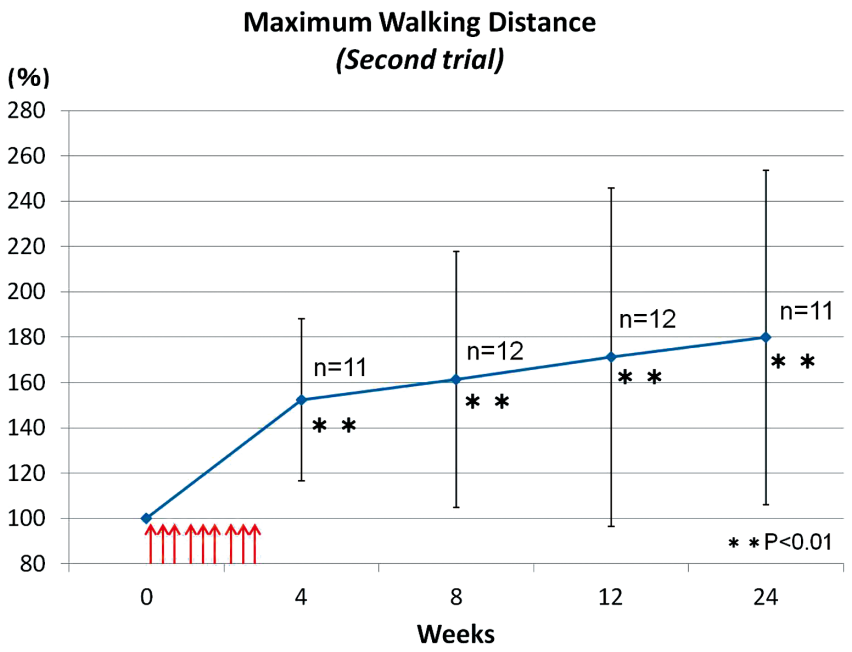

Figure 5. Maximum walking distance during the treadmill test in the second trial was significantly increased and was maintained for 24 weeks after the shock wave therapy.

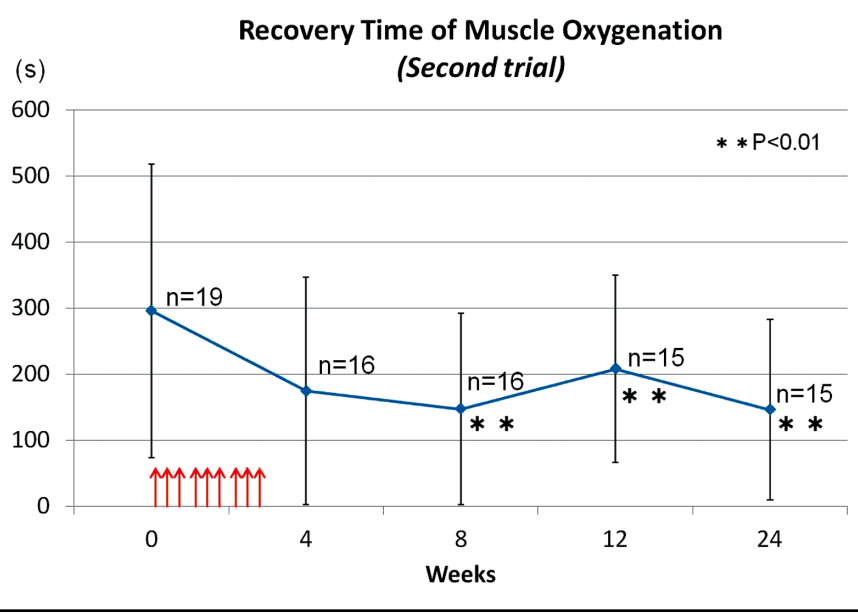

Figure 6. Recovery time of tissue oxygenation index in the second trial was significantly shortened and the improvement was maintained for 24 weeks after the shock wave therapy.

in rabbits.[11] Although the mechanisms for the different optimal SW conditions between the heart and the legs remain unclear, it is conceivable that therapeutic angiogenesis may be more effectively induced in the heart than in the legs. Further studies are needed to address this point.

Effects of Low-Energy SW Therapy on Symptoms

In the second trial, the low-energy SW therapy significantly improved the pain and distance subscale scores of the WIQ, probably because of improved peripheral perfusion and local O_2 supply as evidenced by the improved recovery time of TOI. In contrast, the SW therapy did not sufficiently improve the speed or stairs subscale scores. Most PAD patients with intermittent claudication walk slowly and subconsciously avoid the use of stairs in their daily life, which could be one of the reasons why the SW therapy did not improve the speed and stairs subscale scores. Although cilostazol has also been reported to improve the WIQ scores,[19] the beneficial effect of the SW therapy on the WIQ scores in the present study is superior to that of cilostazol.

Effects of the SW Therapy on Walking Ability

In the second trial, the SW therapy significantly improved the walking ability of PAD patients with intermittent claudication. This beneficial effect was associated with a significant reduction in the recovery time of TOI, reflecting improved calf

muscle blood flow and oxygenation. These results indicate that the SW therapy ameliorates the walking disability by improving peripheral perfusion in ischemic limbs.

Recently, Norgren et al demonstrated that sarpogrelate ameliorated the walking disability and increased the maximum walking distance at 24 weeks by 40% in patients classified as Fontaine II.[20] Regensteiner et al[19] and Pande et al[21] also demonstrated that cilostazol prolonged the maximum walking distance at 24 weeks by 50–76%. Exercise rehabilitation has also been reported to improve walking capacity by 25–65%.[22–24] The present study demonstrates that the SW therapy improves walking ability to the same extent as cilostazol without any adverse effects.

Mechanism of the Low-Energy SW Therapy

We have previously reported that low-energy SW therapy ameliorates myocardial ischemia in patients with severe angina pectoris[10,13] and increases capillary density in ischemic myocardium and ischemic limbs in animal models.[9,11,15,16] There are also several animal studies and case reports in humans showing that SW therapy accelerates wound healing in skin graft and chronic ulcers.[25–28] We and others have demonstrated in cultured human umbilical vein endothelial cells that low-energy SW therapy enhances NO production and expression of VEGF and its receptor, fms-related tyrosine kinase 1 (Flt-1), in vitro[9,29] and that the upregulation of VEGF and eNOS was involved in the SW-induced angiogenesis in vivo.[9,16] In addition, it was reported that low-energy SW applied to bone-marrow-derived mononuclear cells enhances VEGF production from the cells and their differentiation into endothelial phenotype cells[30] and that low-energy SW activates proliferation and differentiation in cardiac primitive cells.[31] Low-energy SW therapy was also reported to increase the expression of stromal-derived factor 1 in ischemic tissue, leading to enhanced recruitment of progenitor cells in a rat model of hindlimb ischemia.[32] Taken together, these data suggest that the beneficial effects of low-energy SW therapy on the walking ability of PAD patients are attributed, at least in part, to enhancement of several intrinsic angiogenic pathways.

Study Limitations

Several limitations of the present study should be mentioned. First, this was not a randomized controlled study and there was a small number of patients. We created the present protocol because patients can easily feel the SW-induced compression sensation (but not pain) when SW is applied to the calf muscle. Furthermore, we found a statistically significant beneficial effect of the SW therapy in the present patients (80% increase in the walking distance at 24 weeks) and the effect was greater than in a previous study in which some placebo effects were noted (35% increase at 6 months in a phase III clinical trial of oral beraprost sodium in PAD patients with intermittent claudication).[33] Thus, we consider that our SW therapy is superior to the placebo effect. However, this point needs to be confirmed in future studies with a large number of patients. Second, SW therapy failed to significantly improve the ABI and no increase in visible collateral vessels was noted by CT angiography although the SW therapy improved not only symptoms and walking ability but also local O_2 supply. Although the effect of the SW therapy appears to be mediated primarily by angiogenesis, the ABI and CT may not be sensitive enough to detect the angiogenesis in the ischemic calf muscle. A similar phenomenon was often observed in exercise rehabilitation studies of PAD patients and a recent meta-analysis reported that exercise rehabilitation could ameliorate the walking disability but did not improve ABI.[23] In PAD patients' calf muscles, increased muscle cell apoptosis and decreased capillary density are noted at the cellular and tissue levels, and muscle energetics are associated with mitochondrial dysfunction.[34,35] Bauer et al reported that mitochondrial dysfunction may affect the muscle oxygen utilization rate and accelerate endothelial cell damage.[36,37] We consider that our SW therapy may contribute, at least in part, to an improvement in mitochondrial dysfunction and muscle oxygen utilization. Although muscle biopsy may be useful to examine the histological changes, biopsy of the calf muscle of PAD patients is not usually recommended because of its invasive nature. Third, although supervised exercise training has been reported to improve walking ability by 25–65% in PAD patients,[22–24] it was not performed in the present study because the patients did not have an access to daily supervised exercise training. The possible effects of low-energy SW therapy combined with conventional therapeutic strategies, such as supervised exercise training, bypass surgery and endovascular intervention, remain to be examined. Fourth, the maximum walking distance at 24 weeks was increased in all patients. However, in only 1 patient wasthe maximum walking distance increased by less than 35% at 24 weeks. This patient had a single lesion caused by an occluded external iliac stent and the vascular tree below the femoral artery was intact. Considering potential mechanisms such as angiogenesis, SW therapy applied to the ischemic calf muscle may be more effective in patients with infrapopliteal lesions. Finally, in the present study, only PAD patients in Fontaine stage II were enrolled. In order to examine whether low-energy SW therapy is also effective in PAD patients with critical limb ischemia, we are now conducting a third clinical trial with PAD patients in Fontaine stages III and IV.

Conclusions

The present study demonstrates for the first time that our non-invasive low-energy SW therapy ameliorates the walking disability of PAD patients without any adverse effects. Further studies are needed to elucidate the detailed mechanisms of the beneficial effects of SW therapy.

Acknowledgments

This study was supported in part by the grants-in-aid from the Japanese Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan (Grant-in-Aid for Scientific Research on Innovative Areas 20117009), the Japanese Ministry of Health, Labor, and Welfare, Tokyo, Japan (H21-rinsyokenkyu-ippan-012).

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007; **45**(Suppl S)**:** S5–S67.
2. Faglia E. Characteristics of peripheral arterial disease and its relevance to the diabetic population. *Int J Low Extrem Wounds* 2011; **10:** 152–166.
3. Soga Y, Yokoi H, Urakawa T, Tosaka A, Iwabuchi M, Nobuyoshi M. Long-term clinical outcome after endovascular treatment in patients with intermittent claudication due to iliofemoral artery disease. *Circ J* 2010; **74:** 1689–1695.
4. Ye W, Liu CW, Ricco JB, Mani K, Zeng R, Jiang J. Early and late outcomes of percutaneous treatment of Transatlantic Intersociety Consensus Class C and D aorto-iliac lesions. *J Vasc Surg* 2011; **53:** 1728–1737.
5. Suzuki K, Iida O, Soga Y, Hirano K, Inoue N, Uematsu M, et al. Long-term results of the S.M.A.R.T. Control™ stent for superficial femoral artery lesions, J-SMART registry. *Circ J* 2011; **75:** 939–944.
6. Ichihashi S, Higashiura W, Itoh H, Sakaguchi S, Nishimine K,

Kichikawa K. Long-term outcomes for systematic primary stent placement in complex iliac artery occlusive disease classified according to Trans-Atlantic Inter-Society Consensus (TASC)-II. *J Vasc Surg* 2011; **53:** 992–999.
7. Troisi N, Dorigo W, Pratesi G, Alessi Innocenti A, Pulli R, Pratesi C. Below-knee revascularization in patients with critical limb ischemia: Long-term comparison of redo vs primary interventions. *J Cardiovasc Surg (Torino)* 2008; **49:** 489–495.
8. Gandini R, Volpi T, Pampana E, Uccioli L, Versaci F, Simonetti G. Applicability and clinical results of percutaneous transluminal angioplasty with a novel, long, conically shaped balloon dedicated for below-the knee interventions. *J Cardiovasc Surg (Torino)* 2009; **50:** 365–371.
9. Nishida T, Shimokawa H, Oi K, Tatewaki H, Uwatoku T, Abe K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. *Circulation* 2004; **110:** 3055–3061.
10. Fukumoto Y, Ito A, Uwatoku T, Matoba T, Kishi T, Tanaka H, et al. Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease. *Coron Artery Dis* 2006; **17:** 63–70.
11. Oi K, Fukumoto Y, Ito K, Uwatoku T, Abe K, Hizume T, et al. Extracorporeal shock wave therapy ameliorates hindlimb ischemia in rabbits. *Tohoku J Exp Med* 2008; **214:** 151–158.
12. Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy as a new and non-invasive angiogenic strategy. *Tohoku J Exp Med* 2009; **219:** 1–9.
13. Kikuchi Y, Ito K, Ito Y, Shiroto T, Tsuburaya R, Aizawa K, et al. Double-blind and placebo-controlled study of the effectiveness and safety of extracorporeal cardiac shock wave therapy for severe angina pectoris. *Circ J* 2010; **74:** 589–591.
14. Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy for ischemic cardiovascular disorders. *Am J Cardiovasc Drugs* 2011; **11:** 295–302.
15. Uwatoku T, Ito K, Abe K, Oi K, Hizume T, Sunagawa K, et al. Extracorporeal cardiac shock wave therapy improves left ventricular remodeling after acute myocardial infarction in pigs. *Coron Artery Dis* 2007; **18:** 397–404.
16. Ito Y, Ito K, Shiroto T, Tsuburaya R, Yi GJ, Takeda M, et al. Cardiac shock wave therapy ameliorates left ventricular remodeling after myocardial ischemia-reperfusion injury in pigs in vivo. *Coron Artery Dis* 2010; **21:** 304–311.
17. Serizawa F, Ito K, Matsubara M, Sato A, Shimokawa H, Satomi S. Extracorporeal shock wave therapy induces therapeutic lymphangiogenesis in a rat model of secondary lymphoedema. *Eur J Vasc Endovasc Surg* 2011; **42:** 254–260.
18. Ikeda S, Kobayashi M, Shigematsu H, Matsuo H, Ota T, Sugimoto I, et al. Development of the Japanese version of walking impairment questionnaire (WIQ). *J Jpn Coll Angiol* 2005; **45:** 233–240.
19. Regensteiner JG, Ware JE Jr, McCarthy WJ, Zhang P, Forbes WP, Heckman J, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: Meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 2002; **50:** 1939–1946.
20. Norgren L, Jawien A, Matyas L, Riegerd H, Arita K. Sarpogrelate, a 5-HT2A receptor antagonist in intermittent claudication: A phase II European study. *Vasc Med* 2006; **11:** 75–83.
21. Pande RL, Hiatt WR, Zhang P, Hittel N, Creager MA, McDermott M. A pooled analysis of the durability and predictors of treatment response of cilostazol in patients with intermittent claudication. *Vasc Med* 2010; **15:** 181–188.
22. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT. Exercise training for claudication. *N Engl J Med* 2002; **347:** 1941–1951.
23. Watson L, Ellis B, Leng GC. Exercise for intermittent claudication. *Cochrane Database Syst Rev* 2008; **4:** CD000990.
24. Tebbutt N, Robinson L, Todhunter J, Jonker L. A plantar flexion device exercise programme for patients with peripheral arterial disease: A randomised prospective feasibility study. *Physiotherapy* 2011; **97:** 244–249.
25. Saggini R, Figus A, Troccola A, Cocco V, Saggini A, Scuderi N. Extracorporeal shock wave therapy for management of chronic ulcers in the lower extremities. *Ultrasound Med Biol* 2008; **34:** 1261–1271.
26. Kuo YR, Wang CT, Wang FS, Chiang YC, Wang CJ. Extracorporeal shock-wave therapy enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of STZ-induced diabetes. *Wound Repair Regen* 2009; **17:** 522–530.
27. Moretti B, Notarnicola A, Maggio G, Moretti L, Pascone M, Tafuri S, et al. The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. *BMC Musculoskelet Disord* 2009; **10:** 54.
28. Ottomann C, Hartmann B, Tyler J, Maier H, Thiele R, Schaden W, et al. Prospective randomized trial of accelerated re-epithelization of skin graft donor sites using extracorporeal shock wave therapy. *J Am Coll Surg* 2010; **211:** 361–367.
29. Mariotto S, Cavalieri E, Amelio E, Ciampa AR, de Prati AC, Marlinghaus E, et al. Extracorporeal shock waves: From lithotripsy to anti-inflammatory action by NO production. *Nitric Oxide* 2005; **12:** 89–96.
30. Yip HK, Chang LT, Sun CK, Youssef AA, Sheu JJ, Wang CJ. Shock wave therapy applied to rat bone marrow-derived mononuclear cells enhances formation of cells stained positive for CD31 and vascular endothelial growth factor. *Circ J* 2008; **72:** 150–156.
31. Nurzynska D, Di Meglio F, Castaldo C, Arcucci A, Marlinghaus E, Russo S, et al. Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. *Ultrasound Med Biol* 2008; **34:** 334–342.
32. Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher AM, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: A new modality to increase efficacy of cell therapy in chronic hind limb ischemia. *Circulation* 2006; **114:** 2823–2830.
33. Lievre M, Morand S, Besse B, Fiessinger JN, Boissel JP. Oral beraprost sodium, a prostaglandin I_2 analogue, for intermittent claudication: A double-blind, randomized, multicenter controlled trial [Beraprost et Claudication Intermittente (BERCI) research group]. *Circulation* 2000; **102:** 426–431.
34. Askew CD, Green S, Walker PJ, Kerr GK, Green AA, Williams AD, et al. Skeletal muscle phenotype is associated with exercise tolerance in patients with peripheral arterial disease. *J Vasc Surg* 2005; **41:** 802–807.
35. Mitchell RG, Duscha BD, Robbins JL, Redfern SI, Chung J, Bensimhon DR, et al. Increased levels of apoptosis in gastrocnemius skeletal muscle in patients with peripheral arterial disease. *Vasc Med* 2007; **12:** 285–290.
36. Bauer TA, Brass EP, Barstow TJ, Hiatt WR. Skeletal muscle StO_2 kinetics are slowed during low work rate calf exercise in peripheral arterial disease. *Eur J Appl Physiol* 2007; **100:** 143–151.
37. Bauer TA, Brass EP, Hiatt WR. Impaired muscle oxygen use at onset of exercise in peripheral arterial disease. *J Vasc Surg* 2004; **40:** 488–493.