Therapeutic Angiogenesis

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Contents

Chapter 12
Low-Energy Extracorporeal Shock Wave Therapy

Kenta Ito, Tomohiko Shindo, and Hiroaki Shimokawa

Abstract Despite recent advances in medical knowledge and technology, ischemic heart disease is still one of the major causes of death, with the morbidity increasing worldwide. We have recently developed a new, noninvasive angiogenic therapy using low-energy shock waves. Low-energy extracorporeal cardiac shock wave therapy improves myocardial ischemia in a porcine model of chronic myocardial ischemia and in patients with refractory angina pectoris. Shock wave therapy also improves walking ability in patients with peripheral arterial disease and ameliorates digital skin ulcers in patients with systemic sclerosis. Furthermore, animal studies suggest that shock wave therapy may be effective to suppress left ventricular remodeling after acute myocardial infarction and to enhance locomotor recovery after spinal cord injury. Here, we summarize the studies in animals and humans and discuss the advantages and perspectives of low-energy shock wave therapy.

Keywords Shock wave therapy • Ischemic heart disease • Growth factors • New technology

12.1   Introduction

Despite recent advances in medical knowledge and technology, ischemic heart disease (IHD) is still one of the major causes of death in developed countries, with the morbidity increasing worldwide [1–4]. The standard management of IHD has three

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major therapeutic options, including medication, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). However, the number of severe IHD patients with multiple comorbidities has been increasing as the population is aging. Thus, new, noninvasive therapeutic strategies are urgently needed for aged and severely diseased patients.

Shock wave (SW) is a longitudinal acoustic wave that propagates through water, fat, and soft tissues as ultrasound does. SW is a single pressure pulse with a short needlelike positive spike <1 μs in duration and up to 100 MPa in amplitude, followed by a tensile portion lasting several microseconds with lower amplitude. Extracorporeal shock wave (SW) therapy was clinically introduced more than 30 years ago, which has markedly improved the treatment of urolithiasis. In extracorporeal SW lithotripsy, high-energy SW is used to break up stones in the urinary tract. We and others have demonstrated that low-energy SW (about 10% of the energy density that is used for urolithiasis) enhances the expression of vascular endothelial growth factor (VEGF) (Fig. 12.1) and nitric oxide (NO) release in cultured human umbilical vein endothelial cells (HUVEC) [5, 6]. Furthermore, we have demonstrated that low-energy cardiac SW therapy improves myocardial ischemia in a porcine model of chronic myocardial ischemia and in patients with refractory angina pectoris [5, 7, 8]. In this chapter, we summarize the studies in animals and humans and discuss the advantages and perspectives of low-energy SW therapy.
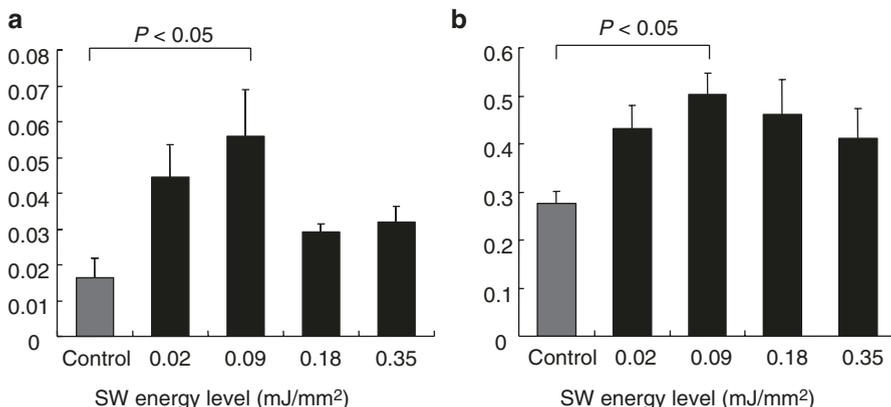
Fig. 12.1 Effects of SW on mRNA expression in HUVECs in vitro. SW therapy upregulated mRNA expression of VEGF (**a**) and Flt-1 (**b**) with a maximum effect noted at 0.09 mJ/mm², in which level is approximately 10% of that used for urolithiasis. Results are expressed as mean ± SEM ($n = 10$ each) (from [5] with permission)

12.2   Extracorporeal Cardiac SW Therapy for Angina Pectoris

12.2.1   Animal Studies

Based on our in vitro studies in HUVEC, we studied whether low-energy SW therapy ameliorates myocardial ischemia in a porcine model in vivo [5]. A porcine model of chronic myocardial ischemia was prepared by placing an ameroid constrictor at the proximal segment of the left circumflex coronary artery (Lcx). This constrictor gradually induced a total occlusion of the Lcx with sustained myocardial dysfunction but without myocardial infarction in 4 weeks. Four weeks after the implantation of the ameroid constrictor, we performed low-energy extracorporeal cardiac SW therapy in the SW group ($n = 8$) three times during the first week, whereas animals in the control group ($n = 8$) received the same anesthesia procedures three times a week but without the SW therapy. Low-energy SW was applied to nine spots (0.09 mJ/mm^2, 200 shots/ spot) in the ischemic Lcx region in the left ventricle (LV) with a guidance of an echo-cardiogram equipped within a specially designed SW generator (Storz Medical AG, Kreuzlingen, Switzerland) with an R-wave-triggered manner. We evaluated cardiac function before (baseline) and at 4 and 8 weeks after the ameroid implantation. Four weeks after the implantation of the constrictor, wall motion of the Lcx region in the LV was reduced to the same extent in both the control and the SW group (Fig. 12.2a, c).
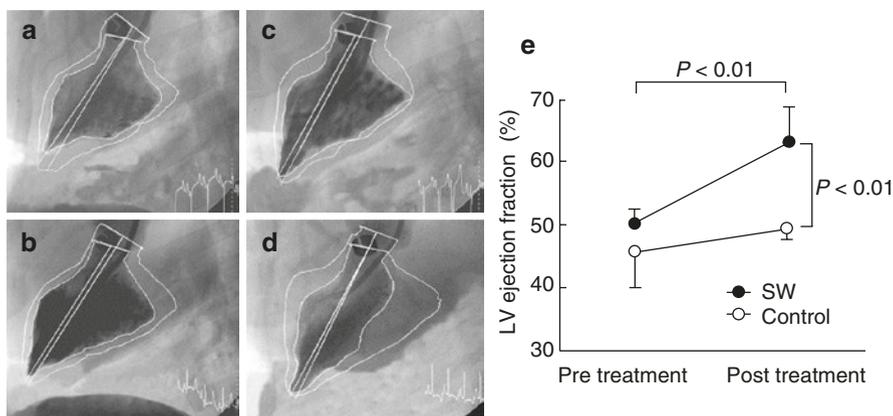
Fig. 12.2 Effects of the SW therapy on LV function in pigs in vivo. The extracorporeal cardiac SW therapy improved ischemia-induced myocardial dysfunction in vivo as evaluated by left ventriculography. Four weeks after the implantation of an ameroid constrictor, LV wall motion of the LCX (posterolateral) region was reduced in both the control (**a**) and the SW group (before the SW therapy) (**c**). Eight weeks after the implantation of an ameroid constrictor, no significant change in LV wall motion was noted in the control group (**b**), whereas marked recovery was noted in the SW group (**d**). (**e**) The SW therapy normalized LV ejection fraction in the SW group but not in the control group. Results are expressed as mean ± SEM ($n = 8$ each) (from [5] with permission)

However, 4 weeks after the SW therapy (8 weeks after the implantation of the constrictor), LV wall motion was marked improved only in the SW group (Fig. 12.2b, d, e). We also confirmed that the SW therapy upregulated the expression of VEGF, increased capillary density (Fig. 12.3), and normalized regional myocardial blood flow in the ischemic myocardium in vivo. No complications or adverse effects, such as tissue injury, hemorrhage, or arrhythmia, were noted during or after the SW therapy. These results suggest that the low-energy cardiac SW therapy enhances the endogenous angiogenic system in pigs in vivo. This was the first report that demonstrates the potential usefulness of low-energy extracorporeal cardiac SW therapy as a noninvasive angiogenic approach to chronic myocardial ischemia.
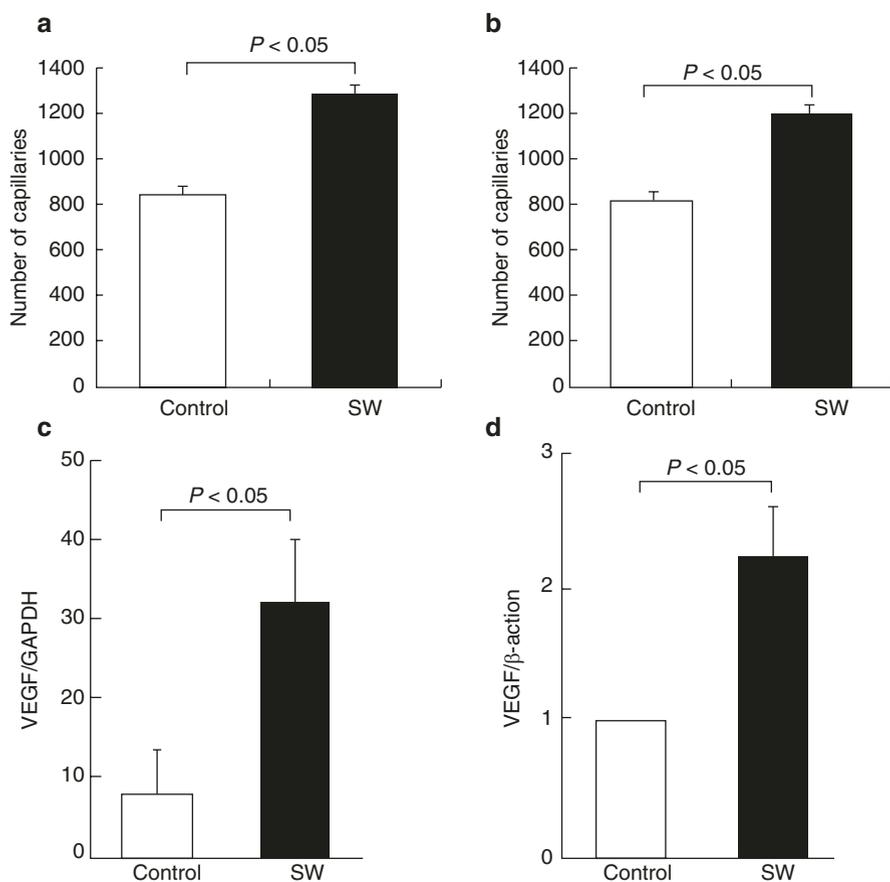
Fig. 12.3 Effects of the SW therapy on capillary density and VEGF expression in the ischemic myocardium in pigs in vivo. The extracorporeal cardiac SW therapy increased the density of factor VIII-positive capillaries and VEGF expression in the ischemic myocardium. Capillary density was significantly greater in the SW group (SW) than in the control group (control) in both the endocardium (**a**) and the epicardium (**b**). The mRNA expression (**c**) and the protein levels (**d**) of VEGF were significantly higher in the SW group than in the control group. Results are expressed as mean ± SEM ($n = 6$ each) (from [5] with permission)

12.2.2   Clinical Studies

Standard therapeutic approaches to ischemic heart disease (IHD) include medication, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). However, the number of IHD patients who are resistant to those therapies is increasing. Based on the promising results in animal studies, we conducted the first clinical trial of low-energy extracorporeal cardiac SW therapy in nine patients with refractory angina pectoris without indication of PCI or CABG (55–82 years old, five men and four women) [7]. Low-energy SW was applied to 20–40 spots (0.09 mJ/mm^2, 200 shots/spot) in the ischemic area in the LV three times during the first week. During the therapy, a patient lays on the bed in a supine position without any anesthesia or analgesics (Fig. 12.4). The low-energy SW therapy significantly improved symptoms and reduced the use of nitroglycerin (Fig. 12.5) and also ameliorated myocardial perfusion as assessed by stress scintigraphy only in the ischemic area treated with the SW therapy (Fig. 12.6). No complications or adverse effects related to the SW therapy were noted. These results indicate that low-energy extracorporeal cardiac SW therapy is a safe, effective, and noninvasive therapeutic
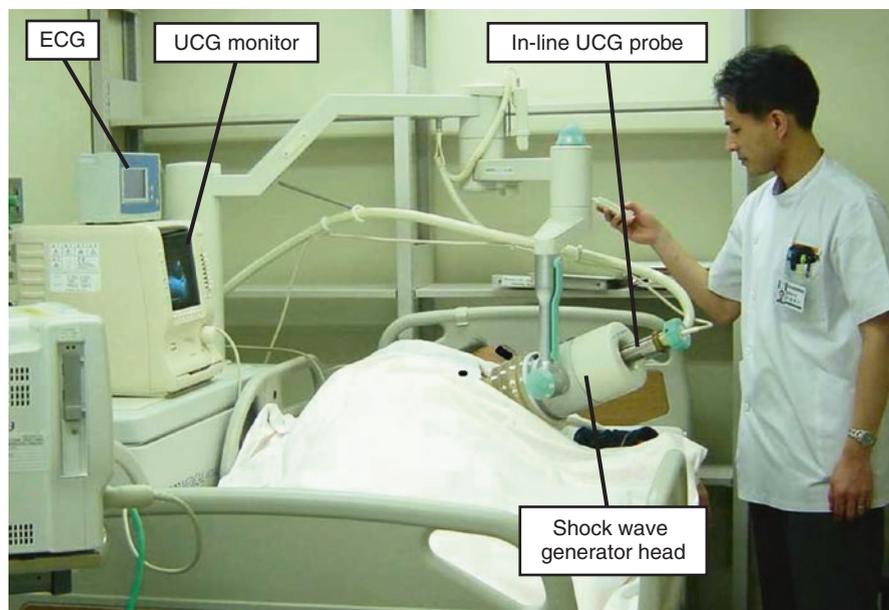
Fig. 12.4 Extracorporeal cardiac SW therapy in action in a patient with refractory angina pectoris. The machine is equipped with a SW generator head and in-line echocardiography probe. The SW generator is attached to the chest wall of the patient when used. The SW pulse is easily focused on the ischemic myocardium under the guidance of echocardiography. There is no need of anesthesia or analgesics
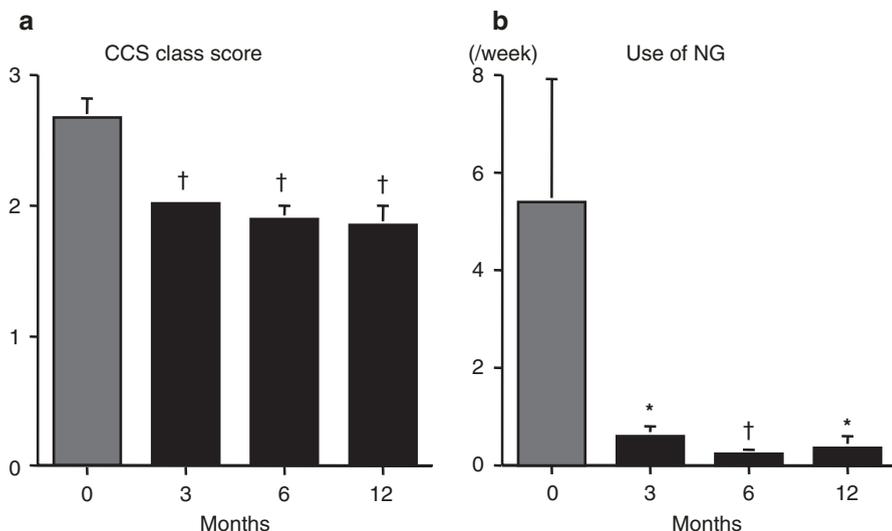
Fig. 12.5 Effects of the extracorporeal cardiac SW therapy on symptom and the use of nitroglycerin. Extracorporeal cardiac SW therapy significantly improved Canadian Cardiovascular Society (CCS) class scores (**a**) and the use of nitroglycerin (NG) (**b**) in patients with refractory angina pectoris. Results are expressed as mean ± SEM. *$P < 0.05$ and †$P < 0.01$ vs. 0 month (statistically analyzed by post hoc test after one-way ANOVA) (from [7] with permission)

strategy for severe ischemic heart disease. To further confirm the effectiveness and safety of the SW therapy, we performed a second clinical trial in a randomized and placebo-controlled manner [8]. In this second clinical trial, we again demonstrated that the low-energy SW therapy not only improves symptoms and reduces the use of nitroglycerin but also improves LV function (Fig. 12.7), establishing cardiac SW therapy as an effective and safe angiogenic strategy for severe ischemic heart disease. Following our initial report, several clinical studies with positive results were reported worldwide [9–15]. Although the SW therapy improves the quality of life (QOL) in patients with angina pectoris as mentioned above, it should be clarified whether the SW therapy improves the long-term prognosis of those patients.

Fig. 12.7 Effects of the extracorporeal cardiac SW therapy in patients with refractory angina pectoris in the placebo-controlled and double-blind study. *CCS* Canadian Cardiovascular Society, *NTG* nitroglycerin, *Max. exercise* maximum exercise capacity in watts (W), *Peak VO₂* peak oxygen uptake, *LVEF* left ventricular (LV) ejection fraction, *LVSV* LV stroke volume, *LVEDV* LV enddiastolic volume, *BNP* brain natriuretic peptide. Results are mean ± SE ($n = 8$ each) (from [8] with permission)
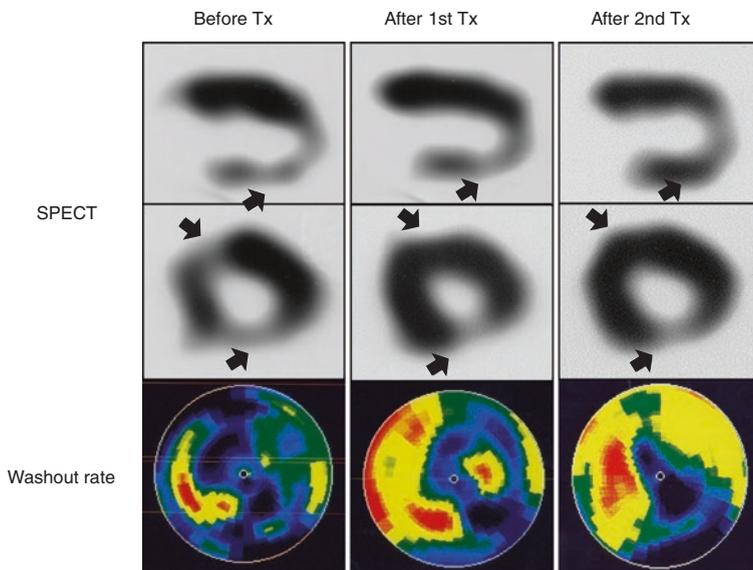
Fig. 12.6 Effects of the extracorporeal cardiac SW therapy on myocardial perfusion in patients with refractory angina pectoris. Dipyridamole stress thallium-201 single-photon emission computed tomography (SPECT) imaging and polar map in a patient with severe three-vessel coronary artery disease before and after the SW therapy. The results clearly demonstrated that the SW therapy ameliorated myocardial perfusion only where SW was applied, in the anteroseptal wall after the first treatment (1st Tx) and in the lateral wall after the second treatment (2nd Tx) (*arrows*) in a stepwise manner after the staged SW treatment. The areas treated with the SW therapy are indicated with dotted lines (from [7] with permission)
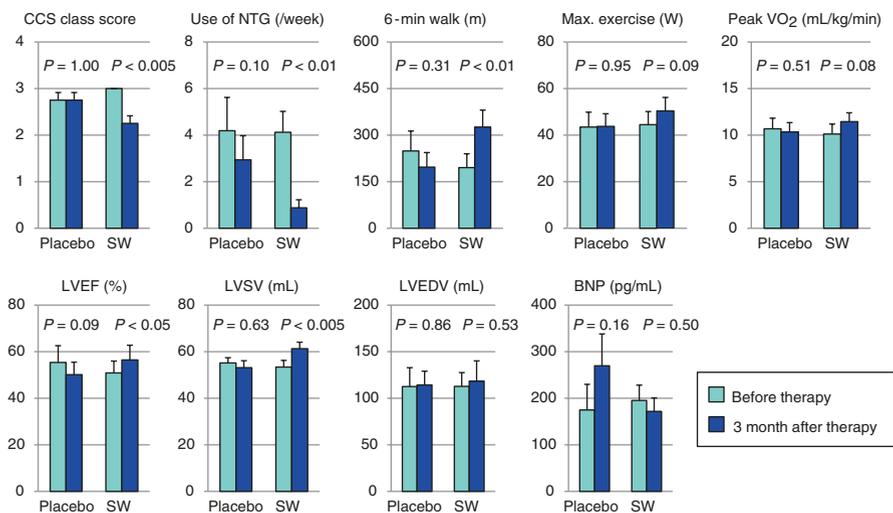
12.3   Extracorporeal Cardiac SW Therapy for Acute Myocardial Infarction

Although primary PCI substantially reduced the mortality of patients with acute myocardial infarction (AMI), LV remodeling after AMI still remains an important issue in cardiovascular medicine [16]. Thus, it is crucial to develop new therapeutic strategies to suppress post-MI LV remodeling. Since capillary density in the border zone adjacent to the infarcted myocardium is negatively correlated with infarct size 1 month after AMI [17], enhancing angiogenesis in the border zone is expected to ameliorate the progression of post-MI LV remodeling in patients. Thus, we studied whether the SW therapy is also effective to ameliorate post-MI LV remodeling in pigs in vivo. First, we created AMI by surgically excising the proximal segment of the Lcx [18]. Low-energy extracorporeal cardiac SW therapy was performed at 3, 5, and 7 days after AMI in the SW group. The animals in the control group were treated in the same manner but without the SW therapy. Four weeks after the therapy, LV ejection fraction and LV end-diastolic volume were significantly improved in the SW group compared with the control group (Fig. 12.8). Furthermore, regional myocardial blood flow and capillary density in the border zone were significantly improved in the SW group compared with the control group. Again, no procedural complications or adverse effects were noted. These results suggest that the low-energy extracorporeal cardiac SW therapy is an effective and noninvasive therapy to ameliorate post-MI LV remodeling as well. This was the first report that demonstrates the usefulness and safety of extracorporeal cardiac SW therapy as a noninvasive treatment of AMI. We also confirmed the beneficial effects and safety of the SW therapy in another porcine model of AMI due to myocardial ischemia (90 min)/reperfusion to mimic the clinical setting [19]. Based on the promising results in two types of AMI models in pigs, the first clinical trial in AMI patients is conducted to examine the feasibility, effectiveness, and safety of cardiac SW therapy. In this trial, low-energy SW is applied to the border zone around the infarcted area in AMI patients who are successfully treated with PCI as an adjunctive therapy.
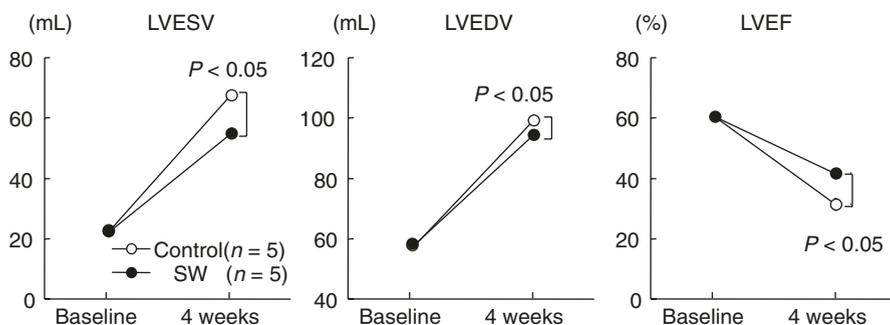
Fig. 12.8 Effects of the extracorporeal cardiac SW therapy on LV remodeling in pigs in vivo. The SW therapy significantly ameliorated LV remodeling characterized by the increase in LV end-systolic volume (LVESV) and end-diastolic volume (LVEDV) and reduced LV ejection fraction (LVEF) in a porcine model of AMI (from [18] with permission)

12.4   Additional Indications of Low-Energy Extracorporeal SW Therapy

12.4.1   SW Therapy for Peripheral Arterial Disease

Peripheral arterial disease (PAD) is often associated with IHD and the prognosis of patients with critical limb ischemia is quite poor [20–22]. Thus, we studied the effects of SW therapy on hindlimb ischemia in rabbits [23]. Hindlimb ischemia was induced by surgical excision of the entire unilateral femoral artery. One week after the operation, low-energy SW was applied to 30 spots (0.09 mJ/mm^2, 200 shots/spot) in the ischemic region three times a week for 3 consecutive weeks. Four weeks after the operation, blood flow, blood pressure, and capillary density were all significantly higher in the SW group than in the control group. Based on the results in animal studies, we conducted a clinical trial in 12 patients with PAD with intermittent claudication (Fontaine stage II; 60–86 years old, ten men and two women) [24]. Low-energy SW was applied to 40 spots (0.1 mJ/mm^2, 200 shots/spot) in the ischemic region three times a week for 3 consecutive weeks. Subjective walking ability was evaluated with a Walking Impairment Questionnaire (WIQ), and walking ability was evaluated with a treadmill test at 4, 8, 12, and 24 weeks after the SW therapy. The low-energy SW therapy significantly improved symptoms, maximum walking distance, and peripheral perfusion (Fig. 12.9). Tara et al. also reported the beneficial effects of low-energy SW therapy in PAD patients including Fontaine stage III and IV [25]. These results suggest that low-energy SW therapy is promising as a new, noninvasive angiogenic therapy for PAD.
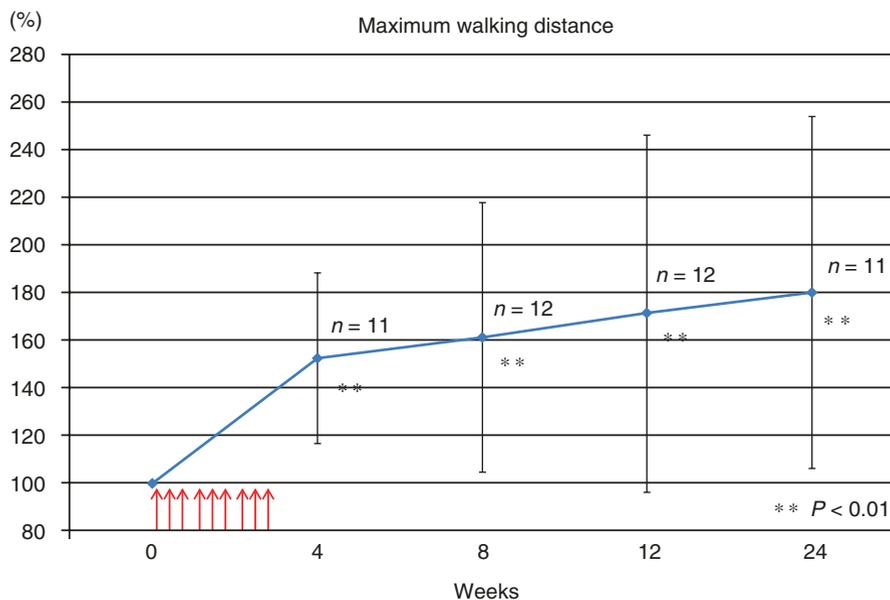
Fig. 12.9 Effects of the extracorporeal cardiac SW therapy on walking ability in patients with PAD and intermittent claudication. Maximum walking distance during the treadmill test was significantly increased and was maintained for 24 weeks after the SW therapy (from [24] with permission)

12.4.2 SW Therapy for Refractory Skin Ulcer

Raynaud's phenomenon and digital skin ulcers are severe complications of systemic sclerosis (SSc) which is related to immune activation, endothelial cell damage, and persistent vasospasms [26]. However, conventional immunosuppressive therapies, vasodilators, and anticoagulants are often ineffective. We and others have reported that low-energy SW therapy enhances wound healing in rodents [27–30] and in patients [31, 32]. We have demonstrated that the SW therapy facilitates wound healing in a mouse model of skin ulcers and that eNOS, VEGF, and angiogenesis play important roles in the repair process. Thus, we studied the effects of low-energy SW therapy on digital skin ulcers in nine patients with SSc [33]. Low-energy SW was applied to 20 areas on both hands and to 15 areas on both feet, totaling 7000 pulses once a week for 9 consecutive weeks with observations over 20 weeks. The low-energy SW therapy significantly improved digital ulcers in terms of size and number. No adverse effect was noted during the study period, demonstrating that this therapy can be safely repeated for a long period. These results suggest that the SW therapy may be added to standard treatments for refractory digital ulcers due to SSc.

12.4.3 SW Therapy for Other Disorders

We and others have reported the effects of low-energy SW therapy on secondary lymphedema in animals [34, 35]. We created a tail model of lymphedema in rats, and the tail was treated with low-energy SW on 2, 4, 6, and 8 days after the surgery [35]. Secondary lymphedema was sustained in the control group, which was significantly attenuated in the SW group. The lymphatic system function, the lymphatic vessel density, and the expression of VEGF-C and bFGF were all enhanced by the SW therapy. These results suggest that the low-energy SW therapy induces therapeutic lymphangiogenesis by upregulating VEGF-C and bFGF and that the SW therapy could be a noninvasive therapeutic strategy for lymphedema in humans. Low-energy SW has been widely used for the treatment of orthopedic diseases, such as bone nonunions, tendinosis calcarea, epicondylitis, and calcaneal spur through anti-inflammatory effects [36–39]. We have recently reported the effects of low-energy SW therapy on locomotor function after spinal cord injury in rats [40]. In this study, thoracic spinal cord contusion injury was inflicted using an impactor. Low-energy SW was applied to the injured spinal cord three times a week for 3 consecutive weeks. The SW therapy enhanced the expression of VEGF, attenuated neural tissue damage, and improved locomotor recovery. This study provides the first evidence that low-energy SW therapy can be a safe and promising therapeutic strategy for spinal cord injury.

12.5   Potential Mechanisms for the Beneficial Effects of SW Therapy

We and others have reported angiogenic effects of low-energy SW therapy in various animal models and in humans as mentioned above. Low-energy SW is reported to enhance VEGF release from bone marrow-derived mononuclear cells (BMDMNCs) and their differentiation into endothelial phenotype cells when applied to BMDMNCs [40]. Low-energy SW also activates proliferation and differentiation in cultured progenitors and precursors of cardiac cell lineages from the human heart [41, 42]. Furthermore, it has been reported that the beneficial effects of cell therapy were enhanced by pretreating BMDMNCs with SW before implantation into infarcted area in rabbits and that the pretreatment of ischemic leg with SW before cell therapy in a rat model of hindlimb ischemia enhanced the expression of stromal cell-derived factor 1 (SDF-1) in ischemic tissue and the resultant recruitment of endothelial progenitor cells [43, 44]. Thus, combination of cell therapy and SW therapy could be one of the potential approaches.

Recently, we have studied the effects of low-energy SW therapy on inflammatory responses in a rat model of AMI [45]. In this study, low-energy SW was applied to whole hearts at 1, 3, and 5 days after AMI. The SW therapy significantly suppressed the infiltration of inflammatory cells during acute phase in addition to enhanced angiogenesis in the border zone. These results suggest that the SW therapy suppressed post-MI LV remodeling through anti-inflammatory effects in addition to its angiogenic effects.

12.6   Conclusions

The beneficial effects of SW (angiogenesis, anti-inflammatory effects, neuroprotection, etc.) may be mediated by the enhancement of various intrinsic pathways. Although the precise intracellular mechanisms remain to be elucidated, low-energy extracorporeal SW therapy is promising as an effective, safe, and noninvasive approach to not only ischemic cardiovascular disorders but a wide range of disorders.

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