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ORIGINAL ARTICLE

Extracorporeal cardiac shock wave therapy for ischemic heart disease

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Abstract Prognosis of severe ischemic heart disease with no indication of percutaneous coronary intervention or coronary artery bypass grafting still remains poor. Extracorporeal shock wave therapy was introduced for medical therapy more than 20 years ago to break up kidney stones. We have demonstrated that extracorporeal cardiac shock wave therapy at a low level of ∼10% of energy density that used for urinary lithotripsy treatment, effectively induces coronary angiogenesis and improves myocardial ischemia in a porcine model of chronic myocardial ischemia in vivo. On the basis of the promising results in animal studies, we have recently developed a new, non-invasive angiogenic therapy with low-energy shock waves for ischemic heart disease. Our extracorporeal cardiac shock wave therapy improved symptoms and myocardial ischemia in patients with severe coronary artery disease. These beneficial effects of the shock wave therapy persisted for at least 12 months. Importantly, no procedural complications or adverse effects were noted. These results indicate that our extracorporeal cardiac shock wave therapy is an effective and non-invasive treatment for ischemic heart disease. To further confirm the usefulness and safety of our SW therapy, we are currently conducting the second clinical trial in a randomized and placebo-controlled manner.

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1 Introduction

Ischemic heart disease is the leading cause of death in developed countries and the number of patients is increasing worldwide [1]. Since the coronary arteries supply blood to the heart muscle, narrowing or closure of the arteries by atheromatous plaques limits blood flow to a part of heart muscle, causing an imbalance between oxygen supply and demand with a resultant development of myocardial ischemia. Myocardial ischemia can cause temporary chest pain (angina pectoris), permanent heart muscle damage (acute myocardial infarction), lethal arrhythmia, and sudden cardiac death. The current management of ischemic heart disease has three major therapeutic options, including medical treatment (drug therapy), percutaneous coronary intervention (PCI; balloon dilation of narrowed arteries), and coronary artery bypass grafting (CABG; heart surgery). However, prognosis of patients with severe coronary artery disease without indication of PCI or CABG still remains poor because medication is the only therapy to treat the disorder. Thus, it is crucial to develop an alternative therapy for severe ischemic heart disease. Currently, gene therapy and cell-based therapy for those patients are under development, however, most of these therapies are invasive in nature and their effectiveness and safety have not been established yet [2–4]. We have recently developed a new, non-invasive angiogenic therapy using low-energy shock waves (SW) [5–7]. In this article, we outline our recent works in animals and humans, and then discuss the

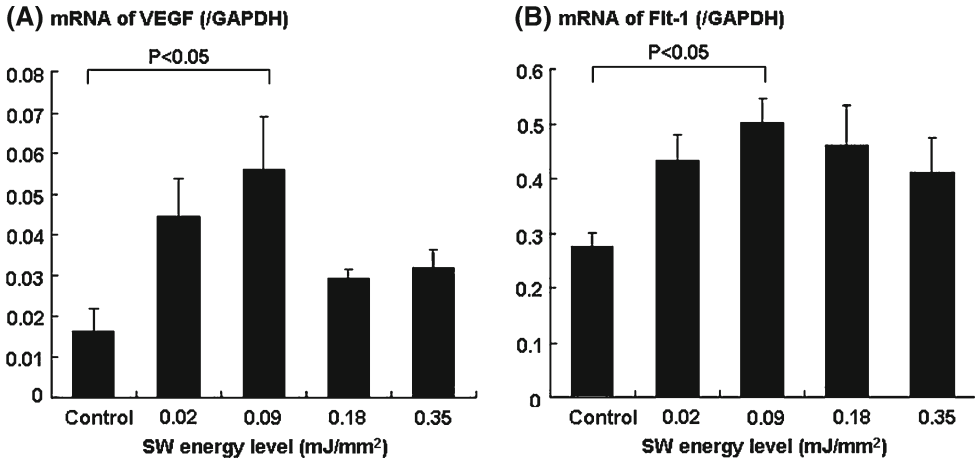

Fig. 1 SW treatment up-regulates mRNA expression of VEGF **a** and Flt-1 **b** in HUVECs in vitro with a maximum effect noted at 0.09 mJ/mm^2. Results are expressed as mean ± SEM ($n = 10$ each) (quoted from Ref. [5] with permission)

mechanisms for SW-induced angiogenesis and advantages of our cardiac SW therapy.

2 Extracorporeal cardiac SW therapy for angina pectoris

2.1 In vitro study

Extracorporeal SW therapy has been introduced for medical therapy more than 20 years ago to break up kidney stones, which has markedly improved the treatment of urolithiasis. Furthermore, the lithotripsy therapy with SW is indicated for gallstones, pancreatic and salivary stones, and is also used for the treatment of certain orthopedic conditions, such as bone fracture and calcifying tendonitis [8,9].

It was demonstrated that a low level of SW could up-regulate angiogenic factors in vitro [10] and induce localized stress on cell membranes that resembles shear stress [11]. We have recently reported that a low level of SW enhances the expression of vascular endothelial growth factor (VEGF) and its receptor, Flt-1, in cultured human endothelial cells (HUVEC) in vitro with a maximum effect noted at 0.09 mJ/mm^2, which level is approximately 10% of that used for urinary lithotripsy treatment (Fig. 1) [5].

2.2 Animal studies

In the clinical setting, the goal for the treatment of ischemic heart disease should include not only enhancement of angiogenesis but also recovery of ischemia-induced myocardial dysfunction. We performed in vivo animal experiments with pigs, in which myocardial ischemia was made by placing an ameroid constrictor at the proximal segment of the left circumflex coronary artery (LCX) that gradually induced a total occlusion of the artery with sustained myocardial dysfunction but without myocardial infarction in 4 weeks [5]. Thereafter, we performed extracorporeal SW therapy to the ischemic myocardial region ($n = 8$). On the basis of our in vitro experiment, we applied a low energy of SW (0.09 mJ/mm^2) to nine spots in the ischemic LCX region (200 shots/spot) with a guidance of an echocardiogram equipped within a specially designed SW generator (Storz Medical AG, Tägerwilen, Switzerland). We were able to focus SW on any part of the heart under the guidance of echocardiography. In order to treat the targeted ischemic myocardium without inducing ventricular arrhythmia, we applied SW at end-diastole during cardiac cycle with a R-wave-triggered system. We performed the SW treatment ($n = 8$) at 4 weeks after the implantation of an ameroid constrictor 3 times within 1 week, whereas animals in the control group ($n = 8$) received the same anesthesia procedures 3 times a week but without the SW treatment. We evaluated cardiac function at ameroid implantation (baseline) and at 4 and 8 weeks after the implantation.

Four weeks after the implantation of an ameroid constrictor, wall motion of the LCX (posterolateral) region in the left ventricle (LV) was equally reduced in both the control and the SW group before the SW therapy (Fig. 2a, c). However, 4 weeks after the SW therapy, left ventriculography showed marked improvement of LV wall motion only in the SW (Fig. 2b, d). The SW therapy normalized LV ejection fraction in the SW group but not in the control group (Fig. 2e). In this study, the SW treatment normalized global and regional myocardial functions as well as regional myocardial blood flow in the chronic ischemic region evaluated with colored microspheres. In addition, the SW treatment increased vascular density in the SW-treated region and up-regulated VEGF expression in the ischemic myocardium in vivo (Fig. 3). Importantly, no procedural complications or adverse effects were noted during or after the SW treatment. These data indicate that the SW treatment up-regulated the endogenous angiogenic system in pigs in vivo, suggesting its usefulness for the treatment of ischemic heart disease in humans.

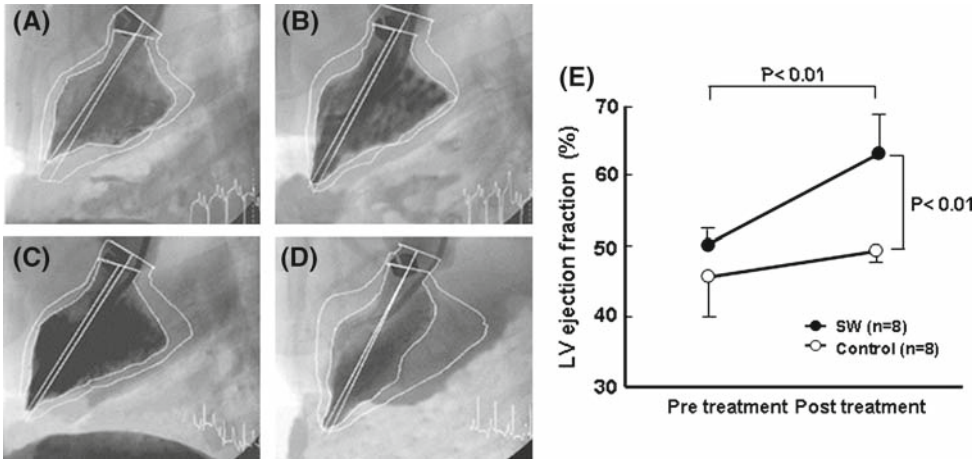

Fig. 2 Extracorporeal cardiac SW therapy improves ischemia-induced myocardial dysfunction in vivo as evaluated with left ventriculography. Four weeks after the implantation of an ameroid constrictor, LV wall motion of the LCX (posterolateral) region was reduced in both the control **a** and the SW group (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) (quoted from Ref. [5] with permission)

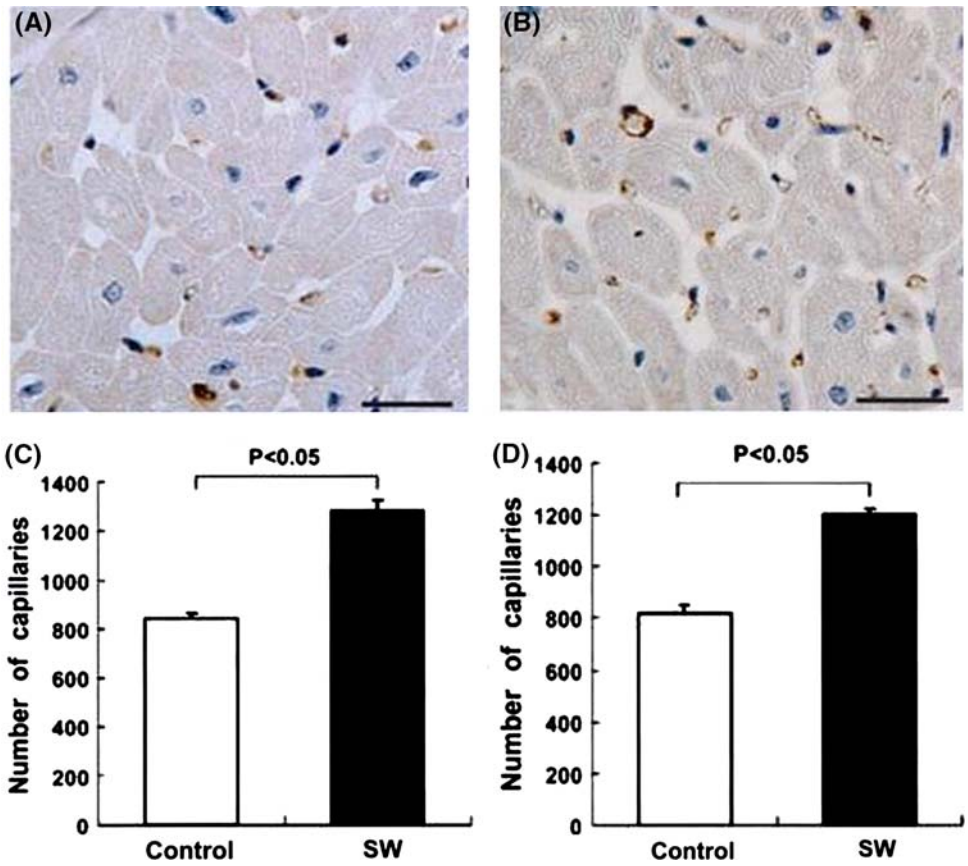

Fig. 3 Extracorporeal cardiac SW therapy increases the density of factor VIII-positive capillaries in the ischemic myocardium. Factor VIII staining of the LCX region from the control **a** and the SW group **b**. *Scale bar* represents 20 μm. Capillary density was significantly greater in the SW group (SW) than in the control group (Control) in both the endocardium **c** and the epicardium **d**. Results are expressed as mean ± SEM ($n = 6$ each) (quoted from Ref. [5] with permission)

2.3 Clinical studies

On the basis of the promising results in animal studies, we started the first clinical trial of cardiac SW therapy in humans in 2003. We treated nine patients with end-stage ischemic heart disease with no indication of PCI or CABG (55–82 years old, five men and four women) with our cardiac SW therapy (200 shots/spot at 0.09 mJ/mm^2 for 20–40 spots, 3 times a week/series) (Fig. 4) [6]. As shown in Fig. 4a, patients just lied down on the bed without anesthesia during

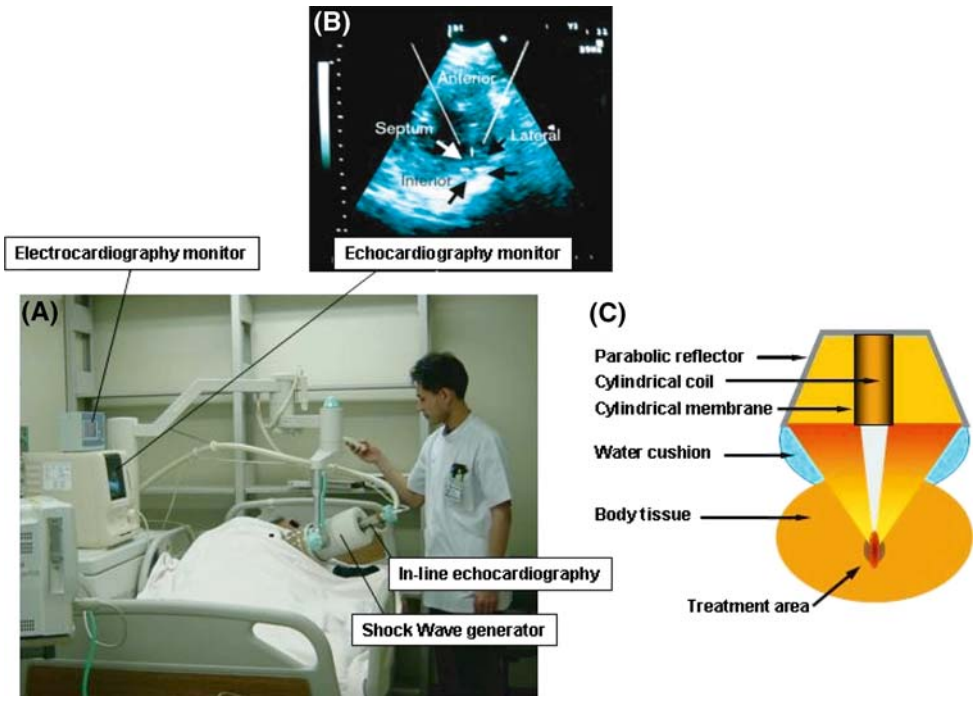

Fig. 4 Extracorporeal cardiac SW therapy in action in a patient with severe coronary artery disease. **a** The machine is equipped with a SW generator and in-line echocardiography. The SW generator is attached to the chest wall when used. **b** The cardiac ultrasound monitor. The SW pulse is easily focused on the ischemic myocardium under the guidance of echocardiography (*black* and *white arrows*). **c** The SW generator is equipped with parabolic reflector, cylindrical coil, and cylindrical membrane with water cushion

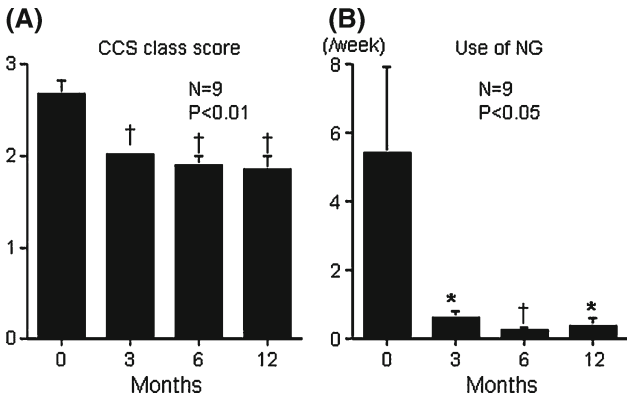

Fig. 5 Extracorporeal cardiac SW therapy significantly improved Canadian Cardiovascular Society (CCS) scores **a** and the use of nitroglycerin (NG) **b**. Results are expressed as mean ± SEM. $*P < 0.05$ and $\dagger P < 0.01$ vs. 0 month (statistically analyzed by post-hoc test after one-way ANOVA) (quoted from Ref. [6] with permission)

the treatment. The SW therapy improved symptoms and reduced nitroglycerin use (Fig. 5) as well as myocardial perfusion as assessed by dipyridamole stress thallium scintigraphy only in the ischemic area treated with the therapy (Fig. 6). These beneficial effects of the SW therapy persisted for at least 12 months (Figs. 5 and 7). No procedural complications or adverse effects were noted. These data indicate that our extracorporeal cardiac SW therapy is an effective and non-invasive treatment for end-stage ischemic heart disease. To further confirm the usefulness and safety of our SW therapy, we are currently conducting the second clinical trial in a randomized and placebo-controlled manner.

3 Extracorporeal cardiac SW therapy for acute myocardial infarction

Acute myocardial infarction (AMI) is associated with a loss of heart muscle. After AMI, the heart is gradually dilated and cardiac ability to pump blood to the rest of the body is impaired. This process is called "LV remodeling" [1]. The development of LV remodeling leads to sudden cardiac death, heart failure, and poor prognosis. If sufficient angiogenesis can be induced in the border zone of infarcted myocardium, the progression of LV remodeling could be suppressed with a resultant improvement of prognosis. Therefore, we examined whether our SW therapy is also effective to ameliorate LV remodeling after acute myocardial infarction in pigs.

Acute myocardial infarction was created by surgically excising the proximal segment of the LCX [7]. In the early treatment protocol, the SW therapy was started 3 days after AMI, whereas in the late treatment protocol, the SW therapy was started 4 weeks after AMI ($n = 5$ each). The remaining animals were treated in the same manner but without the SW treatment in each protocol ($n = 5$ each). In the early treatment protocol in which the treatment was started at 3 days after AMI, LV ejection fraction and LV end-diastolic volume were significantly improved in the SW group compared with the control group at 4 weeks after the treatment (Fig. 8). Furthermore, regional myocardial blood flow and number of capillaries in the border zone were significantly improved in the SW group compared with the control group. By contrast, in the late treatment group in which the SW treatment was started 4 weeks after AMI, no such beneficial

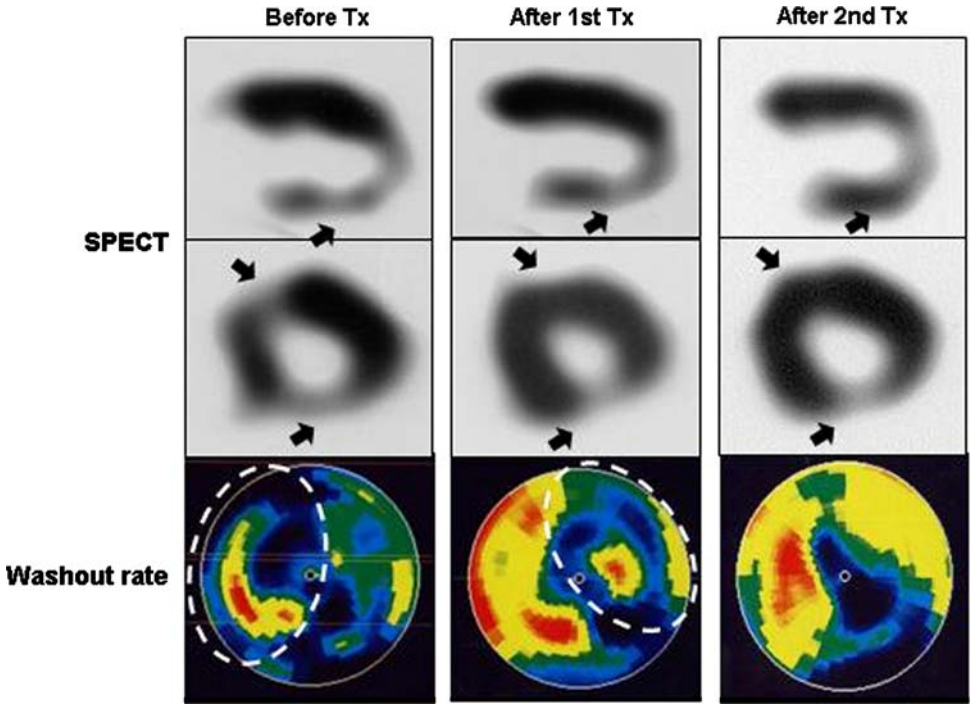

Fig. 6 Dipyridamole stress thallium-201 single photon emission computed tomography (SPECT) imaging and polar map demonstrated that the SW treatment ameliorated myocardial perfusion only where SW was applied; in the anteroseptal wall after the first treatment (Tx) and in the lateral wall after the second treatment (*arrows*). The areas where shock waves were shot were indicated with *dotted lines*. (quoted from Ref. [6] with permission)

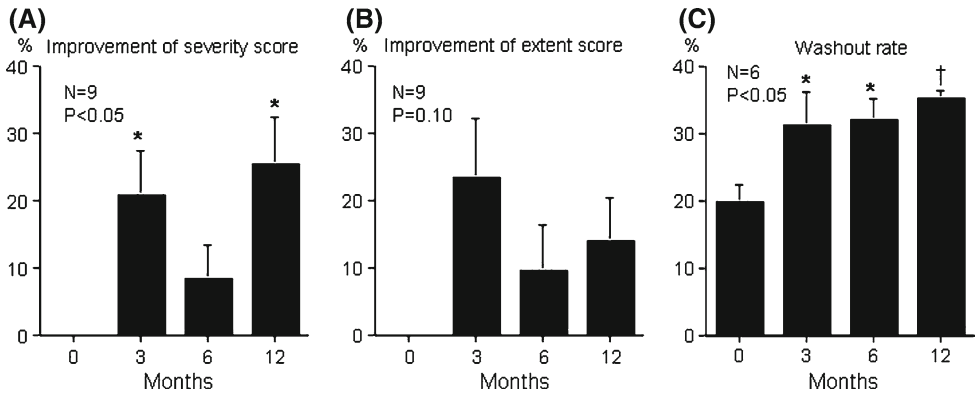

Fig. 7 The SW therapy significantly improved severity score **a**, tended to improve extent score **b**, and significantly improved local washout rate in patients with initial low washout rate (<30%) **c** in the dipyridamole stress thallium scintigraphy. Results are expressed as mean ± SEM. $*P < 0.05$ and $\dagger P < 0.01$ vs. 0 month (statistically analyzed by post-hoc test after one-way ANOVA) (quoted from Ref. [6] with permission)

effects of the SW therapy were noted. These results suggest that our extracorporeal cardiac SW therapy is an effective and non-invasive therapy to ameliorate LV remodeling after AMI when started in the early phase of the disorder. We are currently conducting the first clinical trial in patients with AMI who are successfully treated with PCI, in order to examine whether our SW therapy combined with PCI ameliorates LV remodeling and dysfunction after AMI in humans.

4 Mechanisms for SW-induced angiogenesis

When a SW hits tissue, cavitation (a micrometer-sized violent collapse of bubbles) is induced by the first compression by the positive pressure part and the expansion with the tensile part of a SW [12]. Because the physical forces generated by cavitation are highly localized, SW could induce localized stress on cell membranes, as altered shear stress affects endothelial cells [13]. Recent reports have demonstrated the biochemical effects of SW, including hyperpolarization and Ras activation [14], non-enzymatic nitric oxide synthesis [15], and induction of stress fibers and intercellular gaps [16].

Enhanced expression of multiple angiogenic factors, such as VEGF and stromal-derived factor 1 (SDF-1), is crucial for the recruitment and incorporation of endothelial progenitor cells (EPCs) [17–22]. VEGF is known to induce angiogenesis by activating mobilization and homing of EPCs from the bone marrow to ischemic tissue [17–20]. We have previously demonstrated that our SW therapy up-regulates the expression of both VEGF and its receptor Flt-1 in cultured human endothelial cells and increases capillary density and regional myocardial blood flow in a porcine model of myocardial

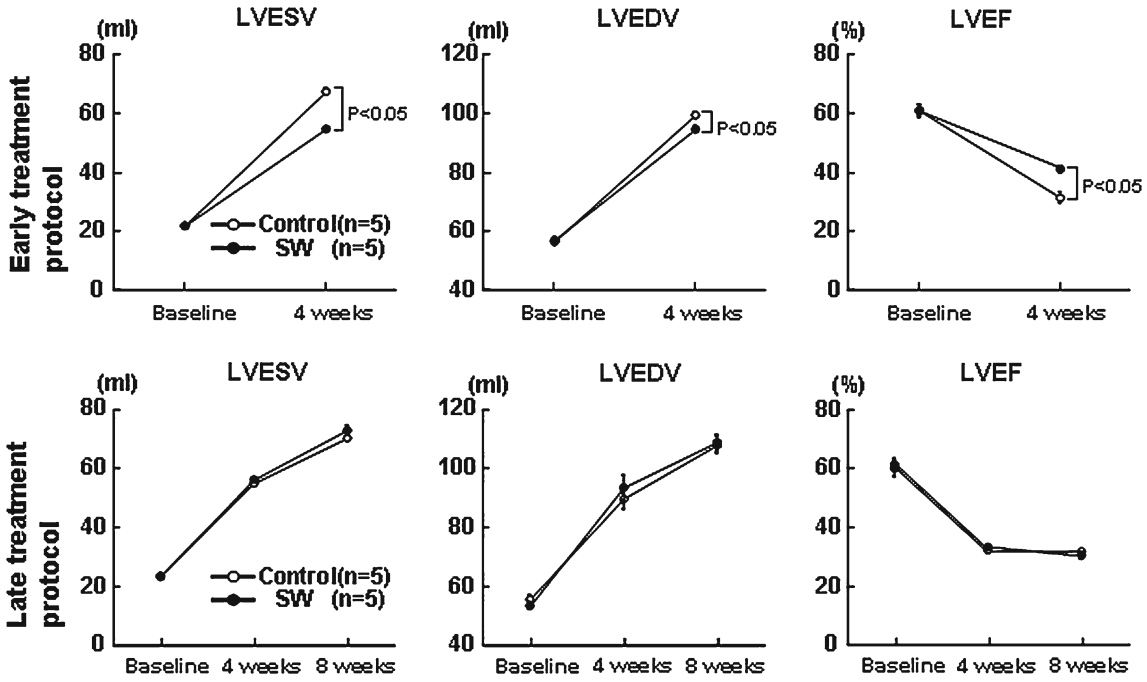

Fig. 8 Results of left ventriculography for the inhibitory effects of the cardiac SW therapy on the development of LV remodeling after AMI. The inhibitory effects of the SW therapy were noted in the early treatment protocol (*upper panel*) but not in the late treatment protocol (lower panel). *LVESV* left ventricular end-systolic volume, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction. Results are expressed as mean ± SEM ($n = 5$ each) (quoted from Ref. [7] with permission)

ischemia [5]. Recently, it was reported that SDF-1 is essential for the retention of pro-angiogenic stem cells in peripheral organs, although the up-regulation of VEGF is sufficient to mobilize stem or progenitor cells from the bone marrow to the systemic circulation [21,22]. Therefore, it is possible that our SW therapy enhances the incorporation of circulating EPCs by up-regulating the expression of SDF-1 in ischemic myocardium. This notion has been supported by the recent study by Aicher et al. [23] that combination of SW therapy enhances the efficacy of the cell-based angiogenic therapy. Further studies are needed to elucidate the precise molecular mechanisms involved in the beneficial effects of SW in the treatment of ischemic heart disease.

5 Advantages of extracorporeal cardiac SW therapy

Recent attempts to enhance angiogenesis in ischemic organs include gene therapy and bone marrow cell transplantation therapy. However, the need of invasive procedure to deliver those cells to the ischemic myocardium severely limits the usefulness of those therapies in clinical situations. A major advantage of our extracorporeal cardiac SW therapy over those strategies is shown by the fact that it is quite non-invasive and safe without any adverse effects. If necessary, we are able to repeatedly treat patients (even outpatients) with our SW therapy because no surgery, anesthesia, or even catheter intervention is required for the treatment. This is an important factor in determining the clinical usefulness of angiogenic therapies in elderly patients with severe coronary artery disease. Indeed, the SW treatment itself already has been clinically established as an effective and safe treatment for lithotripsy and chronic plantar fasciitis [24,25]. Thus, our extracorporeal cardiac SW therapy appears to be an applicable and non-invasive treatment for ischemic heart disease in humans.

6 Conclusions

We have successfully developed an extracorporeal cardiac SW therapy with a low energy SW, which may be an effective, safe, and non-invasive therapy for the treatment of severe ischemic heart disease in humans. Also, the cardiac SW therapy had no procedural complications or adverse effects.

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