



Double-Blind and Placebo-Controlled Study of the Effectiveness and Safety of Extracorporeal Cardiac Shock Wave Therapy for Severe Angina Pectoris

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Background: Low-energy shock wave (SW) therapy has improved myocardial ischemia in both a porcine model and in patients with severe angina pectoris.

Methods and Results: To further confirm the effectiveness and safety of SW therapy, 8 patients with severe angina pectoris were treated with SW therapy in a double-blind, placebo-controlled and cross-over manner. SW therapy, but not placebo, significantly improved chest pain symptoms and cardiac function without any complications or adverse effects.

Conclusions: Extracorporeal cardiac SW therapy is an effective, safe and non-invasive therapeutic option for severe angina pectoris. (*Circ J* 2010; **74**: 589–591)

Key Words: Angina pectoris; Angiogenesis; Myocardial ischemia; Shock wave

The number of patients with severe angina pectoris without indications for coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is rapidly increasing worldwide and their prognosis still remains poor.^{1,2} Thus, it is crucial to develop new therapeutic strategies for these patients. We have previously demonstrated that extracorporeal cardiac shock wave (SW) therapy with low-energy SW ($\approx 10\%$ of the energy density used for urolithiasis) ameliorates myocardial ischemia and dysfunction in a porcine model of chronic myocardial ischemia in vivo.^{3,4} We subsequently demonstrated in an open trial that our SW therapy effectively improved chest pain symptoms and exercise tolerance without any adverse effects in 9 patients with severe angina pectoris.^{3,5} In the present study, to further confirm the effectiveness and safety of our SW therapy, we performed a double-blind placebo-controlled trial in patients with severe angina pectoris.

Methods

We enrolled 8 consecutive patients with severe angina pectoris who already had undergone CABG or PCI, but who no longer had further indications for these therapies even though they still suffered from stable effort angina under

intensive medication (M/F, 5/3; age, 70 ± 3 years) (Table).

The patients were treated with one series of placebo and the SW therapy in a double-blind and cross-over manner with an interval of 3 months. One series of therapy comprised 3 sessions per week. Throughout the study, the patient and the doctor in charge were not informed of the type of therapy. We performed the SW therapy (200 shoots/spot at 0.09 mJ/mm^2 for 40–60 spots per session; Modulith SLC, Storz Medical, Kreuzlingen, Switzerland) as described previously.^{3,5} As placebo, the patients underwent the procedure of SW therapy but without irradiation. The patients were followed-up for 3 months after completion of the therapy. We evaluated symptoms using the Canadian Cardiovascular Society (CCS) class score, the patient's requirement for nitroglycerin,⁵ exercise tolerance in a 6-min walk, and a cardiopulmonary exercise test, and cardiac function assessed by MRI (Achieva 1.5 T, Philips, Eindhoven, Netherlands). The left ventricular ejection fraction (LVEF) was measured using contiguous short-axis slices obtained by cine MRI; end-diastolic and end-systolic endocardial traces were used to determine end-diastolic and end-systolic left ventricular (LV) volumes, respectively. We also evaluated the number of circulating progenitor cells in peripheral blood by FACS analysis 2 days before the 1st session and 1 h after the 3rd session in 7 of the 8 patients

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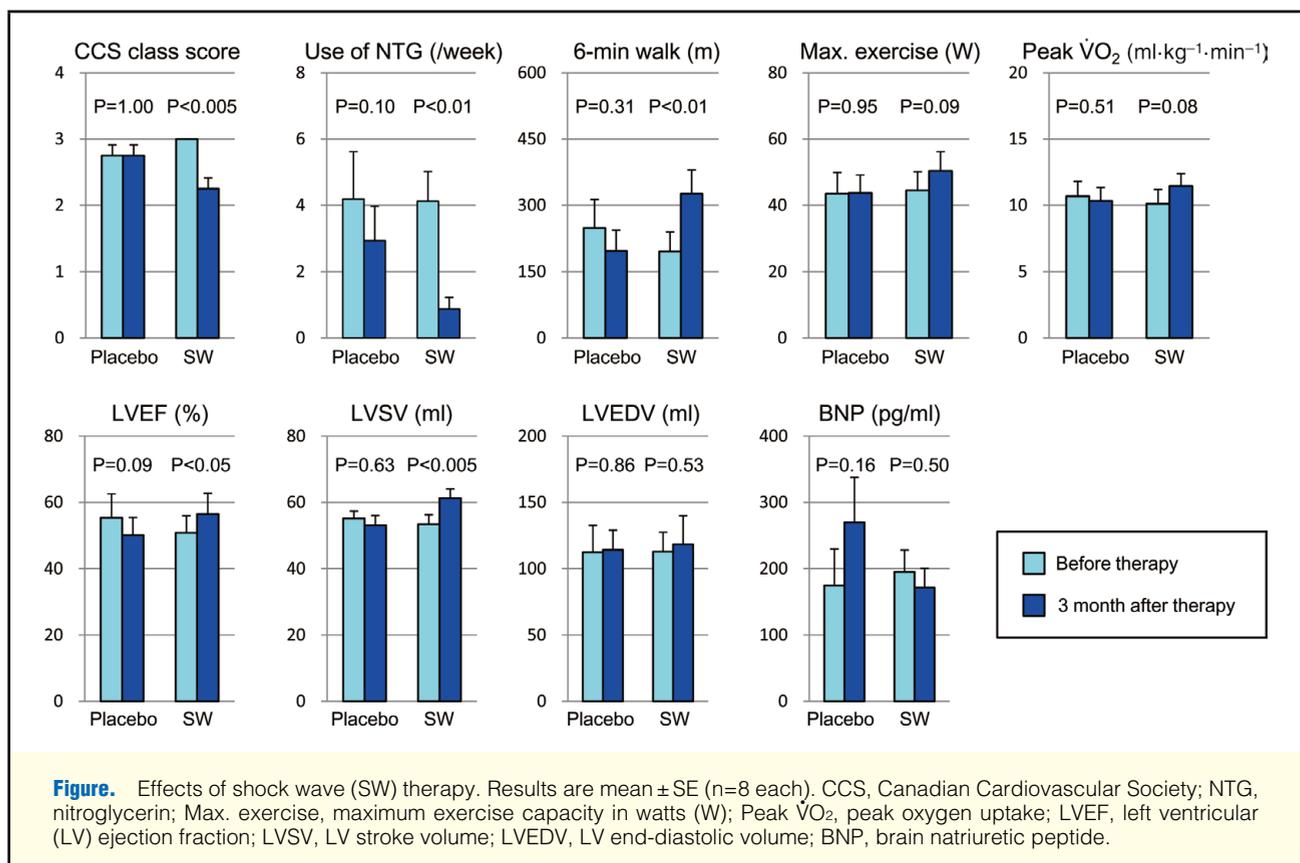
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Table. Baseline Characteristics of the 8 Patients With Severe Angina Pectoris									
Patient no.	Age (years)	Gender	CAD	Previous treatment	OMI	ASO	HT	DM	HL
1	69	M	3VD	CABG, PCI	+	+	+	+	+
2	61	M	3VD	CABG, PCI	+	-	+	+	+
3	70	M	3VD	CABG	+	+	+	-	+
4	78	F	3VD	CABG, PCI	+	-	+	-	+
5	80	M	3VD	CABG, PCI	+	-	+	+	+
6	60	F	3VD	CABG, PCI	+	-	+	+	+
7	72	F	3VD	CABG, PCI	+	-	-	-	+
8	70	M	3VD	CABG, PCI	+	+	+	+	+

CAD, coronary artery disease; OMI, old myocardial infarction; ASO, arteriosclerosis obliterans; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia; VD, vessel disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.



(technical problem in the remaining one patient).

The present study was approved by the Ethical Committees of Tohoku University in 2005, and informed consent was given by each patient.

Results are expressed as mean \pm SEM. Comparisons during the time course after SW therapy were made by repeated measure ANOVA followed by Bonferroni/Dunn post hoc test. All statistical analyses were performed using StatView (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered to be statistically significant.

Results

The SW therapy, but not placebo, significantly improved symptoms (CCS class score) and nitroglycerin use (Figure).

The SW therapy also significantly improved the 6-min walking distance and tended to improve both maximum exercise capacity and peak oxygen uptake (peak $\dot{V}O_2$). LVEF and LV stroke volume evaluated by MRI were significantly improved only with the SW therapy, although LV end-diastolic volume and plasma brain natriuretic peptide level remained unchanged. The number of CD34⁺/KDR⁺ and CD34⁺/KDR⁺/c-kit⁺ cells in peripheral blood also remained unchanged with both therapies (data not shown). No procedural complications or adverse effects were noted during or after either therapy as in the previous studies.³⁻⁷

Discussion

We have previously demonstrated that low-energy SW

therapy enhanced angiogenesis and improved myocardial ischemia in a pig model of chronic myocardial ischemia,^{3,4} and that SW therapy improved the symptoms and myocardial perfusion in patients with severe angina pectoris in an open trial.^{3,5} The present double-blind and placebo-controlled study further demonstrates that our extracorporeal cardiac SW therapy is an effective therapeutic option for severe angina pectoris, providing convincing evidence for its effectiveness and safety.

During the past 2 decades, regenerative therapies using genes, cytokines, and progenitor cells have been under investigation for ischemic cardiovascular diseases.⁸ However, these therapies have not been consistently effective in humans, despite promising results in early preclinical studies.^{9–12} A potential explanation for these inconsistent results is the complex crosstalk among multiple pathways, in which enhancement of only 1 factor among numerous angiogenic factors may not be enough to achieve clinical benefit. Furthermore, animal studies of cell therapy have revealed that the number of newly generated vascular cells is too low to induce any functional improvement, suggesting that the paracrine action of transplanted cells stimulates intrinsic angiogenic capacity.¹³ In contrast, low-energy SW upregulates multiple angiogenic pathways (eg, VEGF, flt-1, SDF-1, and nitric oxide synthase).^{4,7,14}

There are several limitations to the present study. First, the number of patients is small. Although more than 150 patients with severe angina pectoris were reviewed as potential candidates for this study, most of them were excluded due to insufficient medication, potential indications of CABG or PCI, and co-existence of malignant tumor. However, we were able to reconfirm the beneficial effects of SW therapy in the present double-blind and placebo-control study, as we had observed in a previous open study.⁵ A future large-scale trial would validate the present results. Second, maximum exercise capacity and $\dot{V}O_2$ were not significantly improved while the symptoms and 6-min walking distance were significantly improved by the SW therapy. In 6 of the 8 patients, exercise was stopped because of leg pain or fatigue before reaching the anaerobic threshold. Thus, exercise tolerance might have been underestimated because of arteriosclerosis obliterans and/or physical deconditioning. Another parameter, such as arteriovenous difference in lactate concentration under overdrive pacing, might have been a better index of ischemia. Third, the number of circulating progenitor cells in peripheral blood was not increased in the present study. Thus, it remains to be examined whether our SW therapy promotes recruitment of bone marrow-derived cells by the ischemic myocardium of humans.^{14,15} Fourth, the detailed molecular mechanisms of the beneficial effects of SW in humans remain to be clarified in future studies.^{3–7}

In conclusion, the present double-blind, placebo-controlled study further confirmed the effectiveness and safety of our extracorporeal cardiac SW therapy for the treatment of severe

angina pectoris, although large-scale multi-center study is needed.

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