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Extracorporeal cardiac shock wave therapy ameliorates myocardial ischemia in patients with severe coronary artery disease

[Therapy and Prevention]

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Abstract

Objective: Prognosis of severe coronary artery disease with no indication of percutaneous coronary intervention or coronary artery bypass grafting remains poor. We have recently demonstrated that shock wave therapy effectively induces neovascularization and improves myocardial ischemia in a porcine model *in vivo*.

Methods: With permission from the Ethical Committee of our Institute, we treated nine patients with end-stage coronary artery disease with no indication of percutaneous coronary intervention or coronary artery bypass grafting (55–82 years old, five men and four women) with our cardiac shock wave therapy (200 shots/spot at 0.09 mJ/mm^2 for 20–40 spots, 3 times a week/series). We followed-up the patients at 1, 3, 6, and 12 months after the therapy to examine the amelioration of myocardial ischemia. When needed, shock wave therapy was performed up to three series at 0, and 1, 3 or 6 months.

Results: The cardiac shock wave therapy improved symptoms (Canadian Cardiovascular Society functional class score, from 2.7±0.2 to 1.8±0.2, $P<0.01$) and reduced nitroglycerin use (from 5.4±2.5 to 0.3±0.3/week, $P<0.05$). The treatment also improved myocardial perfusion as assessed by dipyridamole stress thallium scintigraphy (severity score, 25.2±7.2% improvement, $P<0.05$; extent score, 23.3±9.0% improvement, $P=0.10$; washout rate, 20±3 to 34±3, $P<0.05$). Myocardial perfusion was improved only in the ischemic area treated with the therapy. These beneficial effects persisted for 12 months. No procedural complications or adverse effects were noted.

Conclusion: These results indicate that our extracorporeal cardiac shock wave therapy is an effective and non-invasive treatment for end-stage coronary artery disease, although further

careful evaluation is needed.

Introduction

The current management of coronary artery disease (CAD) has three major therapeutic options including medical treatment, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) [1]. Prognosis of severe CAD without an indication of PCI or CABG, however, still remains poor because medication is the only therapy to treat the disorder. Angiogenesis by gene or cell therapy may be effective but invasive in nature and is still at a preclinical stage [2–5].

Shock wave (SW) therapy has been widely used in the lithotripsy or the treatment of certain orthopedic conditions including bone fracture or calcifying tendonitis [6,7]. Recently, it has been demonstrated that a low level of SW could upregulate angiogenic factors in cultured endothelial cells *in vitro* [8]. On the basis of this report, we first confirmed 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 *in vitro* [9]. The maximum angiogenic effect of SW was noted at 0.09 mJ/mm^2, which is approximately 10% of that used for lithotripsy treatment [9]. We then performed animal experiments, in which we were able to demonstrate that extracorporeal cardiac SW therapy effectively induces angiogenesis and markedly ameliorates myocardial ischemia and dysfunction in a porcine model *in vivo* without any adverse effects [9]. In the present study, we thus tested our notion that cardiac SW therapy improves myocardial ischemia in patients with severe CAD.

Methods

The Ethical Committees of Kyushu University Hospital approved the study protocol on 17 January 2003, and all patients provided informed consent.

Patient selection

First, we evaluated the indication of coronary revascularization by symptoms, exercise tolerance, dipyridamole stress thallium scintigraphy, and coronary angiography. Cardiac SW therapy was indicated when patients with severe CAD suffered from stable effort angina with evidence of myocardial ischemia even after adequate medications and when PCI or CABG was not indicated because of the diffuse distal coronary artery narrowing. Exclusion criteria were absence of the inclusion criteria, Q-wave or non-Q-wave myocardial infarction within 3 months, unstable angina, cardiac transplantation, breast plastic surgery with silicon, pregnancy, cardiac shock or uncontrolled heart failure, left ventricular thrombus, poorly controlled diabetic retinopathy, malignant tumor (including operation for the tumor within 5 years), PCI and/or CABG within 3 months, and participation in other clinical trial. The final decision to perform the cardiac SW therapy was based on the agreement of cardiologists and cardiac surgeons in our hospital. In the last 2 years, nine patients with severe CAD were finally enrolled for the cardiac SW therapy and were followed-up for 1 year. Five of them had previously undergone PCI and/or CABG, when

indicated. The characteristics of the patients are shown in Table 1. Hypercholesterolemia was defined as total cholesterol >=220 mg/dl or the use of lipid-lowering drug(s). Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or the use of antihypertensive drug(s). Diabetes was defined as fasting blood sugar >=140 mg/dl, blood sugar during a 75-g oral glucose tolerance test >=200 mg/dl, or the use of antidiabetic drug(s). All patients continued their oral medications including nitrates, [beta]-blockers, and calcium channel blockers (Table 1).

Patient	Sex	Age (years)	CAD	Previous treatment	DM	HT	HL	Current smoking	ASO	HD	OMI	Medications
1	M	82	3 VD	CABG	−	+	−	−	+	−	+	AP, ARB, BB, CCB, N, NCD
2	M	66	3 VD	None	+	+	−	−	−	−	−	ASP, BB, CCB, S
3	F	64	3 VD	CABG, PCI	+	+	+	−	−	−	+	ASP, BB, N, CCB, S
4	F	56	3 VD	CABG, PCI	+	−	+	−	−	+	+	ASP, BB, CCB, NCD, S
5	M	70	3 VD	CABG	+	−	−	−	−	−	+	ACEI, ASP, BB, N, CCB, NCD
6	M	76	1 VD	None	−	+	−	−	+	−	+	ASP, BB, N, CCB, NCD
7	M	62	3 VD	None	−	−	+	−	−	+	+	ACEI, ASP, BB, N
8	F	70	3 VD	PCI	+	+	−	−	+	−	+	ACEI, ASP, BB, CCB
9	F	55	3 VD	None	+	−	+	−	−	−	−	ACEI, AP, N, CCB, NCD, S

M, male; F, female; CAD, coronary artery disease; VD, vessel disease; SW, shock wave; DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; ASO, arteriosclerosis obliterans; HD, hemodialysis; OMI, old myocardial infarction; ACEI, angiotensin-converting enzyme inhibitors; AP, anti-platelet; ARB, angiotensin receptor blockers; ASP, aspirin; BB, β-blockers; CCB, calcium channel blockers; N, nitrates; NCD, nicorandil; S. statins; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

Table 1 Characteristics of the patientsM, male; F, female; CAD, coronary artery disease; VD, vessel disease; SW, shock wave; DM, diabetes mellitus; HT, hypertension; HL, hyperlipidemia; ASO, arteriosclerosis obliterans; HD, hemodialysis; OMI, old myocardial infarction; ACEI, angiotensin-converting enzyme inhibitors; AP, anti-platelet; ARB, angiotensin receptor blockers; ASP, aspirin; BB, [beta]-blockers; CCB, calcium channel blockers; N, nitrates; NCD, nicorandil; S. statins; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

Treatment protocol

We treated the nine patients with our SW therapy (3 times a week/series, 200 shoots/spot at 0.09 mJ/mm^2 for 20–40 spots each time, Modulith SLC, with electromagnetic SW source; Storz Medical, Kreuzlingen, Switzerland), as we did in the experimental study (Fig. 1) [9]. Continuous electrocardiography monitoring was performed during and for 24 h after the SW therapy each time. Blood chemistry (including myocardial creatinine phosphokinase) and hematological analyses were performed the day after the therapy each time. On the basis of the recommendation by the Ethical Committee, from an ethical point of view, this study had no placebo-controlled group. In addition, the placebo procedure was considered to be difficult to perform because patients were able to feel, more or less, the compression (but not pain) on the chest with the SW therapy.

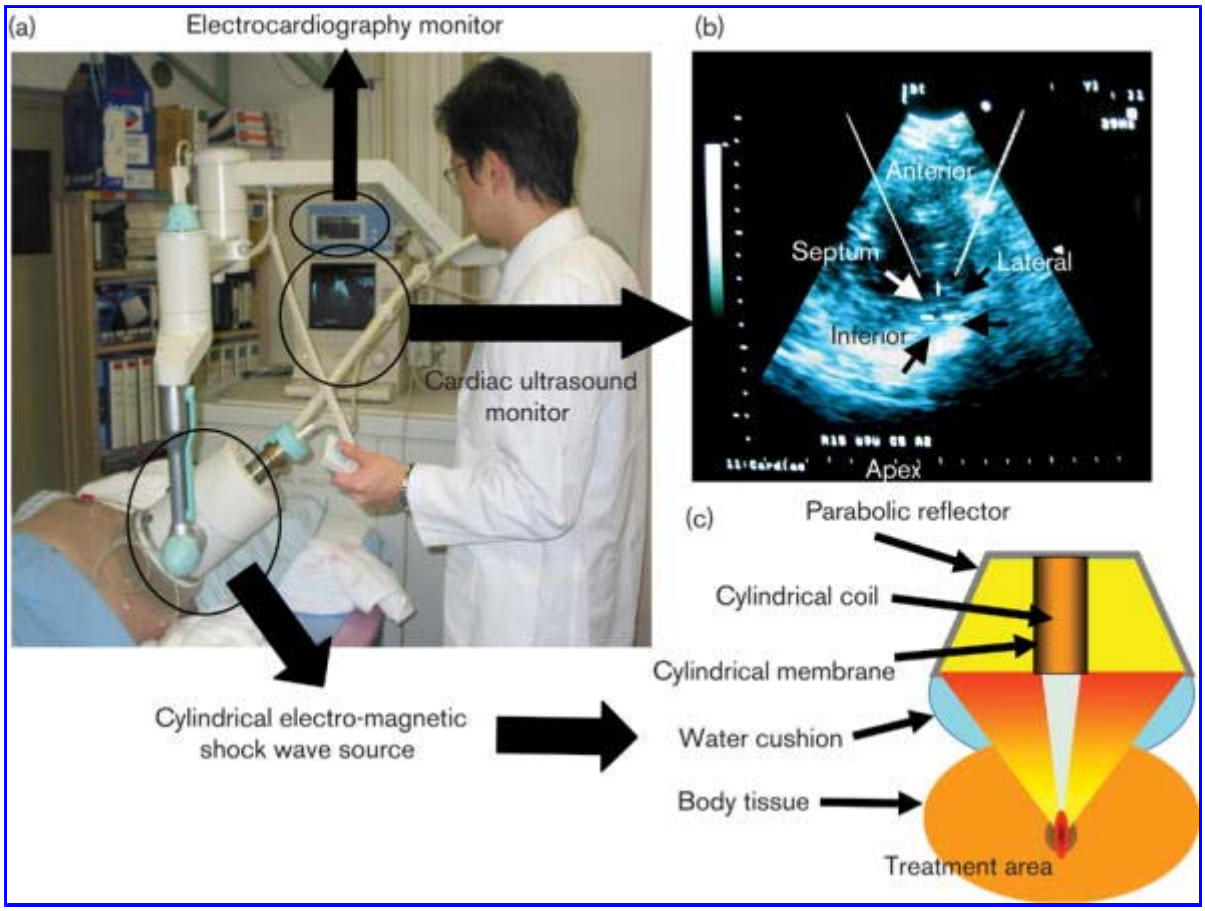

Fig. 1 Extracorporeal cardiac shock wave (SW) therapy in action in a patient. (a) The machine is equipped with a SW generator and in-line echocardiography. The SW generator is attached to the chest wall when used. (b) The cardiac ultrasound monitor. The SW pulse is easily focused on the ischemic myocardium 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.

We were able to follow-up all patients at 1, 3, 6, and 12 months after the SW therapy to evaluate the time course of amelioration of myocardial ischemia, including symptoms, exercise tolerance, dipyridamole stress thallium scintigraphy, and, when applicable, coronary angiography. The patients continued their oral medications throughout the study period (Table 1). When we considered that additional improvement could be expected with an additional SW therapy on the basis of the results at 1 and 3 months, the SW therapy was repeated up to three series at 0, and 1, 3, or 6 months, depending on the results of our evaluation (Table 2).

		SW treatment				CCS class	
Patient	Target area	0 month	1 month	3 months	6 months	0 month	12 months
1	Inf, Lat, Pos	+	−	−	−	3	2
2	Ant, Sep, Inf, Lat, Pos	+	+	+	−	3	2
3	Ant, Sep, Lat	+	+	−	+	3	2
4	Ant, Lat	+	−	+	−	2	2
5	Ant, Lat, Inf, Pos	+	+	+	−	2	2
6	Inf, Pos	+	+	−	−	3	1
7	Inf, Lat	+	+	+	−	3	2
8	Ant	+	+	−	−	3	2
9	Inf, Lat, Pos	+	+	+	−	2	2

SW, shock wave; CCS, Canadian Cardiovascular Society; Inf, inferior; Lat, lateral; Pos, posterior; Ant, anterior; Sep, septal. The '+' and '−' refer to shock wave therapy performed and not performed, respectively.

Table 2 Clinical features and outcome of the shock wave therapySW, shock wave; CCS, Canadian Cardiovascular Society; Inf, inferior; Lat, lateral; Pos, posterior; Ant, anterior; Sep, septal. The '+' and '-' refer to shock wave therapy performed and not performed, respectively.

We evaluated the time course of symptoms with Canadian Cardiovascular Society (CCS) class scores (1, ordinary physical activity; 2, slight limitation of ordinary activity; 3, marked limitation of ordinary activity; 4, inability to carry on any physical activity without discomfort) and the use of nitroglycerin per week before and after the SW therapy.

Exercise test

Before and after the cardiac SW therapy, patients underwent a symptom-limited exercise test using a 6-min walk and exercise treadmill test using modified Bruce or Unit Mets protocol. All tests were performed with 12-lead electrocardiography monitoring by well trained cardiologists. Arterial blood pressure was measured with a mercury sphygmomanometer every minute until recovery.

Dipyridamole stress thallium scintigraphy

Dipyridamole (0.6 mg/kg body weight) was intravenously infused over a 4-min period, followed by a bolus of 3 mCi thallium-201. Continuous electrocardiography monitoring and blood pressure measurement were carried out throughout the test. Single photon emission computed tomography imaging was obtained with the same camera (Toshiba, Tokyo, Japan) in the present study. Redistribution images were obtained 4 h after dipyridamole infusion.

The results of the stress thallium scintigraphy were evaluated with a 48-segment model of the left ventricle in a blind manner. The severity of myocardial ischemia was evaluated as the ratio of percentage thallium uptake in the stress image of the most severe ischemic area in comparison with the normal wall [10]. The extent of myocardial ischemia was determined by the number of ischemic segments that indicate less than 80% uptake in the anterior and lateral walls and less than 70% uptake in the inferior, posterior, and septal walls [10]. We determined the assessment areas just after the first SW treatment and evaluated these two indices (percentage improvement of severity score and extent score) in the local segments treated with the SW therapy in all patients. We also evaluated the change in absolute value of washout rate in six patients who showed a washout rate of less than 30% before the SW therapy in a blinded manner.

Coronary angiography

Coronary angiograms [11] were obtained in multiple projections and evaluated by more than five experienced cardiologists in a blind manner. The degree of coronary artery stenosis was visually estimated as a percentage of the angiographically normal segment preceding the stenosis. We performed diagnostic coronary angiography in all patients before the SW therapy; however, we did not perform follow-up coronary angiography in four out of the nine patients because of renal dysfunction.

Statistical analysis

Continuous variables were expressed as mean± SEM. Comparisons during the time course after the SW therapy were made by one-way ANOVA followed by a post-hoc test. All statistical analyses were performed using Stat View (SAS Institute, Cary, North Carolina, USA), and *P* values of less than 0.05 were considered to be statistically significant.

Results

Patient selection

All nine patients had at least more than 12 months of history of stable effort angina. They had ischemic myocardium as documented by dipyridamole stress thallium scintigraphy but were diagnosed by coronary angiography to have no indication of PCI or CABG (Table 1). Among them, eight had a three-vessel disease and the remaining one patient had a one-vessel disease, and seven of them had old myocardial infarction (Table 1). Two patients had previously undergone CABG alone, one PCI alone, and two both CABG and PCI. All of them had more than two risk factors of atherosclerosis (Table 1).

Cardiac shock wave therapy

We performed our cardiac SW therapy to the ischemic area that was confirmed by dipyridamole stress thallium scintigraphy (Fig. 1, Table 2). Depending on the time course of the improvement of myocardial ischemia, we performed up to three series of the therapy at 0, and 1, 3 or 6, months for seven patients, two series at 0 and 1 month for one patient, and only one series for one patient (Table 2). No procedural complications or adverse effects were noted in any patient.

Effects of the cardiac shock wave therapy

The cardiac SW therapy significantly improved symptoms, as evaluated by the CCS class score (Fig. 2a, Table 2) and the use of nitroglycerin (Fig. 2b), and tended to do so for a 6-min walk and treadmill test (Fig. 3a, b). Importantly, the SW therapy improved myocardial perfusion as evaluated by dipyridamole stress thallium scintigraphy only in the ischemic myocardium where SW was applied (Fig. 4). Indeed, when we treated the anteroseptal area with the SW therapy, myocardial perfusion was improved only in the treated area, and when we subsequently treated the lateral area, myocardial perfusion was improved only in the treated area (Fig. 4). The severity score, extent score, and washout rate obtained from the scintigraphy showed that myocardial ischemia was improved in the treated area, while it tended to be worsened in the untreated area (Fig. 5). The SW therapy significantly improved severity score (Fig. 6a) and tended to do so for the extent

score (Fig. 6b). Especially, in the six patients with an initial low washout rate (<30%), the SW therapy also significantly ameliorated the washout rate in the ischemic myocardium (Fig. 6c). Importantly, these anti-ischemic effects of the SW therapy were noted as early as 3 months after the therapy and persisted for 12 months (Figs 2 and 6). By contrast, coronary angiography showed no significant increase in the number of visible coronary arteries.

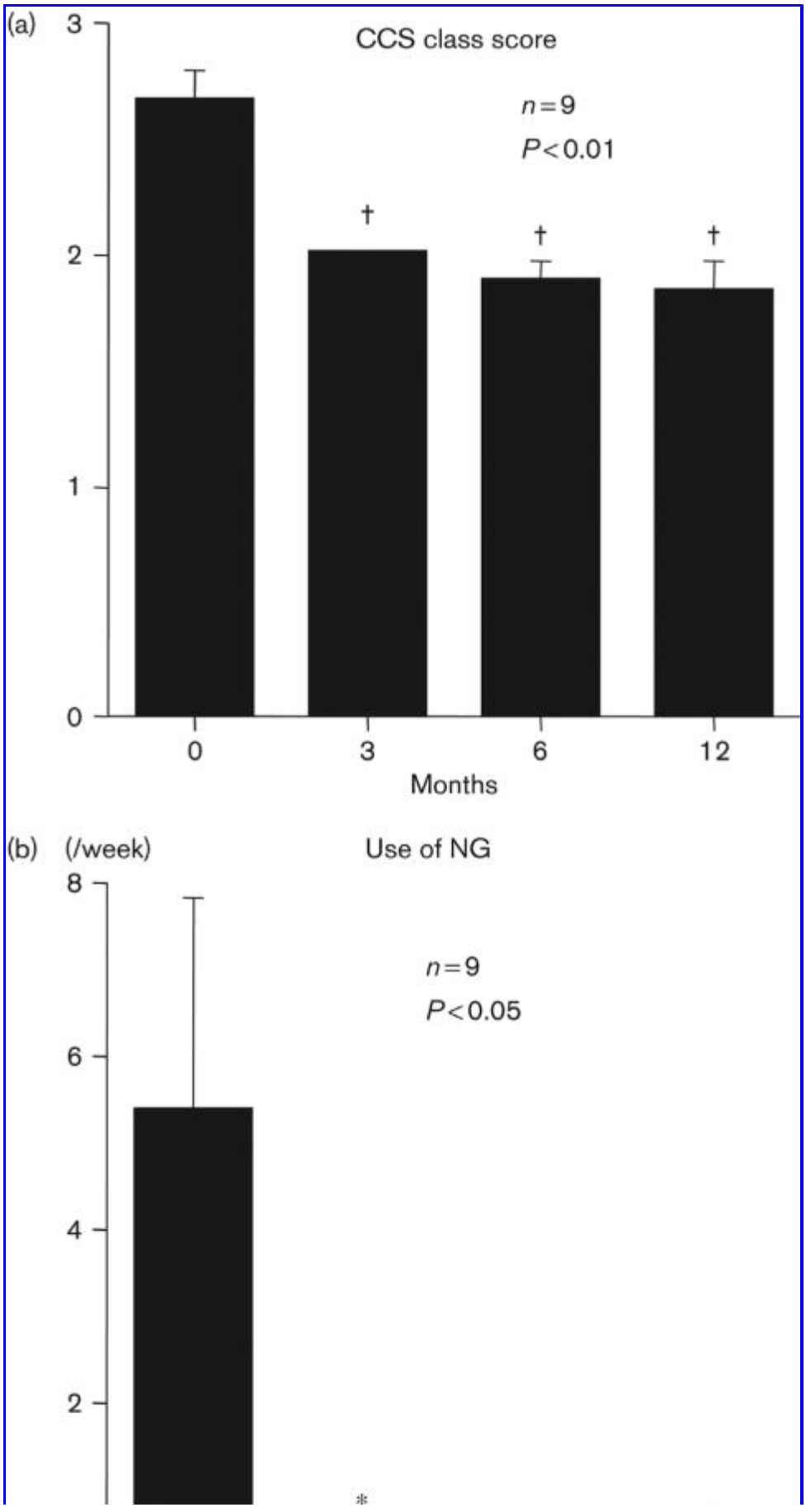
(a)
CCS class score
n=9
P<0.01
†
†
†
3
2
1
0
0
3
6
12
Months
(b)
(/week)
Use of NG
n=9
P<0.05
8
6
4
2
*

Fig. 2 Extracorporeal cardiac shock wave 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 † $P< 0.01$ vs. 0 month (statistically analyzed by post-hoc test after one-way ANOVA).

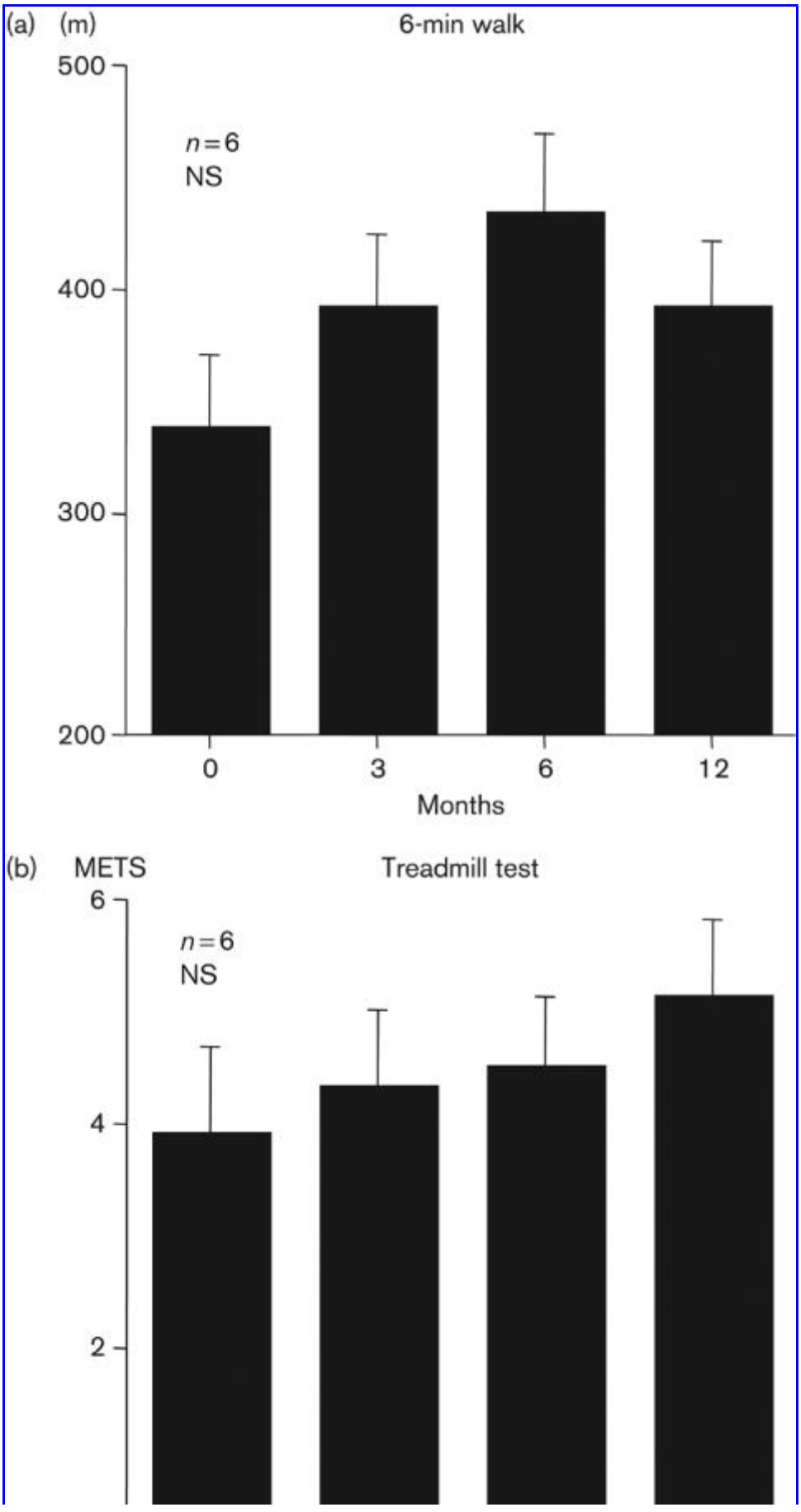
(a) (m)
6-min walk
500
400
300
200
n=6
NS
0
3
6
12
Months
(b) METS
Treadmill test
6
4
2
n=6
NS

Fig. 3 Extracorporeal cardiac shock wave therapy tended to improve exercise tolerance; 6-min walk (a) and treadmill test (b). Results are expressed as mean± SEM.

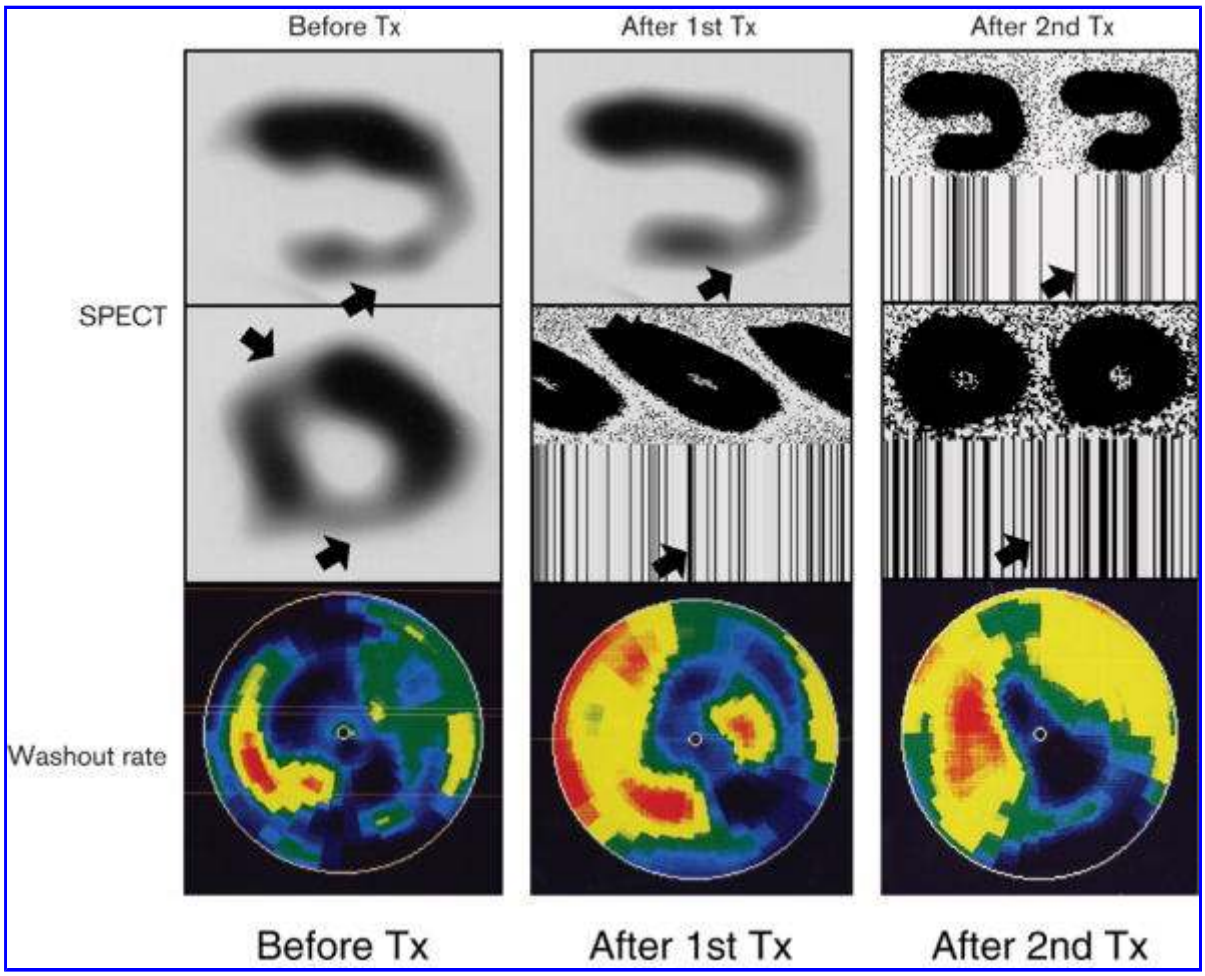

Fig. 4 Dipyridamole stress thallium-201 single photon emission computed tomography (SPECT) imaging and polar map demonstrated that the shock wave (SW) treatment ameliorated myocardial perfusion only where SW was applied; in the anteroseptal wall after the first treatment (Tx) and in the lateral wall after the second treatment (arrows).

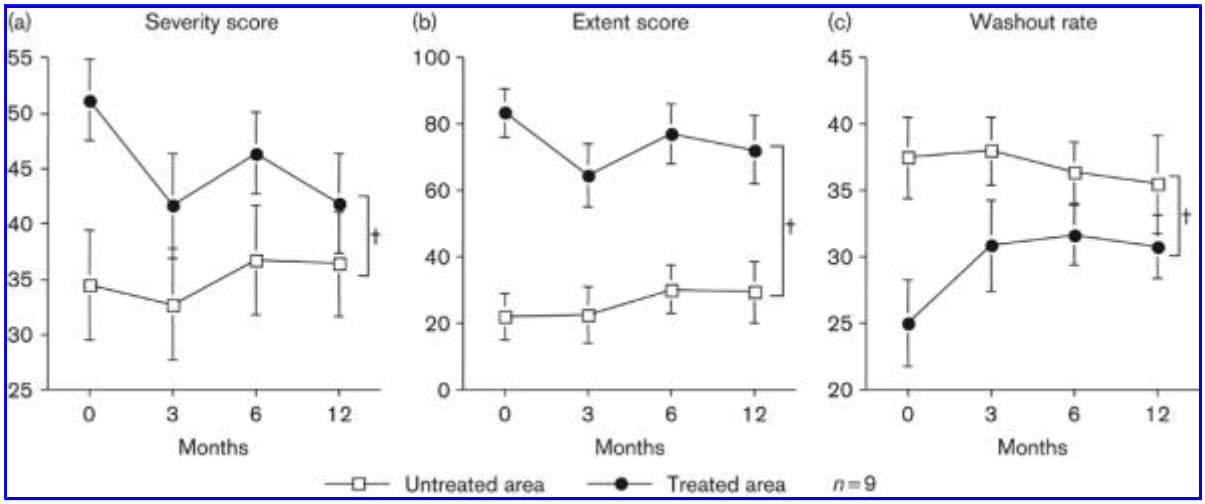

Fig. 5 The severity score (a), extent score (b), and washout rate (c) obtained from dipyridamole stress thallium-201 single photon emission computed tomography imaging. The results showed that myocardial ischemia was improved in the treated area, while in the untreated area, it tended to be worsened. Results are expressed as mean± SEM. †P< 0.01 untreated vs. treated area (statistically analyzed by one-way ANOVA).

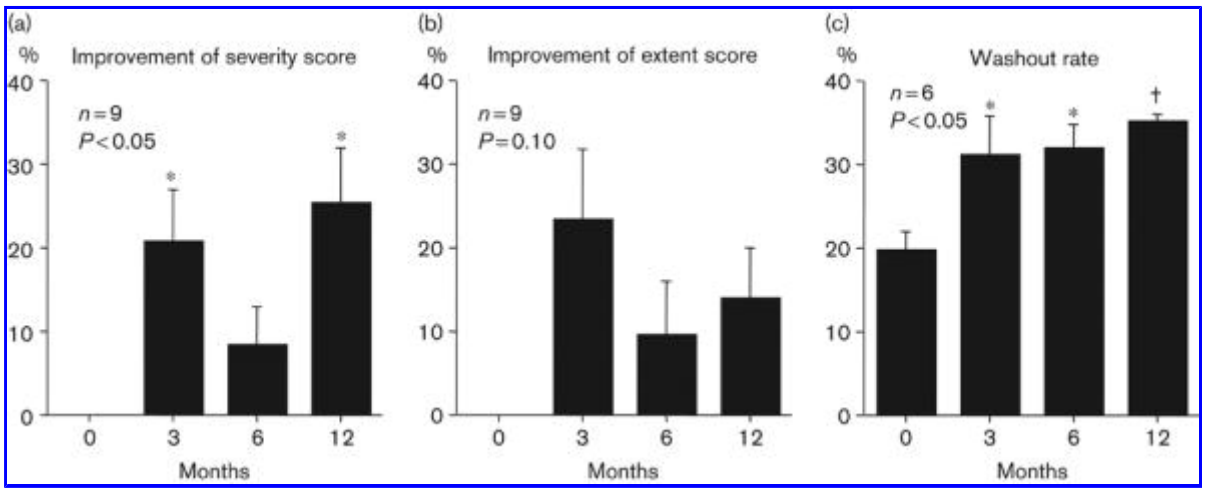

Fig. 6 The shock wave therapy significantly improved severity score (a), tended to improve extent score (b), and significantly improved local washout rate in patients with initial low washout rate (< 30%) (c) in the dipyridamole stress thallium scintigraphy. Results are expressed as mean± SEM. * P< 0.05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

Discussion

The present study demonstrates that our non-invasive extracorporeal cardiac SW therapy ameliorates myocardial ischemia in patients with severe CAD without procedural complications or adverse effects, confirming our findings in a porcine model of chronic myocardial ischemia [9]. The subjective and objective improvements of myocardial ischemia were noted as early as 3 months after the SW therapy in the patients who had at least more than 12 months of history of stable effort angina pectoris. The results with myocardial thallium scintigraphy and coronary angiography suggest that angiogenesis was effectively induced locally at coronary microvascular levels in the ischemic myocardium. The therapeutic effects of the SW therapy persisted during the follow-up period for 1 year. Importantly, no procedural complications or adverse effects were noted in the present study.

Mechanism of the cardiac shock wave therapy

The precise mechanism of SW to induce angiogenesis remains to be fully elucidated. SW is a longitudinal acoustic wave, traveling with the speed in water of ultrasound through body tissue, and could be focused on an area of several millimeters in diameter [12]. SW is known to exert the 'cavitation effect' (a micrometer-sized violent collapse of bubbles inside and outside the cells) [12] and recently has been demonstrated to induce localized stress on cell membranes that resembles shear stress [13]. SW has also been demonstrated to cause non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide [14], which may be involved, at least in part, in the biochemical effects of SW. Furthermore, recent orthopedic studies have demonstrated that SW

therapy induces neovascularization at tendon [7,15], via upregulation of endothelial nitric oxide synthesis, VEGF, and proliferating cell antigen [15]. We have previously confirmed that SW upregulates VEGF and its receptor, Flt-1, in endothelial cells *in vitro* and VEGF in the ischemic myocardium *in vivo* [9]. As the VEGF–Flt system is essential in initiating vasculogenesis and/or angiogenesis, this effect of SW could explain, at least in part, the underlying mechanisms for SW-induced angiogenesis. In this study, myocardial perfusion in the ischemic myocardium was improved only where the SW was applied (Fig. 3), excluding the placebo effect of the therapy.

Advantage of the cardiac shock wave therapy

Transmyocardial laser revascularization is an accepted therapy for an end-stage CAD and is reported to reduce the frequency and the severity of anginal symptoms and to improve exercise tolerance and quality of life, which, however, is an invasive surgical therapy [16]. A major advantage of our extracorporeal cardiac SW therapy over PCI, CABG, and transmyocardial laser revascularization is shown by the fact that it is quite non-invasive and safe, without any procedural complications or adverse effects. If necessary, we could repeatedly treat patients (even outpatients) with the 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 CAD. Thus, the extracorporeal cardiac SW therapy appears to be an applicable and non-invasive treatment for ischemic heart disease, although future randomized, controlled studies are required to validate the present encouraging results.

Limitations of the study

Several limitations should be mentioned for the present study. First, from an ethical point of view as discussed by the Ethical Committee, the present study is not a placebo-controlled study, as is always the case in the initial stage of a novel angiogenic therapy. As we discussed above, we noted the improvement of myocardial perfusion only in the ischemic region where we treated with the SW therapy in all patients. In addition, the objective improvement of myocardial ischemia was noted as early as 3 months after the SW therapy in patients with more than 12 months of history of stable effort angina. We consider that these findings could rule out the placebo effect. Furthermore, as patients are able to feel more or less some compression (but not pain) on the chest by the low level of SW, an effective placebo manipulation is practically difficult. To further confirm the effectiveness of the cardiac SW therapy, however, placebo-controlled, randomized studies are needed in the future. Second, the number of patients (n=9) is small in the present study although it took 2 years for us at one institute to carefully enroll the nine patients for the SW therapy and to follow-up the patients for 1 year. Moreover, the present data are not enough to evaluate the dose dependency of the SW therapy because of the small number of patients. Thus, the present findings including the evaluation of dose-dependent effect of the therapy should be confirmed in a multicenter study with a large number of patients. Third, we need to compare the effectiveness of our cardiac SW therapy with that of gene or cell therapies that are currently being developed with an initial success [2–5].

Conclusion

In the present study, on the basis of the strict inclusion and exclusion criteria approved by the Ethical Committee, we enrolled nine patients with severe CAD without indication of PCI or CABG. We were able to demonstrate that our cardiac SW therapy is effective to treat those patients with severe CAD. Thus, if our present findings are confirmed in future studies with a large number of patients, the use of the cardiac SW therapy may be broadened for the treatment of patients with CAD as a non-invasive therapy.

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