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ORIGINAL ARTICLE

A multicenter trial of extracorporeal cardiac shock wave therapy for refractory angina pectoris: report of the highly advanced medical treatment in Japan

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Abstract

We have previously demonstrated that cardiac shock wave therapy (CSWT) effectively improves myocardial ischemia through coronary neovascularization both in a porcine model of chronic myocardial ischemia and in patients with refractory angina pectoris (AP). In this study, we further addressed the efficacy and safety of CSWT in a single-arm multicenter study approved as a highly advanced medical treatment by the Japanese Ministry of Health, Labour and Welfare. Fifty patients with refractory AP [mean age 70.9 ± 12.6 (SD) years, M/F 38/12] without the indications of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were enrolled in 4 institutes in Japan. Ischemic myocardial regions in the left ventricle (LV) were identified by drug-induced stress myocardial perfusion imaging (MPI). Shock waves (200 shots/spot at 0.09 mJ/mm^2) were applied to 40–60 spots in the ischemic myocardium 3 times in the first week. The patients were followed up for 3 months thereafter. Forty-one patients underwent CSWT and completed the follow-up at 3 months. CSWT markedly improved weekly nitroglycerin use [from 3.5 (IQR 2 to 6) to 0 (IQR 0 to 1)] and the symptoms [Canadian Cardiovascular Society functional class score, from 2 (IQR 2 to 3) to 1 (IQR 1 to 2)] (both $P < 0.001$). CSWT also significantly improved 6-min walking distance (from 384 ± 91 to 435 ± 122 m, $P < 0.05$). There were no significant changes in LV ejection fraction evaluated by echocardiography and LV stroke volume evaluated by cardiac magnetic resonance imaging (from 56.3 ± 14.7 to 58.8 ± 12.8%, $P = 0.10$, and from 52.3 ± 17.4 to 55.6 ± 15.7 mL, $P = 0.15$, respectively). Percent myocardium ischemia assessed by drug-induced stress MPI tended to be improved only in the treated segments (from 16.0 ± 11.1 to 12.1 ± 16.2%, $P = 0.06$), although no change was noted in the whole LV. No procedural complications or adverse effects related to the CSWT were noted. These results of the multicenter trial further indicate that CSWT is a useful and safe non-invasive strategy for patients with refractory AP with no options of PCI or CABG.

Keywords Angiogenesis · Cardiac shock wave therapy · Refractory angina pectoris · Myocardial ischemia

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Introduction

The number of patients with ischemic heart disease has been increasing all over the world and there were eight million deaths in 2013, 41.7% increase from 1990 to 2013 [1]. In addition to medical treatment, development of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have significantly improved symptoms of angina pectoris (AP). However, there is a substantial number of patients who are suffering from AP with no indication of PCI or CABG, because of tortuous, severe calcified, or diffuse narrowing vessel, side branch lesion, vein graft with massive thrombus, or severe comorbidity [2]. In these patients, not only quality of life but also long-term prognosis remains poor [2–4]. Although new technologies have been studied to stimulate coronary collateral vessel growth, a variety of therapeutic angiogenesis such as cell or gene therapy are invasive in nature and have failed to exert desired effects or are still at in a pre-clinical stage [5]. Thus, development of alternative and non-invasive therapeutic approach for severe AP is needed. We have previously demonstrated that extracorporeal cardiac shock wave therapy (CSWT) with low energy ameliorates myocardial ischemia and myocardial function through neovascularization in a porcine chronic myocardial ischemia model [6]. Moreover, we have conducted two small clinical trials, demonstrating that shock wave (SW) therapy improves Canadian Cardiovascular Society (CCS) functional class score and the frequency of nitroglycerin (NTG) use without any adverse effects in patients with refractory AP [7, 8]. Based on the results of these trials, CSWT has been approved in 2010 as a highly advanced medical treatment for refractory AP by the Japanese Ministry of Health, Labour and Welfare, where we were allowed to perform CSWT for additional 50 patients with refractory AP as a single-arm multicenter trial. Accordingly, in the present study, we further addressed the efficacy and safety of CSWT in a multicenter trial in Japan.

Methods

Study population

After CSWT was approved in 2010 as a highly advanced medical treatment for refractory AP by the Japanese Ministry of Health, Labour and Welfare, we enrolled 50 patients with severe AP with no indication of PCI or CABG in 4 institutes in Japan from 2010 to 2016. They were still suffering from stable effort AP despite optimal medical therapy and showed evidence of myocardial ischemia by drug-induced stress myocardial perfusion imaging (MPI). Exclusion criteria included mechanical valve, Q-wave myocardial infarction within 3 months, non-Q-wave myocardial infarction within 6 weeks, PCI and/or CABG within 1 month, cardiac shock or uncontrolled heart failure, left ventricular (LV) thrombus, poorly controlled diabetic retinopathy, malignant tumor (including operation for the tumor within 5 years), breast plastic surgery with silicon, and undetectable target lesion using echocardiography. The present study was approved by the Ethical Committees of each institute, and all patients gave written informed consent.

Treatment protocol

Ischemic myocardial regions in the LV were identified by drug-induced stress MPI. We performed the SW therapy (200 shots/spot at 0.09 mJ/mm^2 for 40–60 spots per session; Modulith SLC, Storz Medical, Kreuzlingen, Switzerland) with the guidance of an echocardiography instrumented within a specially designed SW generator in an R-wave-triggered manner to avoid ventricular arrhythmias as described previously [7, 8]. SW pulse was focused on ischemic myocardium based on drug-induced stress MPI. The patients underwent one series of therapy (3 sessions per week) and were followed-up for 3 months after completion of the therapy.

Clinical Assessment

The primary endpoint was the weekly use of NTG. We also evaluated symptoms using the CCS functional class score, exercise tolerance in 6-min walk and bicycle ergometer test, cardiac function assessed by echocardiography and cardiac magnetic resonance imaging (MRI), and MPI with adenosine-induced (0.15 mcg/kg/min) stress thallium scintigraphy. For the evaluation of MPI, semi-quantitative visual interpretation was performed in a blinded manner by two expert radiologists; they semi-quantitatively scored the uptake for each of the 17 LV segments with 0 ~ 4 points both at rest and during stress. We evaluated summed difference score (SDS), which was the difference between summed stress score and summed rest score. Percent (%) myocardium ischemia was calculated by dividing SDS by 68 (17 segments with a maximal score of 4 per segment) × 100 [9]. We also evaluated percent myocardium ischemia separately divided into the treated and the non-treated segments.

Statistical analysis

The data management and statistical analysis were independently performed by the statisticians in the data center of Tohoku University Hospital. Parametric and non-parametric

data were presented as the mean ± SD and median (interquartile range), respectively. Paired data were compared using paired *t* test or Wilcoxon signed-rank test. A stratified analysis was performed based on sex, age (< 75 or ≥ 75 years), history of myocardial infarction or CABG, smoking habit, the presence or absence of hypertension, diabetes mellitus and dyslipidemia, CKD stage (< 3 or ≥ 3), ejection fraction (< 50 or ≥ 50%), CCS functional class score (< 3 or ≥ 3) and SDS score (< 8 or ≥ 8). The evaluation of the effectiveness of CSWT in the stratified analysis was determined according to the improvement of weekly NTG use, CCS functional class score, and SDS in the treated segments at 3 months after the treatment, respectively. Statistical analyses were performed using SPSS statistics software (SPSS Inc., Chicago, Illinois), and $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics

We enrolled 50 patients with refractory AP. Two patients withdrew the informed consent before CSWT, and one patient canceled because of hip fracture before the treatment. Forty-seven patients underwent CSWT. Five patients were excluded because they had no evidence of myocardial ischemia with MPI before CSWT at final blinded evaluation by the expert radiologists. Finally, we analyzed a total of 42 patients in this trial. Baseline clinical characteristics are shown in Table 1. The mean age was 71.0 years and 81.0% were male. Most of them had the history of PCI, CABG or both. Half of them had previous myocardial infarction. Median weekly NTG use and CCS functional class score were 3.3 (IQR 2 to 5.5) and 2 (IQR 2 to 3), respectively.

Safety of CSWT

No procedural complications or adverse effects related to the CSWT were noted in this study. A 67-year-old female on hemodialysis died of cardiac sudden death 1 month after CSWT. The doctor in the hospital where she was getting hemodialysis reported that she did not feel chest pain after CSWT and underwent hemodialysis 3 days per week regularly without any problems. She collapsed at home after taking a bath. When emergency medical technicians arrived at her home, ventricular fibrillation was documented, which persisted despite cardiopulmonary resuscitation and repeated defibrillations by automated external defibrillator (AED). She was transferred to emergency department of a university hospital by ambulance and cardiopulmonary resuscitation including electrocardioversion was continued without success. Echocardiographic evaluation showed no sign of cardiac tamponade. Although the cardiologist who

Table 1 Baseline patient characteristics (*N*=42)

Age, years	71.0 ± 12.2
Male / Female (*N*)	34/8
BMI	25.0 ± 3.7
HT *N* (%)	33 (79)
DM *N* (%)	17 (40)
DL *N* (%)	26 (62)
Smoking *N* (%)	
Current smoker	2 (5)
Ex-smoker	19 (45)
Non-smoker	21 (50)
Previous myocardial infarction *N* (%)	22 (52)
Atrial fibrillation *N* (%)	2 (5)
Chronic kidney disease (> stage 3) *N* (%)	19 (45)
Previous treatment, *N* (%)	
PCI only *N* (%)	17 (40)
CABG only *N* (%)	6 (14)
Both PCI and CABG *N* (%)	18 (43)
CCS functional class score, median (IQR)	2 (2, 3)
NTG/week, median (IQR)	3.3 (2.0, 5.5)
Target segments	
Anterior (*N*)	22
Anterolateral (*N*)	7
Lateral (*N*)	18
Posterolateral (*N*)	10
Posterior (*N*)	10
Inferior (*N*)	22
Septal (*N*)	9
Apical (*N*)	11
BNP, median (IQR) pg/ml	57.5 (25.2–105.6)
Echocardiography (*N*=41)	
LVDd (mm)	45.0 ± 7.3
LVDs (mm)	34.8 ± 9.5
LVEF (%)	55.6 ± 15.3
MRI (*N*=34)	
LVEDV (ml)	115.9 ± 37.2
LVESV (ml)	62.2 ± 38.4
SV (ml)	52.2 ± 17.1
Medications	
Aspirin *N* (%)	38 (90)
β-blocker *N* (%)	39 (93)
ACE-I r ARB *N* (%)	31 (74)
Nitrate *N* (%)	28 (67)
Other vasodilator *N* (%)	34 (81)
Statin *N* (%)	34 (81)

Results are expressed as mean±SD or median (IQR)

ACE-I angiotensin-converting enzyme-inhibitor, *ARB* angiotensin receptor blocker, BMI body mass index, *BNP* brain natriuretic peptide, *CABG* coronary artery graft bypass, *CCS* canadian cardiovascular society, *DL* dyslipidemia, *DM* diabetes mellitus, *HT* hypertension, *LVDd* left ventricular diastolic diameter, *LVDs* left ventricular systolic diameter, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVESV* left ventricular end-systolic volume, *MRI* magnetic resonance imaging, *NTG* nitroglycerin, *PCI* percutaneous coronary intervention, *SV* stroke volume

provided emergent medical care asked her family for autopsy to clarify the cause of sudden death, her family declined the proposal. Since fetal arrhythmia could occur in patients with severe ischemic heart disease without indication of PCI or CABG and the patient was free of angina after CSWT, the independent data monitoring committee judged that sudden death in this case was not related to CSWT.

Effects of CSWT

Follow-up data at 3 months were obtained from 41 patients. CSWT markedly improved weekly NTG use [from 3.5 (IQR 2 to 6) to 0 (IQR 0 to 1)] and the symptoms [CCS functional class score, from 2 (IQR 2 to 3) to 1 (IQR 1 to 2)] (both $P < 0.001$) (Fig. 1a). CSWT also significantly improved 6-min walking distance (from 384 ± 91 to 435 ± 122 m, $P < 0.05$) and tended to improve maximum exercise capacity with bicycle ergometer test (from 79 ± 25 to 82 ± 27 watts, $P = 0.18$) (Fig. 1b). LV ejection fraction (LVEF) assessed by echocardiography and LV stroke volume (SV) evaluated by MRI was slightly increased after CSWT (from 56.3 ± 14.7 to $58.8 \pm 12.8\%$, $P = 0.10$, and from 52.3 ± 17.4 to 55.6 ± 15.7 mL, $P = 0.15$, respectively), however, these were no statistically significant differences (Fig. 2). CSWT did not significantly changed % myocardium ischemia in the whole LV evaluated by adenosine stress MPI (from 11.1 ± 6.3 to $8.9 \pm 10.7\%$, $P = 0.17$). However, % myocardium ischemia tended to improve only in the treated segments (from 16.0 ± 11.1 to $12.1 \pm 16.2\%$, $P = 0.06$) whereas no difference was noted in the remote non-treated segments (from 6.6 ± 6.5 to $6.1 \pm 9.3\%$, $P = 0.75$) (Fig. 3). The stratified analysis (Tables 2, 3, 4) revealed that the beneficial effects of CSWT were noted throughout the pre-specified subgroups (Fig. 4).

Discussion

We have previously reported that CSWT improves symptoms of AP in an open label trial and a double-blind placebo-controlled crossover trial [7, 8]. However, these studies were performed in a single center with a small number of patients [7, 8]. In the present multicenter trial with 42 patients with refractory AP, we were able to

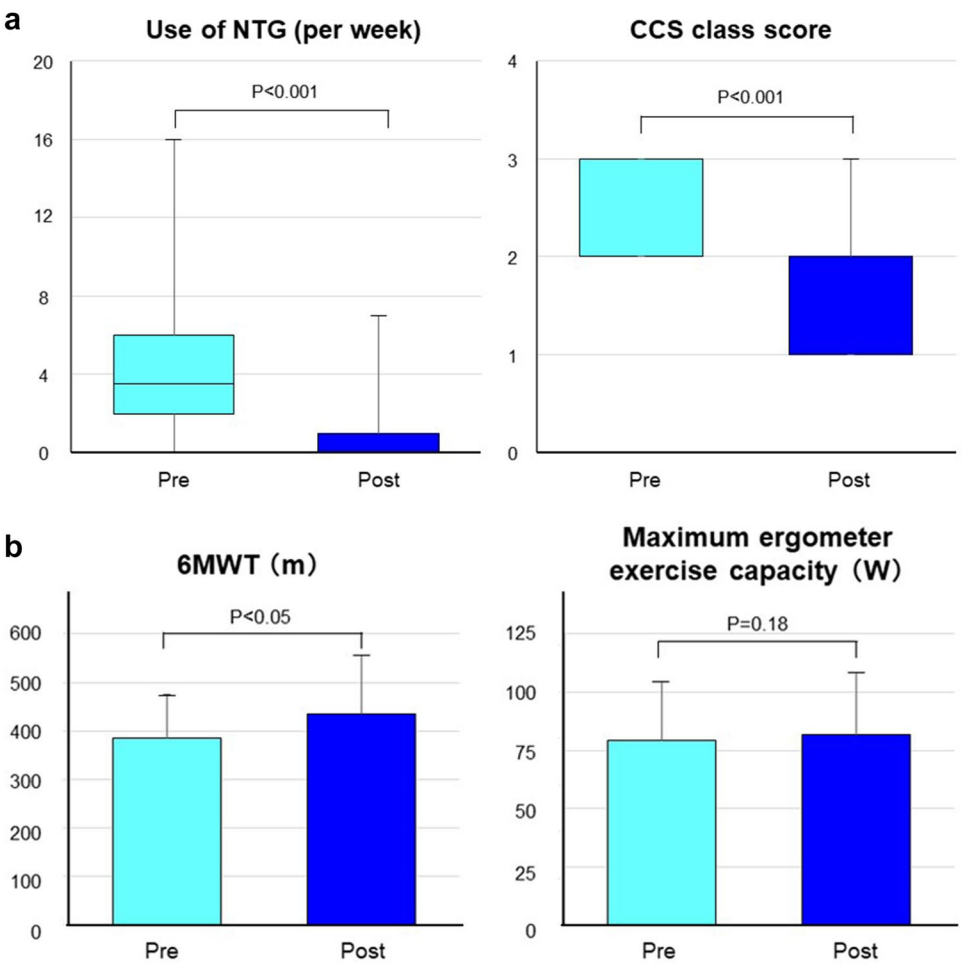

Fig. 1 Weekly NTG use and CCS functional class score (**a**) and exercise capacity assessed by 6-min walk test and ergometer bicycle test (**b**). **a** Cardiac shock wave therapy (CSWT) markedly reduced weekly nitroglycerin (NTG) use and Canadian Cardiovascular Society (CCS) functional class score after 3 months. Results are expressed as median (IQR). (**b**) Six-minute walking distance was significantly increased after CSWT, while improvement of maximum ergometer exercise capacity was limited. Results are expressed as mean ± SD. 6-min walk test, 6MWT

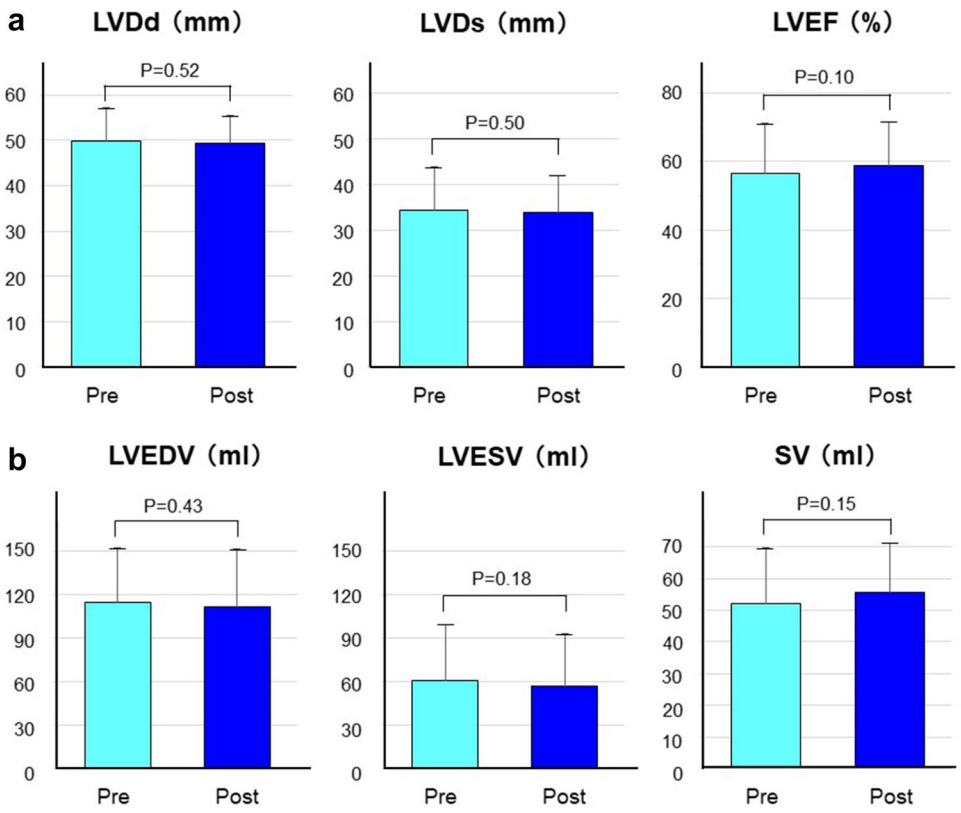

Fig. 2 Cardiac function assessed by echocardiography and MRI. (**a**) Left ventricular ejection fraction (LVEF) evaluated by echocardiography tended to be increased after CSWT. (**b**) Stroke volume (SV) evaluated by magnetic resonance imaging (MRI) also tended to be increased after CSWT. Results are expressed as mean ± SD

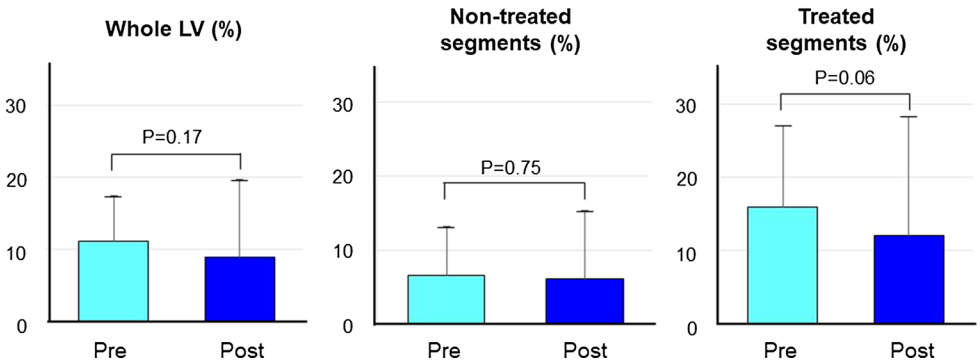

Fig. 3 Myocardial perfusion imaging assessed by adenosine-induced stress thallium scintigraphy. There was no significant difference in % myocardium ischemia in the whole left ventricle (LV) after CSWT. However, when LV was divided into the treated segments and the non-treated segments, % myocardium ischemia tended to improve after CSWT only in the treated segments. Results are expressed as mean ± SD

demonstrate that (1) CSWT significantly improved CCS functional class score and weekly NTG use; (2) CSWT increased myocardial blood flow only in the treated segments; and (3) the beneficial effects of CSWT were observed regardless of the pre-specified subgroups; (4) there were no procedural complications or adverse effects.

Effects of the CSWT on refractory AP

In our previous reports, CSWT ameliorated ischemia-induced myocardial dysfunction through neovascularization in a porcine model of chronic ischemia [6]. CSWT also improved myocardial blood flow, assessed by MPI, in

Table 2 A stratified analysis (improvement of weekly NTG use)

Total (*N*)		Effective (*N*)	OR (95% CI)
Sex			
Female	7	7	1.00
Male	34	28	–
Age			
< 75 years	22	17	1.00
≥ 75 years	19	18	5.29 (0.56–50.08)
OMI			
(−)	19	18	1.00
(+)	22	17	0.19 (0.02–1.79)
CABG			
(−)	18	17	1.00
(+)	23	18	0.21 (0.02–2.00)
Smoking			
None	20	17	1.00
Ex	19	16	0.94 (0.17–5.36)
Current	2	2	–
HT			
(−)	9	7	1.00
(+)	32	28	2.00 (0.30–13.22)
DM			
(−)	25	21	1.00
(+)	16	14	1.33 (0.21–8.29)
DL			
(−)	15	12	1.00
(+)	26	23	1.92 (0.33–10.98)
CKD			
< stage 3	23	20	1.00
≥ stage 3	18	15	0.75 (0.13–4.25)
CCS			
< 3	24	19	1.00
= 3	17	16	4.21 (0.45–39.86)
LVEF			
> 50%	30	27	1.00
≤ 50%	10	7	0.26 (0.04–1.57)
SDS			
< 8	23	21	1.00
≥ 8	17	14	0.44 (0.07–3.01)

CABG coronary artery bypass graft, *CCS* canadian cardiovascular society, *CKD* chronic kidney disease, *DL* dyslipidemia, *DM* diabetes mellitus, *HT* hypertension, *LVEF* left ventricular ejection fraction, *NTG* nitroglycerin, *OMI* old myocardial infarction, *SDS* summed difference score

Table 3 A Stratified analysis (improvement of CCS functional class score)

Total (*N*)		Effective (*N*)	OR (95% CI)
Sex			
Female	7	7	1.00
Male	34	23	–
Age			
<75 yrs	22	16	1.00
≥75 yrs	19	14	1.05 (0.26–4.20)
OMI			
(−)	19	14	1.00
(+)	22	16	0.95 (0.24–3.81)
CABG			
(−)	18	13	1.00
(+)	23	17	1.09 (0.27–4.37)
Smoking			
none	20	14	1.00
Ex	19	15	1.61 (0.37–6.92)
Current	2	1	0.43 (0.02–8.04)
HT			
(−)	9	7	1.00
(+)	32	28	0.73 (0.13–4.20)
DM			
(−)	25	18	1.00
(+)	16	12	1.17 (0.28–4.87)
DL			
(−)	15	12	1.00
(+)	26	18	0.56 (0.12–2.56)
CKD			
< stage 3	23	15	1.00
≥ stage 3	18	15	2.67 (0.59–12.04)
LVEF			
> 50%	30	21	1.00
≤ 50%	10	8	1.71 (0.30–9.72)
SDS			
< 8	23	20	1.00
≥ 8	17	10	0.21 (0.05–1.01)

CABG coronary artery bypass graft, *CCS* canadian cardiovascular society, *CKD* chronic kidney disease, *DL* dyslipidemia, *DM* diabetes mellitus, *HT* hypertension, *LVEF* left ventricular ejection fraction, *OMI* old myocardial infarction, SDS summed difference score

patients with refractory AP [7, 10]. Beneficial effects can be observed relatively early after CSWT, implicating local vasodilating effects induced by enhanced nitric oxide synthesis [11–14]. These early effects were followed by the chronic effects and persisted for up to several months or years via angiogenesis [7, 15, 16]. Furthermore, the present study was the first report that there was no difference in the efficacy of CSWT throughout the subgroups. These results suggest that CSWT is useful regardless of patient background.

Mechanisms for CSWT-induced angiogenesis

We and others have demonstrated that SW enhances angiogenesis via multiple angiogenic pathways, promoted endothelial progenitor cell homing, suppressed apoptosis, preserved mitochondrial functions, reduced oxidative stress, and alleviated inflammation [6, 17, 18]. However, the

Table 4 A stratified analysis (improvement of SDS in treated segments)

Total (*N*)		Effective (*N*)	OR (95% CI)
Sex			
Female	7	6	1.00
Male	33	19	0.23 (0.02–2.10)
Age			
<75 yrs	21	14	1.00
≥75 yrs	19	11	0.69 (0.19–2.49)
OMI			
(−)	19	11	1.00
(+)	21	14	1.46 (0.40–5.26)
CABG			
(−)	18	9	1.00
(+)	22	16	2.67 (0.72–9.95)
Smoking			
None	19	11	1.00
History	19	12	1.25 (0.34–4.59)
Current	2	2	-
HT			
(−)	9	6	1.00
(+)	31	19	0.79 (0.17–3.78)
DM			
(−)	24	15	1.00
(+)	16	10	1.00 (0.27–3.69)
DL			
(−)	15	11	1.00
(+)	25	14	0.46 (0.12–1.86)
CKD			
< stage 3	22	15	1.00
≥ stage 3	18	10	0.58 (0.16–2.12)
CCS			
<3	23	18	1.00
=3	17	7	0.19 (0.05–0.78)
LVEF			
> 50%	29	19	1.00
≤ 50%	10	5	0.53 (0.12–2.26)
SDS			
<8	23	15	1.00
≥8	17	10	0.76 (0.21–2.77)

CABG coronary artery bypass graft, *CCS* canadian cardiovascular society, *CKD* chronic kidney disease, *DL* dyslipidemia, *DM* diabetes mellitus, *HT* hypertension, *LVEF* left ventricular ejection fraction, *OMI* old myocardial infarction, SDS summed difference score

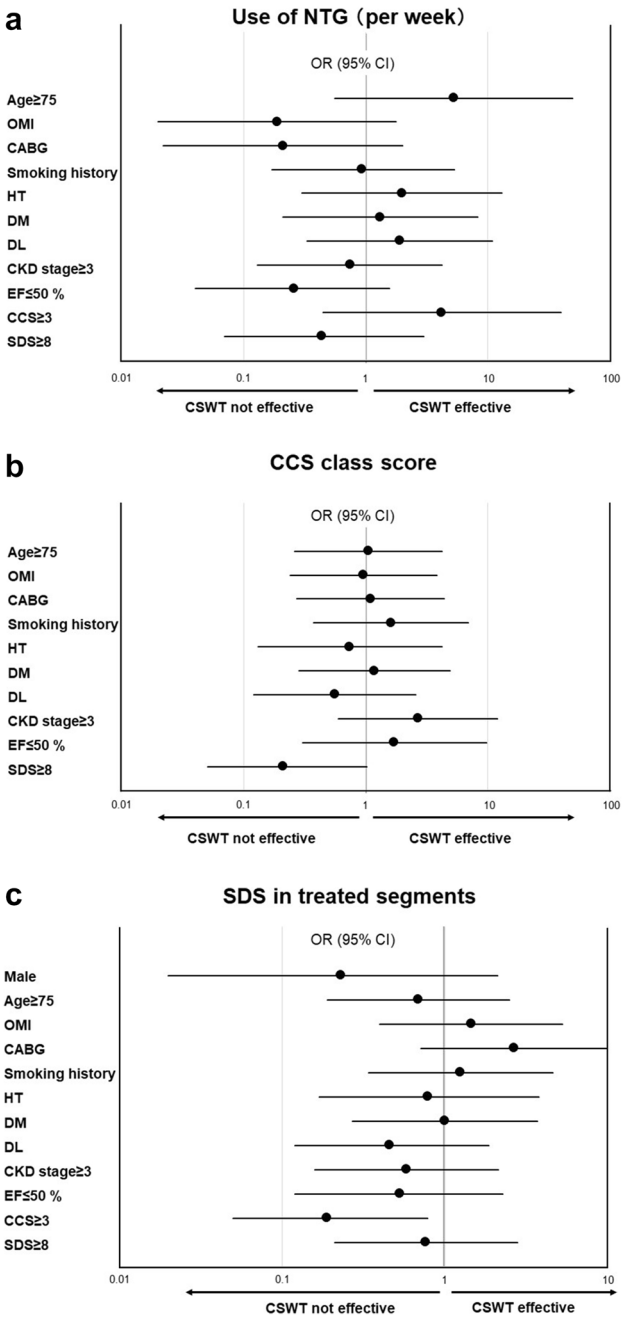

Fig. 4 A stratified analysis of the improvements of weekly NTG use, CCS functional class score, and SDS in treated segments. The beneficial effects of CSWT for weekly NTG use (**a**), CCS functional class score (**b**), and summed difference score (SDS) in treated segments(**c**) were noted throughout the pre-specified subgroups

mechanism for the translation of mechanical stimulation of SW into biological responses remains to be fully elucidated. SW is a single pressure pulse with a short needle positive spike, followed by tensile part of several microseconds with lower amplitude. These negative pressure pulses generate microbubbles inside and outside the cells, which is known as "cavitation effect" [19]. A micro-sized violent collapse of bubbles induces localized stress on cell membranes that resembles shear stress [20]. Vascular endothelial cells are exposed to fluid shear stress from blood flow and transmit extracellular stimulation into intracellular signaling pathways, resulting in angiogenesis, cell proliferation, vasodilation, and antithrombotic effects [21–24]. Recently, we have

identified one of the mechanisms for the mechanotransduction by CSWT, where caveolin-1 and β1-integrin in the caveolae and the downstream pathways with Akt and Erk1/2 phosphorylations are involved in angiogenesis induced by SW [25]. Ha et al. also revealed that SW stimulated Akt/eNOS phosphorylation and angiogenic gene expression via mechanosensory complexes involving VEGFR-2, PECAM-1, and VE-cadherin [26]. Thus, these pathways may lead to the enhancement of eNOS and VEGF expressions and eNOS phosphorylation, which are necessary to initiate angiogenesis.

Advantages of CSWT

Several new approaches to treat refractory AP have been investigated. Although transmyocardial and percutaneous myocardial laser revascularization [27–29] and spinal cord stimulation [30] have been reported to exert beneficial effects, these alternative approaches are invasive in nature. On the other hand, CSWT is non-invasive with no need of general anesthesia, and is safe without any procedural complications or adverse effects. Regenerative therapies including genes, cytokines, and progenitor cells therapy have not been consistently effective in humans [5]. To promote angiogenesis to induce clinical improvement, multiple and complex pathways including various growth factors and their receptors, adhesion molecules, and EPC homing, are known to be involved, indicating that enhancement of a single factor may not be enough. In contrast, CSWT can activate multiple pathways mentioned above. According to these effects, additional indications of low energy SW therapy, such as peripheral artery disease (PAD) [31], skin ulcer [32–34], lymphedema [35], orthopedic diseases [36–41], erectile dysfunction [42] have been under development.

Study limitations

Several limitations should be mentioned for the present study. First, the present study was not a placebo-controlled study because only CSWT without a placebo arm was approved under the highly advanced medical treatment by the Japanese government. Recently, potential placebo effects of PCI on exercise capacity have been reported in stable angina patients with single vessel disease [43]. However, we believe that the beneficial effects of CSWT were not mediated by placebo effects for the following reasons. (1) We previously performed placebo-controlled double-blind study, in which we confirmed the efficacy of our CSWT in the treated group but not in the placebo group [8]. (2) Also, the subsequent randomized placebo-controlled studies also demonstrated the beneficial effects of CSWT on symptoms and myocardial perfusion [44–46]. (3) In addition, the improvement in myocardial perfusion by CSWT was noted only in the treated segments of the heart. Second, we have not fully examined whether more effective treatment protocol exists, such as extent of energy level, number of impulse per spot, and times of sessions. In the present and the previous studies, we performed 3 sessions of CSWT and showed its beneficial effects [7, 8]. On the other hand, other groups treated patients with a total of 9 sessions for 3 months and demonstrated the beneficial effects [10, 44–49]. These results suggest that 3 sessions of CSWT are enough to improve symptoms and myocardial perfusion. However, further studies are needed to clarify its optimal protocol. Third, there was no significant difference in exercise capacity by bicycle ergometer test. This could be explainable by patient's muscle weakness in lower limb due to refractory AP and coexisting PAD or orthopedic problems. Indeed, most patients reached their limit of exercise because of leg fatigue. Fourth, some reports demonstrated that CSWT improved cardiac function [44, 50], although the reported changes in LVEF assessed by echocardiography and SV assessed by MRI were small. In the present study, LVEF and SV in the baseline were preserved; $56.3 \pm 14.7\%$ and 52.3 ± 17.4 ml, respectively, which could explain why CSWT caused no significant effect in cardiac function.

Conclusions

In conclusion, CSWT is an effective and non-invasive therapy for patients with refractory AP with no options of PCI or CABG.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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