Low-energy cardiac shockwave therapy to suppress left ventricular remodeling in patients with acute myocardial infarction: a first-in-human study

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Objective **Although primary percutaneous coronary intervention (PCI) substantially reduces the mortality of patients with acute myocardial infarction (AMI), left ventricular (LV) remodeling after AMI still remains an important issue in cardiovascular medicine. We have previously demonstrated that low-energy cardiac shockwave (SW) therapy ameliorates LV remodeling after AMI in pigs. In this first-in-human study, we examined the feasibility and the effects of the SW therapy on LV remodeling after AMI in humans.**

Patients and methods **Seventeen patients with AMI who successfully underwent primary PCI (peak-creatine kinase < 4000 U/l) were treated with the SW therapy. Low-energy shock waves were applied to the ischemic border zone around the infarcted area at 2, 4, and 6 days since AMI. Next, we compared these patients with historical AMI controls by propensity score matching ($N = 25$).**

Results **There were no procedure-related complications or adverse effects. At 6 and 12 months after AMI, LV function as assessed by MRI showed no signs of deleterious LV remodeling. When we compared the SW-treated group with the historical AMI controls at 6 months after AMI, LV ejection fraction was significantly higher in the SW-treated group ($N = 7$) than in the historical control group ($N = 25$) by echocardiography (66 ± 7 vs. $58 \pm 12\%$, $P < 0.05$). LV end-diastolic dimension also tended to be smaller in the SW than in the control group (47.5 ± 4.6 vs. 50.0 ± 5.9 mm, $P = 0.29$).**

Conclusion **These results suggest that low-energy extracorporeal cardiac SW therapy is feasible and may ameliorate postmyocardial infarction LV remodeling in patients with AMI as an adjunctive therapy to primary PCI.** *Coron Artery Dis* **29:294–300 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Although recent progress in emergency care systems and primary percutaneous coronary intervention (PCI) substantially reduced the mortality of patients with acute myocardial infarction (AMI) [1], left ventricular (LV) remodeling after AMI still remains an important issue in cardiovascular medicine [2,3]. Adverse LV remodeling after AMI is the most common cause of worsening heart failure with resultant poor prognosis. Thus, new therapeutic strategies remain to be developed.

We have previously demonstrated that low-energy extracorporeal cardiac shockwave (SW) therapy induces angiogenesis and improves cardiac function in a porcine model of chronic myocardial ischemia [4]. We also have demonstrated that the SW therapy improves symptoms, reduces the use of nitroglycerin, and improves myocardial ischemia in patients with refractory angina pectoris without any adverse effects or complications [5,6]. Furthermore, we have demonstrated that SW therapy ameliorates LV remodeling in porcine models of AMI owing to permanent coronary ligation or myocardial ischemia–reperfusion [7,8]. In these animal studies, low-energy SW was applied to the ischemic border zone around the infarcted myocardium within 3 days after the onset of AMI. We were able to demonstrate that the beneficial effects of the SW therapy are achieved in part by the upregulation of endothelial nitric oxide synthase associated with enhanced capillary density in the ischemic border zone [7,8]. However, it remains to be examined whether the SW therapy also ameliorates LV

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remodeling after AMI in humans. In the present study, we thus performed a first-in-human study to examine the feasibility and the effects of SW therapy on LV remodeling in patients with AMI.

Patients and methods

Patient population

The present study was approved by the Ethical Committee of Tohoku University and was conducted in accordance with the principles of the Declaration of Helsinki (UMIN000014562). Written informed consent was obtained from all participants. Among the 266 patients with AMI who were admitted to the Tohoku University Hospital from 2007 to 2015, we enrolled 17 patients with ST-segment elevation myocardial infarction (MI) who were successfully treated with primary PCI (Table 1). The inclusion criteria were as follows: age 20–80 years and successful PCI within 12 h after the onset of the symptoms, with final thrombolysis in myocardial infarction (TIMI) grade 3 flow. The exclusion criteria included peak level of total creatine kinase (CK) of 4000 U/l or higher, extensive anterior MI, congestive heart failure, cardiogenic shock, fatal arrhythmias, possible LV thrombus, LV aneurysm, sustained ST-segment elevation, significant pericardial effusion, transplanted hearts, pregnant women, malignant neoplasms, and recent operation for malignant neoplasms (< 5 years). We excluded patients with extensive anterior MI because we limited the size of infarction in this pilot study.

Study design

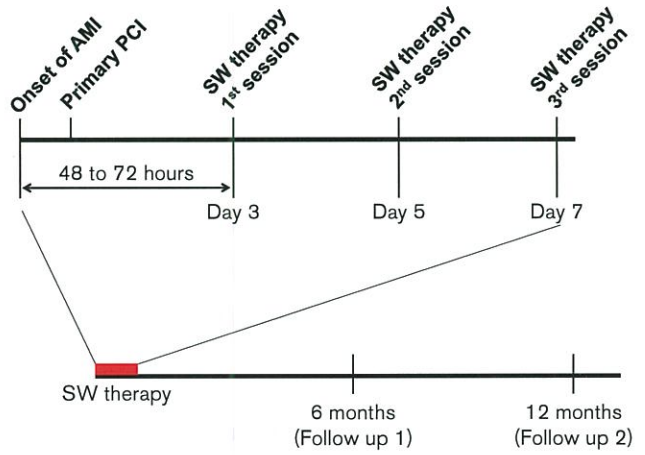
The patients with AMI underwent primary PCI according to the standard guidelines [9]. The use of thrombus aspiration and bare-metal or drug-eluting stents was left to the discretion of the treating physician. The first session of the SW therapy was performed for eligible patients between 48 and 72 h after the onset of AMI (Fig. 1). After three sessions of the SW therapy, the patients were followed up for 12 months. The 12-month follow-up was completed in January 2016.

Table 1 Baseline patient characteristics

Age (years)	65.0 ± 7.3
Male/female (*n*)	16/1
Culprit coronary artery (LAD/LCX/RCA) (*n*)	5/3/9
Peak-creatine kinase (U/l)	1770 ± 1163
BNP [median (range)] (pg/ml)	73.1 (22.8–135.1)
MRI (*N* = 15)	
LVEDV (ml)	105.1 ± 32.0
LVEF (%)	56.8 ± 11.6
LVG (*N* = 13)	
LVEDV (ml)	114.1 ± 29.0
LVEF (%)	67.6 ± 12.7
Technetium-99m-MIBI scintigraphy (*N* = 15)	
LVEDV (ml)	73.3 ± 27.9
LVEF (%)	60.2 ± 12.8
Echocardiography (*N* = 17)	
LVDd (mm)	44.9 ± 4.5
LVEF (%)	61.1 ± 10.7
Medication at discharge (*N* = 16)	
β-Blocker	16 (100)
ACE-I or ARB	16 (100)
Aldosterone antagonist	0 (0)
Statin	16 (100)

Results are expressed as mean ± SD and *n* (%).
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; LAD, left anterior descending; LCX, left circumflex artery; LVDd, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVG, left ventriculography; RCA, right coronary artery.

Fig. 1



Study protocol. The protocol of the present study. The first session of the SW therapy was conducted between 48 and 72 h after the onset of AMI, followed by the second and the third sessions on days 5 and 7, respectively. Patients were followed up for 12 months after the SW therapy. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; SW, shockwave.

Low-energy cardiac shockwave therapy

The first session of the SW therapy was performed between 48 and 72 h after the onset of AMI. Patients underwent a total of three sessions of the SW therapy every other day (Fig. 1). In each treatment session, SW (200 shots/spot at 0.04 mJ/mm^2) was applied to 27 spots in the ischemic border zone around the infarcted myocardium with the guidance of an echocardiography equipped within the SW generator (Modulith SLC; Storz Medical AG, Kreuzlingen, Switzerland) in an R-wave-triggered manner to avoid ventricular arrhythmias [7,8]. This SW device has not been approved yet by the Food and Drug Administration in USA.

Evaluation of cardiac function and left ventricular remodeling

In the SW-treated patients with AMI, cardiac function was evaluated with left ventriculography (LVG), MRI, technetium-99m (^{99m}Tc)-MIBI scintigraphy, and echocardiography at baseline and at 6 and 12 months after AMI. LVG at baseline was performed after successful PCI. Echocardiography at baseline was performed within 24 h after successful PCI. MRI and ^{99m}Tc-MIBI scintigraphy at baseline were performed within 5 days after successful PCI. Adverse LV remodeling was defined as

more than 15% increase in LV end-diastolic volume or LV end-diastolic dimension [10].

Comparisons with historical acute myocardial infarction controls

To further assess the effect of the SW therapy on LV remodeling, we selected 135 patients with AMI in our department, who met the same eligibility criteria for the SW therapy between 2007 and 2014 as historical AMI controls. We performed a propensity score matching, using age, peak level of CK, left ventricular ejection fraction (LVEF), and left ventricular end-diastolic dimension (LVDd) measured with echocardiography between the SW-treated and the historical control groups.

Statistical analysis

Results are expressed as mean ± SD or median (interquartile range) for continuous variables and as numeral (%) for categorical variables. For comparisons between the SW and the historical control groups, we used Welch's *t*-test or Wilcoxon's rank-sum test for continuous variables, and Fisher's exact test for categorical variables. All statistical analyses were performed using R, version 3.2.5 [11], and P value less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics of the shockwave-treated patients with acute myocardial infarction

We enrolled 17 patients with AMI who were successfully treated with primary PCI and met the eligibility criteria. Their baseline characteristics are shown in Table 1.

Effects of the shockwave therapy on postmyocardial infarction left ventricular remodeling in humans

The patients were followed up for 12 months. MRI was the first diagnostic imaging modality used for assessment of LV volume and contractility. LVG, ^{99m}Tc-MIBI scintigraphy, and echocardiography were used as alternative diagnostic methods. MRI study was not performed in one patient with an artificial joint implant. LVG was not performed in four patients with renal dysfunction, whereas ^{99m}Tc-MIBI scintigraphy was not performed in one patient owing to limited availability of the test. There was no significant difference in either left ventricular end-diastolic volume or LVEF between baseline and 6 or 12 months after AMI as assessed by cardiac MRI in the SW group (Fig. 2a). Moreover, there was no significant difference in left ventricular end-diastolic volume or LVEF during the follow-up period as assessed by LVG (Fig. 2b) or ^{99m}Tc-MIBI scintigraphy (Fig. 2c). LVEF and LVDd measured by echocardiography showed no significant change during the follow-up period as well (Fig. 2d). These results suggest that the SW therapy after successful PCI did not cause worsening of cardiac function during the first 12 months after AMI.

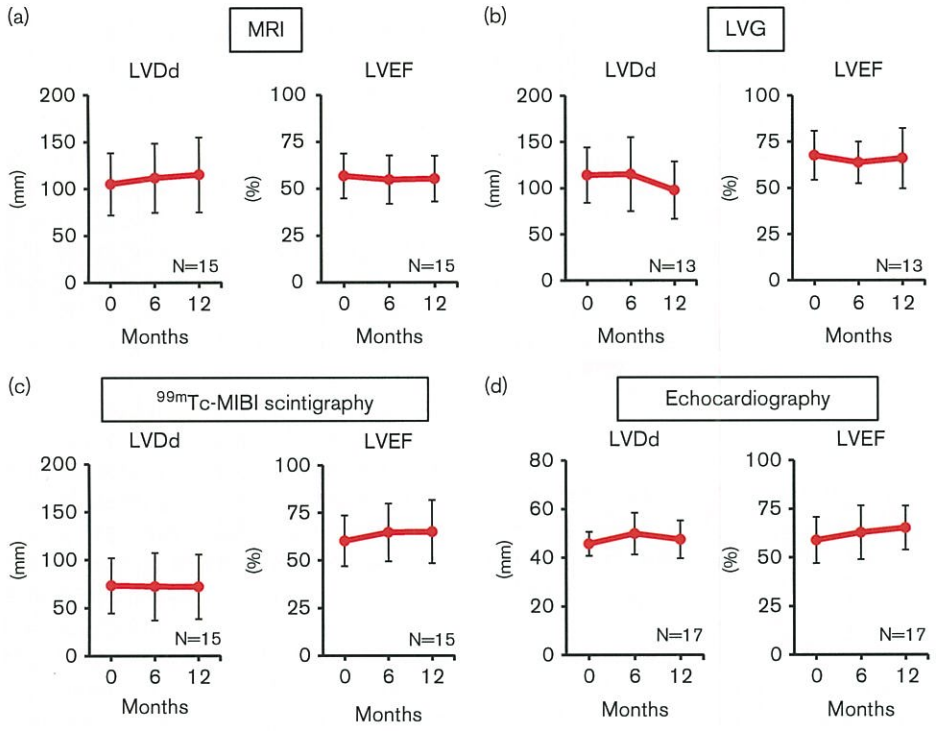
Comparison with historical acute myocardial infarction controls

To further examine the effect of SW therapy on LV remodeling after AMI, we selected 135 patients with AMI in our department as historical controls without the SW therapy. After a propensity score matching, using age, peak level of CK, LVEF, and LVDd, we identified 25 historical controls and compared the SW group ($N=7$) with the historical control group ($N=25$) (Table 2). Although there was no difference in LVDd between the two groups at 6 months after AMI, LVEF was significantly higher in the SW group than in the historical control group (Fig. 3). When adverse LV remodeling was defined as more than 15% increase in LVDd, there was no patients in the SW-treated group and two in the historical control group (0 vs. 8%, $P=0.16$). During the follow-up period, there was no patient who was hospitalized owing to worsening heart failure or acute coronary syndrome in the SW-treated group, whereas four patients were hospitalized owing to cardiovascular reasons in the historical control group: two with worsening heart failure and two with acute coronary syndrome. Although no cardiovascular death was noted in both groups, three patients in the historical control group died of peritonitis, prostate cancer, and glomerulonephritis. These results suggest that the SW therapy following successful primary PCI is feasible and may ameliorate LV remodeling in patients with AMI.

Evaluation of safety

The second case (age 58 years; male) that underwent SW therapy in the present study died the day after the first session of SW therapy owing to cardiac rupture (blow-out type) on defecation despite emergent cardiac surgery. In this patient, the culprit lesion in the middle portion of right coronary artery (RCA) was successfully reperfused and was stented during the primary PCI. Although TIMI grade 3 flow was achieved immediately after PCI, the final coronary angiogram after PCI showed faint antegrade coronary flow in one of the small branches of distal RCA. The autopsy revealed that cardiac rupture occurred in the center of the infarcted area where myocardium was perfused by the aforementioned distal RCA branch. Because the rupture site was remote from the SW-treated area and the rupture occurred more than 24 h after the SW therapy, the independent data monitoring committee judged that the cardiac rupture had been related to AMI itself, but not directly related to the SW therapy. After this case, patients with possible distal embolization were excluded by adding TIMI coronary flow grade 3 after primary PCI to the inclusion criteria in the present study. All other 16 cases that completed the SW therapy survived 12 months after AMI without any adverse effects. In addition, the results of blood tests showed no myocardial damage or adverse effects on liver or renal function by the SW therapy (Table 3).

Fig. 2



Cardiac functions assessed by multiple imaging modalities. Time courses of LVEF, LVEDV and LVDd evaluated by cardiac MRI (a), LVG (b), technetium-99m (^{99m}Tc)-MIBI scintigraphy (c), and echocardiography (d) in patients with acute myocardial infarction after the shockwave therapy. LVEF, LVEDV and LVDd did not change significantly for 12 months after acute myocardial infarction. LVDd, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVG, left ventriculography.

Discussion

In this first-in-human study, we were able to demonstrate that low-energy extracorporeal cardiac SW therapy was feasible and may be effective to ameliorate adverse post-MI LV remodeling in patients with AMI. To the best of our knowledge, this is the first study that suggests the usefulness of the SW therapy in patients with AMI.

Effects of the shockwave therapy on postmyocardial infarction left ventricular remodeling

Although primary PCI substantially reduced the mortality of patients with AMI, LV remodeling still remains one of the unsolved issues in cardiovascular medicine. We have previously demonstrated that SW therapy ameliorates LV remodeling in a porcine model of AMI without reperfusion [7]. In the permanent model, the proximal segment (~15 mm in length) of the left circumflex coronary artery was ligated and was stripped to create AMI. As most patients with AMI receive emergency reperfusion therapy with either primary PCI or thrombolytic agents in the current clinical setting, we also examined the effects of the SW therapy on LV remodeling in a porcine model of coronary ischemia (90 min) and reperfusion and confirmed that the SW therapy also ameliorates LV remodeling in this AMI model [8]. On the basis of the promising results in these animal studies, we performed the present first-in-human study to examine the effects of SW therapy on LV remodeling in patients with AMI. We found that SW therapy could improve LV remodeling in patients with AMI.

To further evaluate the effects of SW therapy on LV remodeling after AMI, we compared LV volume and contractility between the SW and the historical control groups with a propensity score matching for age, peak level of CK, LVEF, and LVDd. Six months after AMI, LVEF was significantly higher in the SW group than in the historical control group, whereas there was no difference in LV volume between the two groups. These results also suggest that the SW therapy ameliorates LV remodeling in patients with AMI.

Potential mechanisms for the beneficial effects of shockwave therapy in patients with acute myocardial infarction

We have previously demonstrated that extracorporeal low-energy SW therapy upregulates the expression of vascular endothelial growth factor and increases capillary density in ischemic myocardium in a porcine model of chronic myocardial ischemia [4]. We also have demonstrated that the SW therapy improves myocardial

Table 2 Comparisons after a propensity score matching

	SW ($N=7$)	Historical control ($N=25$)	P value
Age (years)	65.0±7.3	67.3±12.8	0.59
Male	7 (100)	20 (80)	0.56
Peak-creatine kinase (U/l)	1770±1163	2103±910	0.40
BNP [median (range)]	36.3 (26.6–77.5)	109.2 (46.9–391.9)	0.004
Echocardiography at baseline			
LVDd (mm)	45.1±3.0	50.8±6.5	0.005
LVEF (%)	58.7±8.2	54.4±12.3	0.32
Echocardiography at 6 months after AMI			
LVDd (mm)	47.5±4.6	50.0±5.9	0.29
LVEF (%)	66.1±7.2	58.0±11.7	<0.05
Medications at discharge			
β-Blocker	7 (100)	18 (72)	0.3
ACE-I or ARB	7 (100)	25 (100)	1.0
Aldosterone antagonist	0 (0)	0 (0)	1.0
Statin	7 (100)	22 (88)	1.0
Follow-up (years)	4.7±3.1	6.0±2.0	0.34
Cardiovascular events and death			
Hospitalization owing to Cardiovascular events	0 (0)	4 (16)	0.55
In-stent restenosis of The culprit lesion of AMI	0 (0)	4 (16)	0.55
Cardiovascular death	0 (0)	0 (0)	1.0
All-cause death	0 (0)	3 (12)	1.0

Results are expressed as mean±SD and *n* (%).
ACE-I, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; SW, shockwave.

perfusion and symptoms in patients with refractory angina pectoris [5,6]. Furthermore, we demonstrated that the SW therapy enhances endothelial nitric oxide synthase activity and capillary density in the myocardium of the border zone in porcine models of AMI [7,8]. Capillary density in the border zone has been reported to be negatively correlated with infarct size at 1 month after AMI, suggesting the importance of adequate growth of the capillary microvasculature [12]. Also, myocardial edema and vasoconstriction are considered to contribute to no reflow phenomenon in the reperfused myocardium [13–15]. Thus, SW-induced enhancement of vasodilation and angiogenesis in the border zone could suppress LV remodeling in patients with AMI.

Inflammatory responses immediately after AMI accelerate wound healing in the infarcted myocardium [16]. However, prolonged and excessive inflammatory responses could delay tissue repair and enhance fibrotic changes, leading to adverse LV remodeling [17,18]. In this regard, we and others have recently reported that low-energy SW therapy suppresses infiltration of inflammatory cells and the release of proinflammatory cytokines early after AMI [16,19]. Thus, anti-inflammatory effects of low-energy SW, in addition to its angiogenic effects, may contribute to the beneficial effects of SW therapy on post-MI LV remodeling.

The lymphatic system plays a crucial role in the maintenance of tissue fluid balance and immune surveillance in most vascularized tissues [20]. AMI causes vascular hyperpermeability and lymphatic malfunction, which leads to myocardial edema [21]. Recently, it has been reported that targeted stimulation of cardiac lymphangiogenesis improved myocardial fluid balance and attenuated post-MI LV remodeling associated with reduced inflammation and fibrosis [22]. We have previously demonstrated that low-energy SW therapy enhances lymphangiogenesis in a rat model of secondary lymphedema [23]. Thus, the SW-induced lymphangiogenesis may contribute to the beneficial effects of the SW therapy in patients with AMI. Moreover, we have demonstrated that low-energy SW therapy enhances lymphangiogenesis, skin wound healing, and neuroprotection in addition to angiogenic and anti-inflammatory effects in various animal models and humans [23–27]. Thus, multiple mechanisms appear to be involved in the beneficial effects of the SW therapy on post-AMI LV remodeling.

A meta-analysis suggested that intracoronary bone marrow cell therapy might improve LV function and remodeling in patients with AMI [28]. The low-energy SW therapy has been reported to promote migration of bone marrow-derived mononuclear cells to the ischemic tissue and to promote differentiation into endothelial phenotype cells [29,30]. When applied to the ischemic tissues, SW therapy also enhances recruitment of circulating endothelial progenitor cells to the ischemic tissue via enhanced expression of stromal-derived factor-1, a key regulator of stem cell migration [31–33]. Thus, it is possible that SW-facilitated cell migration is also involved in the beneficial effects of the SW therapy on post-MI LV remodeling.

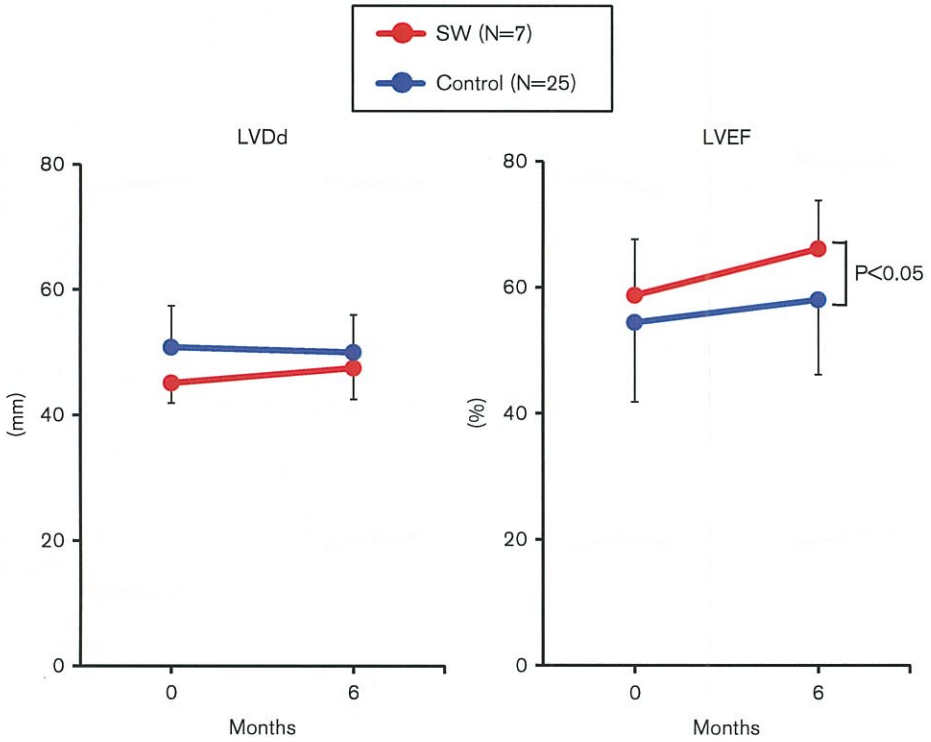
Optimal timing of the shockwave therapy

We have previously shown that the SW therapy ameliorated post-MI LV remodeling when started within 3 days after AMI but had no beneficial effects when started at 4 weeks after AMI [7]. Thus, the SW therapy should be started during the acute phase of AMI. On the basis of these findings, we started the SW therapy 48–72 h after the onset of AMI. However, the optimal timing of SW therapy remains to be further examined in future studies.

Study limitations

Several limitations should be mentioned for the present study. First, in the present pilot study, the number of patients was relatively small. Second, the present study was conducted in a single center in a nonrandomized manner. Thus, to confirm the beneficial effects of SW therapy on post-MI LV remodeling, a large-scale multicenter, randomized, placebo-controlled clinical trial is needed. Third, in the present study, we set strict

Fig. 3



Comparison between the SW and the control groups. Six months after acute myocardial infarction, although LVDd was comparable between the SW and the historical control groups, LVEF was significantly higher in the former compared with the latter. LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; SW, shockwave.

Table 3 Results of blood tests before and after each shockwave treatment session

	First session			Second session			Third session		
	Pre	Post	*P*	Pre	Post	*P*	Pre	Post	*P*
WBC	8813±1624	8050±1570	0.20	7389±1723	7673±1811	0.72	7130±1565	7881±3481	0.48
RBC	390.2±37.7	350±135.3	0.28	359.1±126.9	384.5±109.1	0.64	334.8±166.7	374.8±145.3	0.56
Hb	12.3±1.12	12.5±1.08	0.52	12.8±0.77	13.1±1.18	0.38	13.6±1.11	13.6±1.05	0.91
Hct	36.8±3.0	37.2±3.0	0.69	37.5±2.0	38.8±3.2	0.24	39.7±3.1	39.9±2.9	0.89
PLT	182.4±41.4	191.1±41.9	0.57	215.4±41.4	229.7±42.8	0.45	248.4±57.3	263.3±55.4	0.54
T-bil	0.88±0.23	0.77±0.18	0.30	0.67±0.19	0.68±0.17	0.94	0.77±0.19	0.63±0.16	0.43
AST	65.4±25.4	41.8±12.7	0.005	36.5±10.1	37.5±10.2	0.82	33.9±8.1	33.3±16.1	0.89
ALT	25.7±8.8	24.6±11.3	0.78	29.5±13.6	33.1±3.1	0.52	37.5±12.6	36.8±16.8	0.89
LDH	408±134.4	357.1±115.0	0.29	348.4±104.6	328.6±91.1	0.64	299.7±76.1	276.5±58.7	0.42
CK	351.3±217.9	176.8±122.1	0.012	127.7±83.6	101.67±56.7	0.39	96.7±61.7	78.0±59.6	0.46
CK-MB	26.4±20.1	14.5±5.4	0.048	12.0±4.0	9.2±2.9	0.08	8.9±2.5	8.4±3.0	0.70
BUN	10.6±2.4	10.6±3.1	0.95	11.3±2.3	11.7±1.9	0.73	12.3±2.3	13.2±3.2	0.42
Cre	0.83±0.2	0.82±0.16	0.92	0.76±0.15	0.81±0.14	0.38	0.78±0.15	0.86±0.16	0.18

Results are expressed as mean±SD.
Presession results show the results of blood tests performed in the morning of the day of each shockwave treatment. Postsession results show the results of blood tests performed on the following day of each shockwave treatment.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; Cre, creatinine; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; PLT, platelet; RBC, red blood cell; T-bil, total bilirubin; WBC, white blood cell.

exclusion criteria that excluded patients with a peak CK level of 4000 IU/l or above and those with congestive heart failure. It is known that adverse LV remodeling and resultant congestive heart failure are more frequently noted in patients with AMI with a greater extent of AMI [34]. Thus, clinical trials with patients with AMI with larger infarct size are also needed in the future. Finally, in the present study, we did not examine the detailed molecular mechanisms of the effects of the SW therapy. Although we have previously demonstrated that anti-inflammatory effects of the SW therapy may explain the beneficial effects of the therapy in porcine models of

AMI [7,8], this point also remains to be examined in future studies.

Conclusion

In the present first-in-human study, we were able to demonstrate that extracorporeal low-energy cardiac SW therapy is feasible and may be effective to ameliorate post-MI LV remodeling in humans, suggesting that the therapy could be a novel promising option to suppress LV remodeling after AMI as an adjunctive therapy to primary PCI.

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Conflicts of interest

There are no conflicts of interest.

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