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Original Article

Clinical study of cardiac shock wave treatment in patients with non-revascularized coronary heart disease

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Abstract: Objective: The aim of this study was to investigate the efficacy and safety of cardiac shock wave treatment (CSWT) in patients with non-revascularized coronary heart disease (nRCHD). Methods: A total of 87 nRCHD patients were randomly selected and divided into Group CSWT (62 cases, further subdivided into Group routine CSWT [A, 32 cases] and Group expanded CSWT [B, 30 cases]) and controls (Group CON [C, 25 cases]). Differences in clinical outcomes, cardiac perfusion, myocardial metabolism, and cardiac functional indexes were compared between these groups. Results: 1) No angina worsening, malignant arrhythmia, or other adverse reactions occurred during CSWT; 2) The secondary hospitalization rate in Group CSWT was less than that in Group CON; 3) Myocardial perfusion and metabolism, New York Heart Association functional class, Canadian Cardiovascular Society angina classification, Seattle Angina Questionnaire scores, 6-minute walking test results, and left ventricular ejection fraction (LVEF) were significantly improved with decreased nitroglycerin dosage in Group CSWT after treatment. Results were also better than those in Group CON during the same period ($P < 0.05$). Moreover, improvements in myocardial perfusion, myocardial metabolism, and LVEF in Group B were more significant than those in Group A ($P < 0.05$). Conclusion: 1) CSWT can be used in patients with complex coronary artery disease with/without prior revascularization; 2) Early CSWT can alleviate myocardial ischemic symptoms, improve myocardial perfusion and metabolism, improve coronary reserve, quality of life, and exercise tolerance, inhibit ventricular remodeling, and improve cardiac function. In addition, expanded CSWT is superior to routine CSWT.

Keywords: Coronary heart disease, angiogenesis, extracorporeal cardiac shock wave, clinical study

Introduction

Extracorporeal cardiac shock wave treatment (CSWT) has proven to be useful, as confirmed by *in vitro* experiments and in animal models, as well as in coronary artery disease (CAD) patients revascularized for myocardial ischemia [1-5]. Low-energy shock wave targeted therapy for CAD is a noninvasive, safe, and effective modality that promotes angiogenesis of ischemic myocardial capillaries, accelerates the development of collateral circulation, and relieves myocardial ischemia. It is an additional option for treatment of coronary heart disease (CHD) [5-9]. If its effectiveness and safety can be verified, CSWT may provide great social and economic benefits, relieving symptoms in non-revascularized CAD patients [10-13].

Patients and methods

General information

A total of 87 consecutive old myocardial infarction (OMI) patients that did not undergo revascularization were recruited in the Department of Cardiology, the First Affiliated Hospital of Kunming Medical University, between October 2008 and January 2011. Patients included 68 males and 19 females, aged 43-80 years (range, 66.80 ± 8.41), with a disease history ranging from 1 to 15 years. Of these, 62 patients, including 48 males and 14 females, aged 43-80 years (range, 67.03 ± 8.57), were randomly divided into Group A (32 patients, including 24 males and 8 females, aged 47-80 years [range, 68.31 ± 8.72], that underwent

routine CSWT, with each ischemic target receiving 9-point treatment) and Group B (30 patients, including 24 males and 6 females, aged 43-79 years [range, 65.67 ± 8.33], that underwent expanded CSWT, with each ischemic target receiving 25-point treatment). Group CON (25 controls, including 20 males and 5 females, aged 48-79 years [range, 66.24 ± 8.14]) received 9-point treatment without shock energy. This randomized, single-blind, controlled study compared changes between Group CSWT and Group CON, as well as between group A and group B. Inclusion criteria: At least one confirmed acute myocardial infarction (AMI) based on medical history, physical examinations, electrocardiograms (ECG), or myocardial necrosis markers. Diagnostic criteria for AMI were based on guidelines published by the European Society of Cardiology in 2012 [14]. All patients had a ≥ 3-month history of myocardial infarction. None had undergone coronary revascularization (thrombolysis, percutaneous coronary intervention [PCI], or coronary artery bypass grafting [CABG]) for the following reasons: contraindication to coronary revascularization (renal failure, thrombocytopenia, or gastrointestinal bleeding), failure of coronary revascularization, or patient refusal. Inclusion criteria included occasional chest pain, chest tightness, poor exercise tolerance, or hospitalization more than 3 times within one year for myocardial ischemia-related symptoms despite standard drug treatment, in addition to Canadian Cardiovascular Society (CCS) angina pectoris grade II or above, New York Heart Association (NYHA) functional class I-III, left ventricular ejection fraction (LVEF) > 30%, stable hemodynamics, and heart rate of 40-120 bpm.

Exclusion criteria: AMI within 3 months, prior PCI and/or CABG, cardiac thrombosis after heart transplantation, left atrial myxom, after heart valve replacement, hemodynamic instability (LVEF < 30%), NYHA class IV, chronic obstructive pulmonary disease, malignant tumors, or skin ulceration/infections near the chest wall treatment area. There were no statistical differences in age, sex, disease history, or other general characteristics among the 3 groups (**Table 1**). This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Kunming Medical University. Written informed consent was obtained from all participants.

Localization of myocardial ischemia and viable myocardial segment

Single photon emission computed tomography (SPECT) (Discovery VH Millennium; General Electric, CT, USA) was used for dual-isotope myocardial imaging (^{99m}Tc-methoxy-isobutyl-isonitrile [MIBI] perfusion and fludeoxyglucose (^{18}F) [FDG] metabolism). Based on criteria recommended by the American Heart Association (AHA), the left ventricle was divided into 17 segments to analyze perfusion and metabolism [15] for myocardial viability. Semi-quantitative scoring was used for myocardial perfusion and metabolic isotope uptake [16]: normal = 1 point, sparse = 2 points, apparently sparse = 3 points, and defect = 4 points. SPECT criteria for assessing myocardial viability included ^{99m}Tc-MIBI and (^{18}F) FDG uptake scores ≤ 2 points, or sparse ^{99m}Tc-MIBI uptake with the scores increased for (^{18}F) FDG by ≥ 1 point (severely sparse perfusion or defect with good metabolism considered a perfusion/metabolism mismatch). Non-viable myocardium: ^{99}mTc-MIBI and (^{18}F) FDG uptake exhibited severely sparse perfusion or defects, scored as 3 or 4 points. Radioactivity scores of the 17 perfusion and metabolic imaging segments were then added. Total scores reflected myocardial perfusion and metabolic levels.

Specific implementation method for CSWT

Informed consent for CSWT was obtained before inclusion in this study. A MODULITH SLK instrument (STORZ MEDICAL, Switzerland), equipped with an on-board real-time ultrasonic probe (ALOKA SSD-900) with ECG monitoring, was used for CSWT, while patients continued standard drug treatment and lifestyle intervention. During surgery, patients remained conscious and were placed in a stable supine position. The chests were exposed. The ECG monitor was connected (defibrillator and rescue drugs were prepared simultaneously). The on-board real-time ultrasound probe was first used to locate the target myocardium (dual-isotope SPECT inspection revealed the viable myocardial ischemic segment), the contact between the water sac and chest wall was reduced, and the shock wave release button was depressed. Shock wave energy was triggered and released

Table 1. Comparison of baseline information between Group CSWT and CON

Item	A (n = 32)	B (n = 30)	CON (n = 25)	*P*
General information				
Age (years)	68.31 ± 8.72	65.67 ± 8.33	66.24 ± 8.14	NS
M/F [n (%)]	24 (75.0)	24 (80.0)	20 (80.0)	NS
	/8 (25.0)	/6 (20.0)	/5 (20.0)	NS
Disease history (years)	6.0 (5.0, 10.0)[a]	6.5 (5.0, 10.5)[a]	5.0 (4.5, 10.0)[a]	NS
Smoking [n (%)]	11 (34.4)	8 (26.7)	7 (28.0)	NS
BMI (kg/m^2)	23.49 ± 1.53	24.04 ± 2.00	23.01 ± 1.65	NS
Hypertension [n (%)]	21 (65.6)	18 (60.0)	16 (64.0)	NS
DM [n (%)]	13 (40.6)	15 (50.0)	11 (44.0)	NS
Hyperlipidemia [n (%)]	17 (53.1)	15 (50.0)	13 (52.0)	NS
MI site [n (%)]				NS
Anterior wall	17 (53.1)	14 (46.7)	11 (44.0)	
Inferior wall	10 (31.3)	8 (26.7)	9 (36.0)	
Anterior + inferior wall	2 (6.3)	3 (10.0)	2 (8.0)	
Anteroposterior wall	1 (3.1)	3 (10.0)	2 (8.0)	
Lateral wall	2 (6.3)	2 (6.7)	1 (4.0)	
NYHA cardiac function grade [n (%)]				NS
I	4 (12.5)	6 (20.0)	5 (20.0)	
II	17 (53.1)	14 (46.7)	11 (44.0)	
III	11 (34.4)	10 (33.3)	9 (36.0)	
CCS angina grade [n (%)]				NS
II	13 (40.6)	11 (36.7)	11 (44.0)	
III	19 (59.4)	19 (63.3)	14 (56.0)	
Standard medication for CHD [n (%)]				
AP [n (%)]	13 (40.6)	10 (33.3)	11 (44.0)	NS
ACEI/ARB [n (%)]	20 (62.5)	22 (73.3)	15 (60.0)	NS
ASP [n (%)]	24 (75.0)	18 (60.0)	19 (76.0)	NS
BB [n (%)]	23 (71.9)	24 (80.0)	17 (68.0)	NS
CCB [n (%)]	17 (53.1)	14 (46.7)	14 (56.0)	NS
S [n (%)]	22 (68.8)	19 (63.3)	17 (68.0)	NS
N [n (%)]	24 (75.0)	22 (73.3)	19 (76.0)	NS
D [n (%)]	12 (37.5)	9 (30.0)	10 (40.0)	NS

Note: M: male; F: female; BMI: body mass index; DM: diabetes mellitus; MI: myocardial infarction; NYHA: New York heart association; CCS: Canadian Cardiovascular Society; AP: antiplatelet; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor antagonist; ASP: aspirin; BB: beta blockers; CCB: calcium channel blockers; S: statins; N: nitrates; D: diuretics; a: quartile method; NS: $P > 0.05$.

Table 2. Comparison of myocardial necrosis markers between different groups before and after treatment

Group	Time point	CK (IU/L)	CK-MB (IU/L)	CTNI (ng/mL)
A (n = 32)	Before treatment	79.35 ± 9.84	8.07 ± 1.92	0.07 ± 0.02
	2nd day of 3rd treatment	77.31 ± 9.86	9.03 ± 1.79	0.06 ± 0.02
	2nd day of 6th treatment	80.21 ± 9.67	8.61 ± 1.71	0.07 ± 0.01
	2nd day of 9th treatment	75.84 ± 9.26	8.22 ± 1.76	0.06 ± 0.02
B (n = 30)	Before treatment	76.17 ± 8.87	7.82 ± 1.80	0.08 ± 0.01
	2nd day of 3rd treatment	78.37 ± 8.90	8.25 ± 1.78	0.08 ± 0.01
	2nd day of 6th treatment	75.72 ± 8.76	8.60 ± 1.74	0.07 ± 0.01
	2nd day of 9th treatment	75.21 ± 8.49	7.70 ± 1.79	0.07 ± 0.01

Note: $P > 0.05$.

according to the R wave of the real-time surface ECG in the absolute refractory period. Shock wave energy was increased up to 0.09 mJ/mm^2 if the patient perceived no chest pain or discomfort. Group A received 9-point treatment (bi-combination of 1, 0, and +1, respectively), while Group B rece-

ived 25-point treatment (bi-combination of 2, -1, 0, +1, and +2, respectively). Both shock wave treatment programs provided 200 hits/points, 3 times/week, with rest on days 1, 3, and 5 during 1 (1 week of treatment each month, followed by 3 weeks of rest during a 3-month treatment course, for a total of 9 sessions) [3, 11, 17]. Group CON received simulated 9-point treatment at each ischemic target, while shock wave energy was not applied. Vital signs were closely monitored and recorded during treatment. Any abnormalities were treated promptly. Any patient that underwent PCI/CABG during follow-up was removed from the study.

Detection of myocardial necrosis markers

Peripheral fasting venous blood was sampled at different time points (1 day before treatment and the second day of the 3rd, 6th, and 9th treatments) for myocardial necrosis markers using a chemiluminescence detector (ADVIA CENTAUR CP; Siemens, Germany). Markers included serum creatine kinase (CK, reference range: 14-190 IU/L), creatine phosphokinase isoenzyme (CK-MB, reference range: 0-25 IU/L), and troponin I (cTnI), reference range: 0-0.14 ng/mL).

Cardiac ultrasonographic indexes

Left ventricular end-diastolic diameter (LVEDD) and LVEF were assessed using echocardiography (ViViD7; General Electric, probe frequency 2.5 MHz, USA) at different time points (before treatment and at months 3, 6, and 9 during follow-up) to assess left ventricular function.

Assessment of clinical indexes

Based on CCS angina grade, NYHA functional class, and Seattle Angina Questionnaires (SAQ), patients were assessed for nitroglycerin dosage, 6-minute walking test (6MWT) results, rehospitalization rates, recurrent myocardial infarction rates, and mortality.

Follow-up

All subjects were closely monitored and followed up as outpatients or inpatients, or by telephone, at intervals of not less than 12 months. Acute heart failure, worsening heart failure, frequent angina, and recurrent myocardial infarction during follow-ups were promptly treated.

Statistical analysis

SPSS 15.0 software was used for analysis, with $P < 0.05$ indicating statistical significance. Measurement data are expressed as mean ± standard deviation. Intergroup comparisons used the group t-test and subgroup comparisons used analysis of variance and the paired q-test. Count data are expressed as rates. Intergroup comparisons used the group Chi-squared test. Non-normally distributed data are expressed as medians (quartile). Intergroup comparison used the rank sum test. The Kruskal-Wallis test was used to compare data among multiple groups, with $P < 0.05$ indicating statistical significance for inclusion in a regression equation.

Results

Comparison of myocardial necrosis markers

Intragroup comparisons of CK, CK-MB, and cTnI, at different time points, and paired tests between Groups A and B, at the same time point, showed no statistical differences ($P > 0.05$, **Table 2**).

Comparison of clinical indicators

NYHA class, CCS angina grade, SAQ scores, and 6MWT were improved, while the nitroglycerin dose was reduced in Group CSWT at 3, 6, and 12 months after treatment ($P < 0.05$). The same indexes showed improvement in Group B, compared with Group A, after 6 months of treatment. At month 12 of follow-up, CCS angina grade was improved and nitroglycerin dosage was reduced in Group B, compared with Group A ($P < 0.05$). The same indexes showed significant improvement in Group CSWT, compared with Group C, in months 3, 6, and 12 of follow-up ($P < 0.05$). There were no significant differences in paired comparisons of the above indexes in Group C ($P > 0.05$, **Table 3**), except that the 6MWT result was worse in month 12 ($P < 0.05$).

Comparison of cardiac ultrasound indexes

There were no significant differences in LVEF (%) and LVEDD (mm) among the 3 groups at month 0 ($P > 0.05$). There was significant improvement in LVEF in Groups A and B in months 3, 6, and 12, compared with month 0 ($P < 0.05$). LVEF in Group B in month 12 was significantly improved, compared to that in

Table 3. Comparison of clinical indicators among the three groups at different time points

Group	Time point	NYHA classification	CCS angina classification	SAQ score (points)	6MWT (m)	Nitroglycerin dosage (times/week)
A (n = 32)	Month 0	2.22 ± 0.66	2.59 ± 0.50	68.66 ± 11.05	346.78 ± 82.42	2.00 (0.25, 3.00)
	Month 3	1.47 ± 0.50*	1.63 ± 0.49*	75.63 ± 8.36*	409.34 ± 66.27*	1.00 (0.00, 2.00)*
	Month 6	1.38 ± 0.49*	1.44 ± 0.50*	77.72 ± 7.20*	425.16 ± 59.37*	1.00 (0.00, 1.00)*
	Month 12	1.28 ± 0.46*	1.41 ± 0.56*	75.47 ± 6.76*	447.81 ± 55.48*	1.00 (0.00, 1.00)*
B (n = 30)	Month 0	2.13 ± 0.73	2.63 ± 0.49	66.57 ± 10.13	362.20 ± 83.60	2.50 (1.00, 3.00)
	Month 3	1.50 ± 0.63*	1.60 ± 0.56*	73.53 ± 8.32*	411.70 ± 76.56*	2.00 (0.75, 2.00)*
	Month 6	1.13 ± 0.35$^{*,\#,\Delta}$	1.17 ± 0.38$^{*,\#,\Delta}$	82.20 ± 5.46$^{*,\#,\Delta}$	459.57 ± 57.43$^{*,\#,\Delta}$	0.00 (0.00, 1.00)$^{*,\#,\Delta}$
	Month 12	1.10 ± 0.31$^{*,\#}$	1.07 ± 0.25$^{*,\#,※}$	78.50 ± 5.67$^{*,\#}$	454.83 ± 56.18$^{*,\#}$	0.00 (0.00, 1.00)$^{*,\#,※}$
CON (n = 25)	Month 0	2.16 ± 0.75	2.56 ± 0.51	69.44 ± 9.18	368.40 ± 77.39	2.00 (1.00, 3.00)
	Month 3	2.28 ± 0.79	2.32 ± 0.75	67.52 ± 8.46	344.88 ± 66.45	2.00 (1.00, 3.50)
	Month 6	2.04 ± 0.89	2.16 ± 0.69	65.88 ± 7.81	335.72 ± 60.19	2.00 (1.00, 3.00)
	Month 12	2.12 ± 0.78	2.20 ± 0.71	67.92 ± 7.75	320.60 ± 67.36*	1.00 (1.00, 3.00)

Note: Intragroup comparison with the data in Month 0, $^{*}P < 0.05$; intragroup comparison with the data in Month3, $^{\#}P < 0.05$; compared with the data in Group A in Month 6, $^{\Delta}P < 0.05$; compared with the data in Group A in Month 12, $^{※}P < 0.05$.

Table 4. Comparison of cardiac ultrasound indexes among the three groups at different time points

Group	Time point	LVEF	LVEDD
A (n = 32)	Month 0	52.84 ± 6.75	56.66 ± 4.74
	Month 3	56.81 ± 7.31*	58.56 ± 3.64
	Month 6	57.53 ± 6.79*	58.72 ± 4.08
	Month 12	59.34 ± 5.84*	58.43 ± 3.47
B (n = 30)	Month 0	50.63 ± 5.98	58.23 ± 5.76
	Month 3	59.60 ± 7.09*	58.70 ± 5.52
	Month 6	60.37 ± 6.45*	59.50 ± 5.24
	Month 12	62.50 ± 5.58$^{*,\#}$	58.87 ± 4.70
CON (n = 25)	Month 0	52.32 ± 6.55	56.92 ± 6.03
	Month 3	52.76 ± 6.17	58.28 ± 5.69
	Month 6	50.64 ± 4.83	59.36 ± 6.01
	Month 12	50.20 ± 4.46	61.56 ± 5.27*

Note: Intragroup comparison with the data in Month 0. $^{*}P < 0.05$; compared with the data in Group A in Month 12, $^{\#}P < 0.05$.

Group A ($P < 0.05$). There were no significant differences in LVEDD between Groups A and B at different time points or in intragroup comparisons ($P > 0.05$). There were no significant differences in LVEF in Group C at different time points ($P > 0.05$), but LVEDD in Group C, at month 12, was significantly greater than that at month 0 ($P < 0.05$). Paired comparisons at other time points showed no statistical differences ($P > 0.05$, **Table 4**).

Comparison of myocardial perfusion and metabolism

Groups A, B, and C underwent evaluation at a total of 544, 510, and 425 myocardial segments, respectively. There were no statistical differences in paired intergroup comparisons of segments with ischemia or abnormal metabolism, as well as in comparisons of total myocardial perfusion and total myocardial metabolism scores, before treatment (month 0) ($P > 0.05$). The same indexes in Group CSWT at month 12 were significantly improved, compared with those at months 0 and 3 ($P < 0.05$), with no significant differences compared with those at month 6 ($P > 0.05$). The same indexes in Group B at months 3, 6, and 12 were all improved, compared with those in Group A ($P < 0.05$). Furthermore, all indexes in Group CSWT, at different time points, were improved, compared to those in Group C ($P < 0.05$). The same indexes in Group C, at month 12, were worse than those at month 0 ($P < 0.05$, **Table 5**).

Comparison of mortality, recurrent MI rates, and rehospitalization rates

One patient with an old extensive anterior-wall MI in Group A died of ventricular tachycardia and fibrillation, induced by acute diarrhea with hypokalemia, at month 10. There were no deaths in Group B. One patient in Group C died suddenly in month 10 due to malignant ventricular arrhythmia (ventricular tachycardia/ventricular fibrillation) and cardiac arrest. One patient in Group C had an AMI in month 9 and underwent emergency CABG + PCI. There were no recurrent MI cases in Groups A and B and there were no differences in mortality and recurrent MI rates among the 3 groups ($P >$

Table 5. Comparison of myocardial perfusion and metabolism among the three groups at different time points

Group	Time point	Ischemia (n)	Abnormal metabolism (n)	Total myocardial perfusion score (points)	Total myocardial metabolism score (points)
A (n = 32) (544 segments)	Month 0	289 (53%)	243 (45%)	35.03 ± 4.81	30.22 ± 4.38
	Month 3	245 (45%)*	172 (32%)*	30.09 ± 3.79*	25.56 ± 2.74*
	Month 6	211 (39%)*,Δ	139 (26%)*,Δ	27.31 ± 3.27*,Δ	23.53 ± 2.69*,Δ
(n = 30) (510 segments)	Month 12	199 (39%)*,Δ	132 (25%)*,Δ	26.53 ± 3.32*,Δ	23.09 ± 2.60*,Δ
B (n = 30) (510 segments)	Month 0	242 (47%)	204 (40%)	32.63 ± 5.49	28.60 ± 4.22
	Month 3	173 (34%)*,#	133 (26%)*,#	27.60 ± 4.05*,#	23.97 ± 3.09*,#
	Month 6	136 (27%)*,Δ,#	92 (18%)*,Δ,#	24.23 ± 2.64*,Δ,#	21.47 ± 2.01*,Δ,#
	Month 12	127 (25%)*,Δ,#	82 (16%)*,Δ,#	22.90 ± 2.41*,Δ,#	20.67 ± 1.75*,Δ,#
C (n = 25) (425 segments)	Month 0	198 (47%)	160 (38%)	32.52 ± 5.83	28.36 ± 4.33
	Month 3	222 (52%)	190 (45%)	33.80 ± 5.80	29.64 ± 4.82
(n = 24) (408 segments)	Month 6	219 (54%)	186 (46%)	34.52 ± 6.07	29.72 ± 5.22
(n = 22) (374 segments)	Month 12	214 (57%)*	183 (50%)*	37.08 ± 5.18*	32.20 ± 4.81*

Note: Intragroup comparison with the data in Month 0, *P < 0.05; intragroup comparison with the data in Month 3, ΔP < 0.05; compared with the data in Group A in the same period, #P < 0.05.

Table 6. Comparison of mortality, recurrent MI rates, and rehospitalization rates between different groups

Group	Dead patient	Recurrent MI	rehospitalization
A (n = 32)	1	0	7
B (n = 30)	0	0	5
C (n = 25)	1	1	14*

Note: Intragroup comparison with the data, *P < 0.05.

0.05). A total of 26 patients were re-hospitalized due to MI-related symptoms, including 7 patients in Group A, 5 in Group B, and 14 in Group C. A comparison of rehospitalization rates between Groups A and B showed no significance ($P > 0.05$), but a comparison between Groups A/B and Group C showed statistical significance ($P < 0.05$, **Table 6**).

Discussion

Efficacy of CSWT in CAD

1) Improved myocardial perfusion and metabolism. Because patients selected in this study had been definitively diagnosed with MI, only a very small proportion underwent coronary angiographies with failure of coronary revascularization. However, most patients did not undergo coronary angiographies, thus specific statistical analysis of coronary artery disease classification was not performed. Dual-isotope SPECT was used to evaluate myocardial ischemia and perfusion, comparing changes in myocardial ischemia, perfusion, and other important indexes before and after CSWT. On the basis of high specificity and sensitivity of ^{99m}Tc-MIBI and (^{18}F) FDG dual-isotope SPECT myocardial imaging for detection of viable myocardium in MI patients [18, 19], it was found that myocardial perfusion and metabolism in Group A and B at months 3, 6, and 12 were significantly improved, compared to those in Group CON and at month 0. Results suggest that both CSWT treatment protocols can improve myocardial perfusion and metabolism and that efficacy can be maintained for at least 1 year. Efficacy in Group B was superior to that in Group A, which may be because expanded shock wave energy can increase the unit treatment area, thus promoting capillary angiogenesis in an ischemic myocardium. Although Group CON received the same standard medication and lifestyle management, these patients still exhibited a decreasing trend in myocardial perfusion and metabolism during follow-ups. This suggests that CAD patients without revascularization or CSWT may still be at risk for progressive myocardial ischemic injuries.

2) Improvement in clinical symptoms. Results of previous studies have shown that CSWT can improve NYHA functional class, CCS angina grade, quality of life, and exercise tolerance, as well as decreased nitroglycerin dosage [3, 7, 10, 20]. Previous results are consistent with present results. However, patients enrolled in this study did not undergo revascularization, suggesting that CSWT is suitable and beneficial not only for end-stage/non-end-stage CAD patients (through improvement in angina symptoms and quality of life), but also for non-revascularized CAD patients.

There were no statistical differences in usage rates of aspirin, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta blockers, and statins among the A, B, and C subgroups in this study. Over 60% of the patients in the 3 subgroups were treated with standard secondary prevention of coronary heart disease, but efficacy was poor. This study aimed to explore the efficacy of standard drug treatment-based CSWT treatment in selected patients, comparing the efficacy with the control group. Present results suggest that both CSWT protocols can effectively improve angina symptoms, reduce nitroglycerin dosage, and improve quality of life and exercise tolerance. Results can be maintained for at least 1 year. Furthermore, because the ischemic target area in Group B was expanded, the corresponding improvement in myocardial perfusion and metabolism was also more obvious. Capillary angiogenesis was also greater. As more time was required to develop the capillary network, Group B exhibited more significant improvements in cardiac indexes after month 6. CCS angina grade and nitroglycerin dosage, which have greater specificity and sensitivity for the degree of CAD, still exhibited significant improvement at month 12. Results suggest that the 25-point CSWT has greater efficacy than the 9-point CSWT.

3) Inhibition of ventricular remodeling and improvement in cardiac function. A Japanese double-blind controlled study of CSWT in patients with complex CHD found that LVEF and stroke volume were significantly improved, compared to those in the placebo group [7]. However, the change in left ventricular end-diastolic volume (LVEDV) was not obvious. Results of this study indicate that LVEDD in Groups A and B showed no significant changes before and after treatment, which may be related to the longer OMI course in the enrolled patients (average, 6.0 years), so that ventricular remodeling was irreversible. However, this also suggests that CSWT can effectively inhibit the progression of ventricular remodeling for at least 1 year. LVEDD in Group CON, at month 12, was significantly greater than that at month 0. Differences were statistically significant. This suggests that, although medication and lifestyle intervention can inhibit ventricular remodeling in the short term, such methods cannot effectively inhibit the progression of ventricular remodeling or stop ventricular enlargement in the long term. The current study showed that both CSWT protocols can effectively improve LVEF and maintain improvement for at least 1 year, while Group CON showed no significant changes in LVEF during follow-up. This may be related to improved perfusion and metabolism of ischemic myocardium. With improved myocardial systolic function, the corresponding end-systolic volume can be significantly increased and LVEF is, thus, significantly increased. After expanding the treatment range, the degree and extent of myocardial perfusion and metabolism were significantly improved, compared with those in Group A, thus achieving stable improvement in LVEF, even at month 12, compared with that in Group B ($P < 0.05$). Results suggest that the efficacy of expanded CSWT for cardiac systolic function is better than that with conventional CSWT.

Research results reported in 2013 were based on randomized and double-blind controlled studies. The average follow-up was 1 year and the number of cases was small. The studies applied dual-isotope SPECT to evaluate myocardial perfusion and metabolism, in addition to clinical indexes and echocardiography. The conventional 9-point shock program was normally used. This study expanded the sample size and used a randomized single-blind controlled trial. The patients showed better compliance. Based on the results reported in 2013, the patients were further sub-grouped, with the CSWT group divided into a conventional shock wave group and an expanded shock wave group. Indicators included dual-isotope SPECT to evaluate myocardial perfusion and metabolism, clinical indicators, myocardial necrosis markers (to evaluate safety), and ultrasound.

The study found that, compared with the conventional 9-point program, the expanded 25-point CSWT program can improve myocardial perfusion, myocardial metabolism, and cardiac function (clinical and ultrasound indicators), without damage to the myocardium. As a study limitation, coronary angiography or cardiac magnetic resonance imaging should be performed to assess efficacy before and after CSWT.

Mechanisms of CSWT

CSWT applies *in vitro* low-energy physical shock waves to the myocardium, which can produce mechanical shear forces, cavitation effects, ultra-fine air flow, or intrusive explosive force in the cardiomyocytes. This leads to changes in subcellular structures, increased permeability of cell membranes, micro-vessel rupture, and increased vascular endothelial gaps. The stimuli will upregulate expression of vascular endothelial growth factor mRNA and fms-like tyrosine receptor-1, fibroblast growth factor, endothelium-derived nitric oxide synthase, insulin-like growth factor, mature platelet-derived growth factor, and transforming growth factor beta. Thus, cardiac vascular permeability is increased and the migration and proliferation of endothelial cells will lead to the formation of new blood vessels [21-25]. In addition, locally secreted stromal cell-derived factor-1 can promote chemotaxis and mobilize endothelial progenitor cells in the circulation, causing them to migrate, adhere to, and invade ischemic tissues. This is followed by *in situ* development of mature vascular endothelial cells involved in neovascularization [26, 27], as blood flow in the target area is increased. At the same time, anti-inflammatory activity and inhibition of ventricular remodeling may occur as mechanisms by which CSWT treats CHD.

Safety of CSWT

Studies have reported good tolerance to CSWT in CHD patients. This study showed that patients in Group CSWT showed no worsening of angina or heart failure, bleeding, embolism, malignant arrhythmia (ventricular tachycardia/ventricular fibrillation), or other complications. Furthermore, blood pressure, heart rate, and oxygen saturation were not significantly affected. The energy delivered by CSWT is only one-tenth that of extracorporeal shock-wave lithotomy, which is also performed during the absolute refractory period using ECG trigger mode. No anesthesia, thoracotomy, or intervention is needed, resulting in patient acceptance. In this study, treatment times, extent, and energy intensity in Group B were significantly higher than those in Group A. However, neither of the CSWT protocols increased myocardial necrosis markers, suggesting that CSWT causes no damage.

In short, although the sample size in this study was small and the follow-up time was short, CSWT can probably mitigate MI-related symptoms in CAD patients, improve cardiac function, inhibit ventricular remodeling, and improve quality of life and exercise tolerance, while reducing the risk of sudden death. CSWT is a safe, effective, and non-invasive means of promoting angiogenesis in CHD.

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Disclosure of conflict of interest

None.

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