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Cardiac shock wave therapy shows better outcomes in the coronary artery disease patients in a long term

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Abstract. – OBJECTIVE: Almost all the past CSWT studies show the beneficial effects on CAD patients in a maximum duration of 1-year follow-up. The aim of this study was to evaluate the actual CSWT effects in 6 years follow-up period.

PATIENTS AND METHODS: The subjects were selected exclusively on the basis of inclusion criteria. The total number of patients was 52, out of which control group (n = 11) and the shock wave group (SW group, n = 41) was selected.

RESULTS: The wall motion, MPI, nitrate dosage, NYHA classification, SAQ scores, CCS grading, 6 MWT were markedly improved in the long-term (6 years) follow-up for SW group than the control group.

CONCLUSIONS: Following 6 years of follow-up, the CSWT provided agreeable results that improved myocardial function and quality of life in comparing to the month 0 and the control group. These outcomes advise that on a long-term (72 months) CSWT shows better parameters than the control group. These findings highlight that CSWT can improve clinical symptoms, morphology, functions of the heart and quality of life in patients with CHD than the patients just on drug therapy for a long-term.

Key Words:
Shock wave therapy, Angina pectoris, Myocardial infarction, Perfusion.

Abbreviations

CSWT: cardiac shock wave therapy; NYHA: New York heart association; PSSR: peak systolic strain rate of the regional wall motion; MPI: myocardial perfusion imaging; 6MWT: 6-minute walk test; CAD: coronary artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; LVEF: left ventricular ejection fraction; EPCs: endothelial progenitor cells; SDF-1: stromal-derived factor 1; LV: left ventricle; EDV: end diastolic volume; ESV: end systolic volume. CCS: Canadian Cardiology Society for the Grading of the Angina; SAQ: Seattle angina questionnaire.

Introduction

Coronary artery disease (CAD) is the most common result of cardiovascular atherosclerotic disorder and the leading cause of ischemia, infarction and death in the developed countries. CAD is resulted due to the lipid-filled plaque due to hyperlipidemia leading to the thickening of the artery wall, therefore, reducing the size of the inner lumen of the wall which ultimately partially blocks the supply of the oxygen in the heart muscle resulting in metabolic products accumulation i.e. ischemia[1,2] which eventually result in coronary artery stenosis. CAD patients usually suffer from refractory angina and are treated with medications, PCI and CABG. But the patients with end-stage CAD, refractory angina and with failures of PCI are not usually eligible for multiple surgical interventions. Different treatment modality increases myocardial perfusion in end-stage CAD and refractory angina. Some therapy induces angiogenesis by injecting mitogens into the myocardium layer or by use of progenitor cells.

Shock wave therapy has been used in the past in renal calculi and orthopedics which proved to be effective in most of the cases[3,4]. The shock wave is an acoustic wave, entering with the speed of water of ultrasound through body tissue. It is a single pressure pulse with a needle-like positive spike < 1 microsecond in duration and up to 100 MPa in amplitude, followed by a tensile part of several microseconds with lower amplitude[5]. Past studies with animal models of CAD showed that CSWT at approximately ten percent of the energy used for lithotripsy in renal stones could improve LV size, EF, EDV, and myocardial blood exchange[5]. Myocardial ischemia or infarction are the results of coronary artery diameter reduction or occlusion by atheroma or plaque that affect all cardiac cells, which

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leads to the blockage of blood flow and results in necrosis which eventually can result in the CAD or the heart failure[6]. Recent researches[7] show that shock waves provide a new and non-invasive technique to neo vascularization and angiogenesis with just 10% of energy output of lithotripsy. All of the CSWT researches till date only gave the result of maximum 1-year follow-up of the patients.

Thus, the purpose of this clinical experiment was to evaluate long-term outcomes of CSWT regarding cardiac functions and the quality of life in CAD patients.

Patients and Methods

This clinical research was approved by the Institutional Review Board and Ethical Committee of the 1st Affiliated Hospital of the KMU (Kunming Medical University), and all patients signed written consent for participation in the clinical study and research undertaken by the 1st Hospital of KMU. Patients were from the 1st Affiliated Hospital of the KMU with diagnosed CAD.

Inclusion Criteria

Patients were selected for the clinical study and the 6-years follow-up if they met any 1 of the following criteria. (1) Computed tomography coronary angiography (CTCA) or CA referring coronary artery stenosis. (2) Sonogram resulting more than 50% of infarction. (3) Angina or refractory angina not responding to the drug therapy. (4) NYHA classification 1 or higher than 1. (5) CAD confirmed by the sonogram and imaging examination and, at least, more than 2 weeks after surgical intervention or 1 month after AMI.

Exclusion Criteria

Patients were excluded from the clinical study if they had any of the following: (1) Acute Myocardial Infarction (AMI) or surgical procedures of the heart before the 1 month of the clinical study. (2) Heart transplantation surgery in the past. (3) History of double valve replacement surgery or single valve replacement surgery. (4) LVEF < 30%. (5) Ventricular Fibrillation (VF) or with HR < 40 bpm or > 120 bpm. (6) Chronic skin diseases like infection, ulceration, eczema in the area to be given shock waves. The patients were divided into 2 groups namely control group and shock wave group (SW group). The management of all the patients was strictly in accordance with the related mainland China and European guidelines of CAD/CHD management initiated in 2007. (1) The control group (n = 11) was designed only for 11 patients as it was 72 months study who received all the treatment modalities except CSWT treatment. (2) The SW group (n = 41) received additional cardiac shock wave therapy and was monitored till 72 months. One treatment session was 9 times, 1 week 3 times given on 1, 3, and 5th day of a week.

Examination

Some of the examinations were done under dobutamine. Dobutamine Stress Echocardiography (DSE) was done if patients result showed vascular lesion in the imaging analysis. M-type echocardiography allows pre-analysis of wall motion which can be unveiled as an M-mode echocardiography. Myocardial layer were demarcated as the 2 neighboring abnormal layers with enhancement in contraction after dobutamine loading (reduction ≥ 1 point)[8]. PSSR technique was elicited for resting and loading (dobutamine) conditions[9,10]. Before shock wave treatment, echocardiography under dobutamine loading condition and radionuclide imaging echocardiography were used to trace the ischemic and infarcted areas in each subject. Initial IV dobutamine does at the rate of 5-12 μg/kg/min was injected, and the rate was improved to 30-40 μg/kg/min if regional echo wall motion abnormalities could not be illustrated. Echo wall motion was calculated by wall motion score index (WMSI). Tissue Doppler was used to analyze peak PSSR under baseline and dobutamine stressed situations. MPI was also calculated under resting and dobutamine stress conditions. MPI and the grading system was in accordance to the American Society of Nuclear Cardiology (ASNC)[11]. An upsurge of 1 or increase in more than 1 point in Myocardial Perfusion Imaging (MPI) compared to the baseline under both resting and dobutamine stress situations was taken as the criteria for tissue blood flow improvement in the myocardium. Six-minute walks test or 6MWT-patients were asked to walk for 6 minutes without any physical assistance and the distance covered was measured. The test was performed at the fastest speed possible. If patients encountered any difficulty, it was stopped and the maximum distance covered was recorded. The control group was not given any shock wave therapy but was under regular medications and other treatment modalities and regular follow-up

for 72 months. SW group was additionally given CSWT therapy. If the subject was comfortable with no chest pain or tightness, SW energy was raised subsequently. In total, eighteen hundred shock waves shots were given for each infarcted or ischemic segment (diagnosed by previous imaging or preoperative procedures).

Follow-up

Patients were called for follow-up at 3, 6, 12, 24, 36, 48, 60 and 72 months (6 years). Cardiologists were not aware of the patients treatment modalities either control group or shock wave group. We evaluated NYHA functional classification, SAQ, 6MWT. Echocardiography was done to illustrate LVDd, EDV, ESV, LVEF, echo wall motion analysis under baseline (resting) and dobutamine stress conditions (M-mode), SR similarly under baseline (resting) and dobutamine stress conditions, MPI (Myocardial Perfusion Imaging) under both baseline and stress conditions were calculated.

Statistical Analysis

Data were calculated as (mean ± SD) for data with a normal distribution, for data of abnormal distribution represented as median with interquartile range and as number (%) for data with categorical distribution. Groups differences were calculated by one-way ANOVA Kruskal-Wallis (KW) test. Levene's test for equality of variances was done to illustrate p-value. $p < 0.05$ represented statistically significant values. SPSS 19 software (SPSS Inc., Chicago, IL, USA) was used for the analysis of data.

Results

A total of 52 patients who met the inclusion criteria were enrolled in the clinical study. Patients' characteristics are illustrated in Table I. The 52 patients were divided into control group (n = 11) and shock wave group (n = 41). The average age in the control group and SW group was 71 ± 6.52 and 63.4 ± 10.8 respectively with no significant differences. In the control group (n = 11), all patients accomplished 72 months of follow-up. In SW group (n = 41), 38 patients completed the 72 months follow-up because there were 3 mortality at 12, 36, and 60 months respectively. All 3 deaths were due to end-stage coronary heart disease resulting in heart failure. Thus, 38 patients finished the full CSWT therapy and 72 months follow-up without major arrhythmia, heart failure, shortness of breath, hemorrhage, embolism, or cardiogenic shock. In our study, no patients had any major side effects during the 6 years follow-up period. Only10 patients in SW group felt chest

Table I. Patients characteristics.

	Control group (n = 11)	SW group (n = 41)	p
Age (years)	71 ± 6.52	63.4 ± 10.8	0.14
Sex (male %)	8	35	0.378
BMI (kg/m^2)	23.21 ± 2.35	23.9 ± 2.7	0.53
Smokers	4	15	1.00
Underwent stenting	8	24	0.497
Comorbid conditions			
Essential HTN	6	27	0.50
DM	5	11	0.28
Ulcerative colitis	1	1	0.38
Chronic renal failure	0	3	N.A
Atrial fibrillation	0	0	N.A
COPD	0	0	N.A
Hyperlipidemia	0	1	N.A
Ventricular aneurysm	5	11	0.28
Location of ischemia			
Ventricular septum	0	0	N.A
Anterior wall	3	16	0.72
Inferior wall	6	14	0.299
Posterior wall	0	1	N.A
Lateral wall	0	1	N.A
Mortality	0	3	N.A
Shock waves (9 times/treatment course)	N.A	1.95 (1,4)	N.A

discomfort during the SW therapy of the lateral, apical and posterior segment, and it was comforted with the decrease of energy in the range of 0.08-0.06 mJ/mm^2. Table II represents the relationship of NYHA classification, SAQ score, and 6MWT at 3, 6, 12, 24, 36, 48, 60, 72 months after treatment. 6MWT in the control group was suggestively reduced at 60 and 72 months in comparison with 0 months. In SW group, 6MWT was increased at 12 months later decreased at 24 and 36 months but finally increased at 72 months in comparison to 0 months. The NYHA classification was remarkably diminished in the SW group at 72 months compared to 0 months, but in the control group, the NYHA classification was increased eventually in compared to 0 months.

SAQ in the control group was decreased significantly around 60 and 72 months but in the SW group SAQ increased eventually around 60 and 72 months in compared with 0 months. In Figure 1 wall motion, PSSR, MPI is compared both under resting and dobutamine loading conditions. Wall motion has been decreased subsequently in the control group than the SW group at both resting and loading conditions.

PSSR shows significant differences between the baseline and dobutamine loading conditions in between control group and SW group comparing at 12 months and 72 months. MPI shows that perfusion in the myocardium segment has extensively decreased in the control group at 24 and 72 months, but the perfusion in the myocardium has increased significantly in the SW group both at resting and loading conditions. In Figure 2 CCS grading of angina and nitroglycerine dosage was compared. Data is presented as a mean±SD. CCS grading has been increased at the maximum level for control group than the SW group at 60 and 72 months compared with 0 months. Thus, increasing the dosage of nitrates for control group subsequently according to the CCS grading of angina.

Table II. Comparison of 6MWT, NYHA, SAQ classification.

Months	Control group (n = 11)	SW group (n = 41)	p
6MWT			
0	491.72 ± 91.19	336.65 ± 120.46	0.408
3	429.81 ± 86.24	403.36 ± 79.21	0.797
6	424.63 ± 86.62	419.43 ± 101.89	0.787
12	428.45 ± 91.46	430.65 ± 126.50	0.521
24	410.09 ± 79.27	426.51 ± 122.95	0.244
36	418.90 ± 83.71	422.43 ± 146.27	0.160
48	413.18 ± 91.98	431.92 ± 160.00	0.113
60	390.72 ± 78.44	430.58 ± 173.33	0.075
72	388.90 ± 83.04	445.80 ± 172.41	0.095
NYHA			
0	1.36 ± 0.67	1.85 ± 0.96	0.05
3	1.54 ± 0.68	1.29 ± 0.51	0.081
6	1.54 ± 0.68	1.17 ± 0.38	0.001
12	1.63 ± 0.80	1.12 ± 0.45	0.001
24	1.36 ± 0.67	1.12 ± 0.45	0.042
36	1.45 ± 0.68	1.09 ± 0.53	0.046
48	1.81 ± 0.87	1.14 ± 0.57	0.011
60	2.09 ± 0.94	1.07 ± 0.51	0.000
72	2.09 ± 0.94	1.04 ± 0.49	0.000
SAQ			
0	84.00 ± 7.61	66.34 ± 12.34	0.038
3	78.36 ± 6.81	73.02 ± 12.22	0.070
6	73.36 ± 8.01	75.58 ± 11.29	0.124
12	78.18 ± 6.40	77.43 ± 16.03	0.222
24	77.27 ± 5.72	78.68 ± 15.80	0.214
36	76.36 ± 7.61	77.90 ± 20.34	0.174
48	76.00 ± 9.11	78.39 ± 20.85	0.259
60	74.18 ± 10.75	77.70 ± 24.69	0.288
72	72.72 ± 12.33	79.92 ± 25.14	0.456

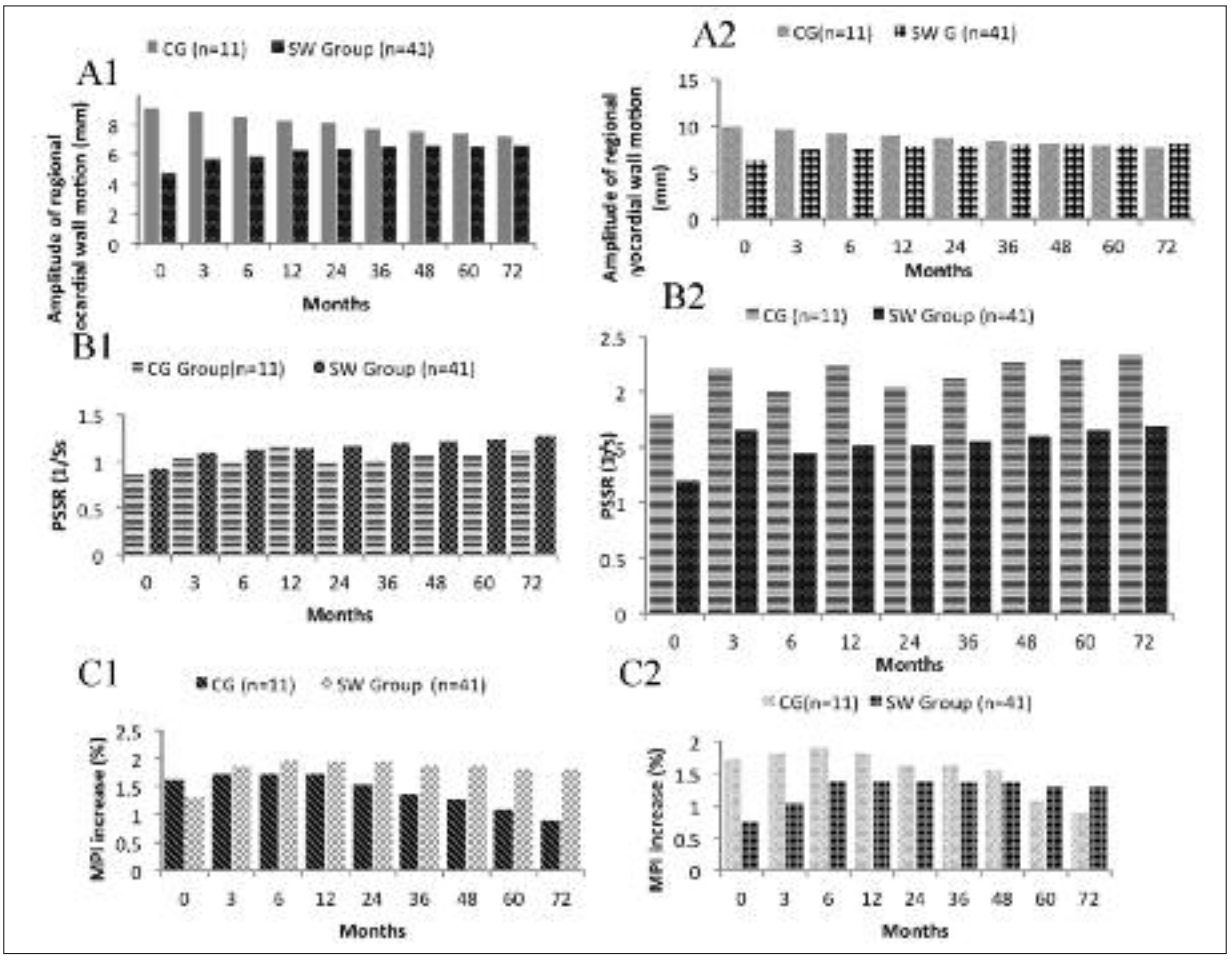

Figure 1. Comparison of amplitude of regional myocardial wall motion at baseline ***(A1)*** and after dobutamine loading ***(A2)***, PSSR score at baseline ***(B1)*** and after dobutamine loading ***(B2)*** and MPI at Baseline ***(C1)*** and after Dobutamine loading ***(C2)***. Data were presented as mean ± SD as described in the statistical analysis. $p < 0.05$, indicated there was significant difference as comparing with time = 0 month for a given baseline or after loading conditions in the corresponding group.

Discussion

According to our study following 6 years of follow-up, the CSWT provided better results that improved myocardial function and quality of life in comparing to the month 0 and the control group. These outcomes advise that on a long-term (72 months) CSWT shows better parameters than the control group. Another technique used in this research called PSSR has better resolution than M-type echocardiography[12]. The present work used PSSR to evaluate the cardiac function and its abnormality because it was a more precise study. It has a complete tissue Doppler imaging and SR imaging technology. Siemens Acuson Sequoia 512 Ultrasound (Siemens, Munich, Germany) was used to evaluate 2D-strain at the late study. Consistencies of the results were maintained by not altering the measurement variables. Past studies have successively shown the significant results of CSWT. For example, Fukumoto et al[13] cured nine patients with CAD at the end-stage not suitable for surgical interventions, and at twelve months of follow-up testified that patients reduced nitrate use (from 5.4 ± 2.5 to 0.3 ± 0.3 times/wk), upgraded CCS grading of angina (2.7 ± 0.2 to 1.8 ± 0.2), and enhanced myocardial perfusion. The treatment strategy of SW group followed the protocol established by Tohoku University of Japan and by the University of Essen, Germany Khattab et al[14] did a clinical study for ten patients with angina (CCS class III-V) with shock wave therapy and found aver-

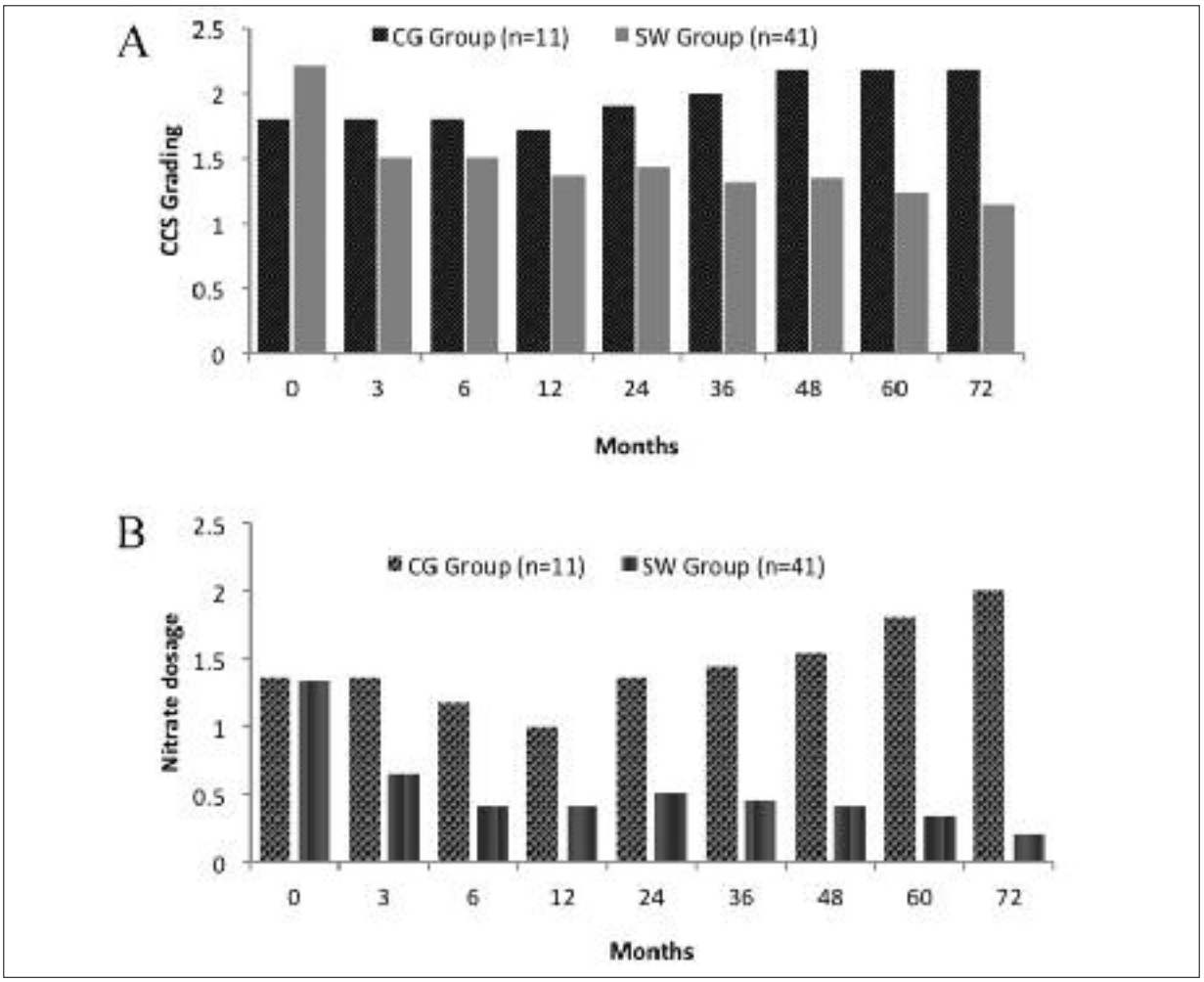

Figure 2. Comparison of CCS grading of angina ***(A)*** and nitrate dosage ***(B)*** at 0, 3, 6, 12, 24, 36, 48, 60, 72 months between Control group and shock wave group. $p < 0.05$ shows its statistically significant as presented in Table III as mean ± SD.

age CCS grading of angina reduced from 3.3 ± 0.5 to 1.0 ± 13 at baseline. Belcaro et al[15] proved the effect of SW therapy on microcirculation in patients who had critical limb ischemia. Most of the studies[16-19] has shown that shock waves activate Ras, stimulation, NO synthesis, by anti-inflammatory pathways of metalloproteases, chemokines and up-regulation VEGF and VEFG receptors. It's still unclear the mechanism of action of the shock waves. Some theories say that shock waves increase EPCs by up-regulation of SDF-1 in ischemic myocardium[20]. In our clinical work, 72 months have shown better follow-up results in term of CCS grading of angina, nitroglycerine use reduction, NYHA classification, PSSR, MPI, echo wall motion and SAQ (mentioned in figures) compared to control group. We hypothesize that the shock waves may be related with the molecular and cellular mechanisms of neovascularization[21-23]. In the era of CSWT, this is the first study which has shown the follow-up of the patients up to 6 years and the only limitation was that it had 11 patients in the control group because it was a long-term study.

Conclusions

Thus, we can conclude that CSWT can improve clinical symptoms, morphology, functions of the heart in the diagnosed CAD patients with no option in a long-term without any major side effects in compare to patients just on the drug therapy or repeated surgical interventions.

Table III. Comparison of echo wall motion baseline (A1), echo wall motion under dobutamine (A2), PSSR baseline (B1), PSSR under dobutamine (B2), MPI baseline (C1), MPI under dobutamine (C2), CCS grading of angina and nitrate dosage (only to compare Figures in text file).

Months	Control group (n = 11)	SW group (n = 41)	p
Echo wall motion (A1)			
0	9.11	4.77	0.066
3	8.86	5.71	0.047
6	8.49	5.93	0.033
12	8.27	6.22	0.004
24	8.12	6.35	0.002
36	7.74	6.51	0.008
48	7.50	6.58	0.010
60	7.35	6.48	0.019
72	7.15	6.60	0.020
Echo wall motion (A2)			
0	9.96 ± 1.61	6.34 ± 2.84	0.050
3	9.68 ± 1.48	7.51 ± 3.00	0.015
6	9.16 ± 1.45	7.58 ± 3.20	0.013
12	8.97 ± 1.26	7.83 ± 3.37	0.005
24	8.66 ± 1.03	7.83 ± 3.09	0.009
36	8.32 ± 1.26	8.00 ± 3.27	0.012
48	8.14 ± 1.38	8.06 ± 3.19	0.009
60	7.93 ± 1.40	7.89 ± 3.40	0.009
72	7.73 ± 1.36	8.07 ± 3.41	0.008
PSSR (B1)			
0	0.87 ± 0.35	0.92 ± 0.39	0.712
3	1.02 ± 0.49	1.09 ± 0.55	0.747
6	0.98 ± 0.29	1.12 ± 0.56	0.040
12	1.17 ± 0.44	1.14 ± 0.61	0.227
24	0.99 ± 0.34	1.16 ± 0.53	0.265
36	1.01 ± 0.35	1.19 ± 0.56	0.325
48	1.08 ± 0.35	1.21 ± 0.52	0.399
60	1.08 ± 0.35	1.23 ± 0.56	0.312
72	1.13 ± 0.40	1.27 ± 0.56	0.562
PSSR (B2)			
0	1.79 ± 0.55	1.20 ± 0.48	0.824
3	2.20 ± 0.58	1.65 ± 0.94	0.330
6	2.00 ± 0.46	1.44 ± 0.59	0.196
12	2.24 ± 0.72	1.52 ± 0.65	0.988
24	2.04 ± 0.49	1.52 ± 0.61	0.407
36	2.11 ± 0.53	1.55 ± 0.68	0.427
48	2.26 ± 0.56	1.61 ± 0.70	0.414
60	2.30 ± 0.64	1.65 ± 0.79	0.389
72	2.34 ± 0.57	1.69 ± 0.79	0.187
MPI (B1)			
0	1.63 ± 1.20	1.31 ± 0.98	0.347
3	1.72 ± 1.10	1.85 ± 0.85	0.236
6	1.72 ± 1.00	1.97 ± 0.85	0.614
12	1.72 ± 1.00	1.95 ± 0.89	0.755
24	1.54 ± 0.82	1.95 ± 0.89	0.824
36	1.36 ± 0.80	1.87 ± 0.95	0.574
48	1.27 ± 0.78	1.87 ± 0.95	0.451
60	1.09 ± 0.70	1.80 ± 0.98	0.063
72	0.90 ± 0.70	1.80 ± 0.98	0.063

Table III *(Continued).* Comparison of echo wall motion baseline (A1), echo wall motion under dobutamine (A2), PSSR baseline (B1), PSSR under dobutamine (B2), MPI baseline (C1), MPI under dobutamine (C2), CCS grading of angina and nitrate dosage (only to compare Figures in text file).

Months	Control group (n = 11)	SW group (n = 41)	p
MPI (B2)			
0	1.72 ± 1.27	0.75 ± 0.79	0.012
3	1.81 ± 1.16	1.04 ± 0.86	0.145
6	1.90 ± 1.13	1.39 ± 0.83	0.374
12	1.81 ± 1.07	1.39 ± 0.83	0.547
24	1.63 ± 0.92	1.39 ± 0.83	0.996
36	1.63 ± 0.92	1.36 ± 0.88	0.729
48	1.54 ± 0.93	1.36 ± 0.88	0.975
60	1.09 ± 0.70	1.31 ± 0.90	0.070
72	0.90 ± 0.70	1.31 ± 0.90	0.070
CCS grading			
0	1.81 ± 0.75	2.21 ± 0.85	0.472
3	1.81 ± 0.75	1.51 ± 0.67	0.868
6	1.81 ± 0.75	1.51 ± 0.67	0.967
12	1.72 ± 0.78	1.36 ± 0.53	0.045
24	1.90 ± 0.83	1.43 ± 0.59	0.228
36	2.00 ± 0.77	1.31 ± 0.60	0.809
48	2.18 ± 0.75	1.34 ± 0.69	0.819
60	2.18 ± 0.75	1.24 ± 0.66	0.524
72	2.18 ± 0.75	1.14 ± 0.57	0.143
Nitrate Dosage			
0	1.36 ± 1.62	1.34 ± 1.35	0.398
3	1.36 ± 1.62	0.65 ± 1.01	0.012
6	1.18 ± 1.47	0.41 ± 0.80	0.007
12	1.00 ± 1.34	0.41 ± 0.77	0.009
24	1.36 ± 1.43	0.51 ± 0.95	0.004
36	1.45 ± 1.29	0.46 ± 0.97	0.048
48	1.54 ± 1.36	0.41 ± 0.92	0.008
60	1.81 ± 1.25	0.34 ± 0.93	0.116
72	2.00 ± 1.18	0.21 ± 0.82	0.037

Clinical Trial

Clinical trial registered on www.ClinicalTrials.gov, the ID is NCT01578876.

Authors' Contributions

We declare that all the listed authors have participated actively in the clinical study conducted in the 1st affiliated hospital of the Kunming Medical University. Prof. Tao Guo designed the clinical study, arranged CSWT machine and wrote the protocol. Dr. Sanjeev Nirala, Yu Wang performed the research/study. Dr Peng Yunzhu, Yang Ping followed up the control group patients. Dr. Sanjeev Nirala accomplished the literature searches and analysis. Dr. Sanjeev Nirala wrote the thesis and the first manuscript. At the end of the study all the authors read and approved the final manuscript.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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