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Extracorporeal Cardiac Shock Wave Therapy (CSWT) for Treatment of Coronary Artery Disease in China

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Extracorporeal Cardiac Shock Wave Therapy (CSWT) for Treatment of Coronary Artery Disease in China

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Abstract- **Coronary artery disease (CAD) is a leading cause of mortality worldwide. Common therapies in the treatment of CAD are invasive, insufficient and pose additional risks in patients with advanced refractory CAD. Cardiac shock wave therapy (CSWT) is a safe and effective non-invasive intervention in the management of patients with refractory CAD. In this article, we briefly outline our work in animals and humans, and discuss the advantages and perspectives of CSWT in China.**

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I. Introduction

Current therapies in the treatment of CAD include drug interventions, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and transmyocardial laser revascularization (TMR). However, these approaches are invasive and often inadequate in the treatment of advanced CAD and are associated with serious cardiovascular risks and complications. Thus, there is need for a safe and effective, noninvasive approach toward the treatment of CAD. Cardiac shock wave therapy (CSWT) is a novel, noninvasive intervention that can ameliorate myocardial ischemia and improve cardiac function. Evidence indicates that CSWT may reduce the ischemic burden and provide angina relief by promoting angiogenesis and revascularization in ischemic myocardium[1-7]. Earlier in vivo animal studies and human clinical studies demonstrated that low-energy pulse waves produced by CSWT induced a "cavitation effect", exerting a mechanical shear force and on myocardial and vascular endothelial cells. Shock wave treatment promoted angiogenesis in ischemic porcine myocardium by up-regulating vascular endothelial growth factor (VEGF) mRNA and its receptor fms-like tyrosine -1 (flt-1). Furthermore, improved regional myocardial blood flow and capillary density were also observed [1,2]. Subsequent clinical studies have shown that CSWT can significantly improve cardiac function in patients with severe CAD and refractory angina who are not candidates for PCI or CABG [3 -12]. Based on the promising results from animal and clinical studies. We initiated a series study of CSWT in China on porcine model, cells and CAD patients to prove up the angiogenetic mechanism and effect of CSWT in vivo and vitro experiments, also to evaluate the feasibility and efficiency of CSWT for treatment of CAD and to establish the inclusion and exclusion criteria and summarize the methodological outlines of CSWT in China. (Picture 1)

Picture1 : CSWT for clinical and porcine trials

II. In Vitro Study

Cai et al. reported that[13,14] human umbilical vein endothelial cells (HUVECs) lines were performed by different level of shock wave energy (0, 0.03, 0.09, 0.18, 0.24mj/mm^2) in vitro. HUVECs proliferation and the changes in mRNA and protein of VEGF、interleukin-8(IL-8)、intercellular adhesion mole cule-1 (ICAM-1) were observed before and 24 hours after CSWT. Compared with the non-treated control, the results from real time PCR revealed the 0.09mJ/mm^2

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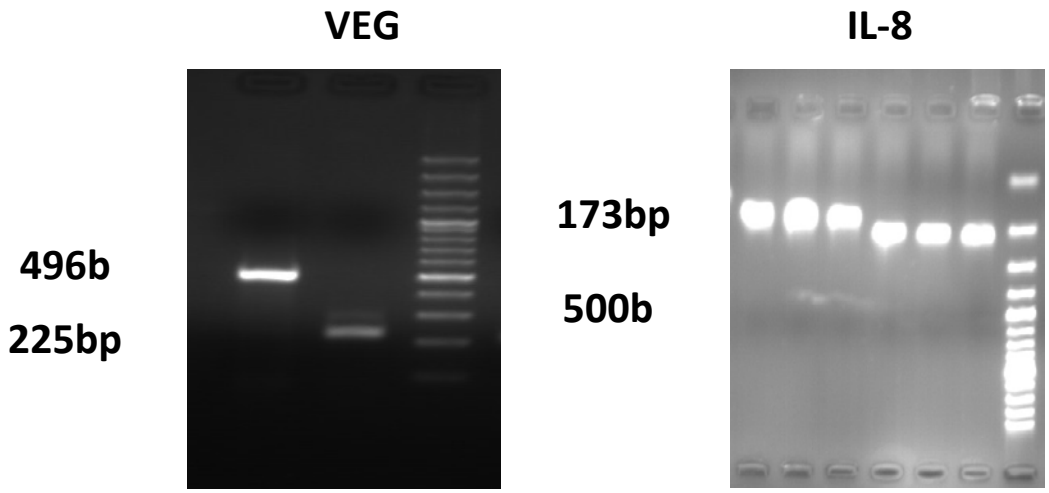
shock energy significantly promoted the HUVECs proliferation (P<0.05), and also markedly increased the expression of VEGF, IL-8, ICAM-1(P<0.001); The expression of ICAM-1 0.03 mJ/mm^2 group were increased significantly (P<0.01) while the expression of VEGF, IL-8 showed no significant changes(P>0.05); 0.18mJ/mm^2 treatment markedly increased the expression of VEGF (P<0.001) while the expression of ICAM-1, IL-8 showed no significant changes(P>0.05); 0.24mJ/mm^2 had no significant effect on the expression of VEGF, IL-8, ICAM-1(P>0.05). Western blot analysis and Flow Cytometry showed that the expression of VEGF, IL-8, ICAM-1 in 0.09mJ/mm^2 group were markedly increased (P<0.05); The expression of VEGF in 0.03, 0.18, 0.24mJ/mm^2 group was obviously higher (P<0.05) while the expression of ICAM-1, IL-8 had no changes (P>0.05). In addition, a total of 26 patients with history 1～16 years of old myocardial infarction, stable and unstable angina pectoris from August 2008 to December 2010 were enrolled, which were applied by standard CSWT procedure. Before and at 30 days after CSWT treatment, mononuclear cells were obtained from peripheral blood and endothelial Progenitor cells (EPCs) were cultured in EGM-2-MV medium. Morphology and the number of colonies of EPCs were observed and the level of VEGF, IL-8, stromal cell-derived factor-1(SDF-1) and matrix metalloproteinase-9 (MMP-9) was determined. The cultured EPCs and EPC-CFU number in vitro were significantly increased after CSWT [EPCs (18.85±4.30) cell /high power field vs (30.12±6.77) cell/high power field; (5.08±1.79) cell/high power field vs (12.27±2.75) cell/high power field, P<0.001]; Circulating EPCs were significantly increased [(0.015±0.003)% vs (0.021±0.005)%, P<0.001]; VEGF, IL-8 level were significantly increased[VEGF (120.26±19.85) pg/ml vs (155.19±24.67)pg/ml; IL-8 (21.81±5.94) pg/ml vs (149.70±44.11)pg/ml, P<0.01], whereas SDF-1and MMP-9 had no significant changes [SDF-1(2750.87±636.74)pg/ml vs (2700.47±415.19) pg/ml;MMP-9 (19.66±3.96)ng/ml vs (18.55±3.78)ng/ml, P>0.05], compared with pre-treatment[14]. We conclude the different shock wave energy promotes the HUVECs proliferation in different degree, the effect of 0.09 mJ/mm^2 energy is the most evident, and it also increases the expression of mRNA and protein of IL-8、ICAM-1 significantly. The 0.03～0.24 mJ/mm^2 energy also has some effects on facilitating the secretion of VEGF, IL-8 and ICAM. Furthermore, CSWT appears to promote the expression of VEGF and IL-8 protein, also stimulate the EPCs proliferation, significantly increase the number and function of EPCs, whereas not influence on the expression of SDF-1、MMP-9. (Picture 2)

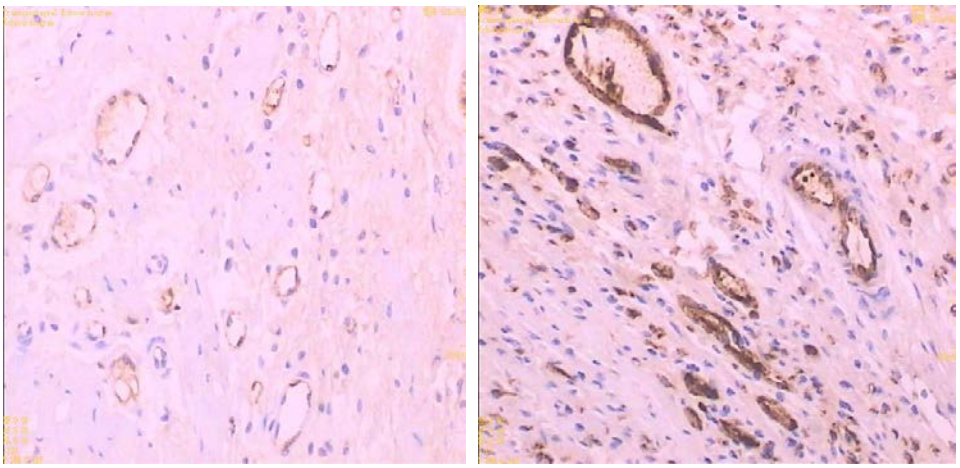


Picture 2 : VEGF and IL-8 increased significantly after CSWT

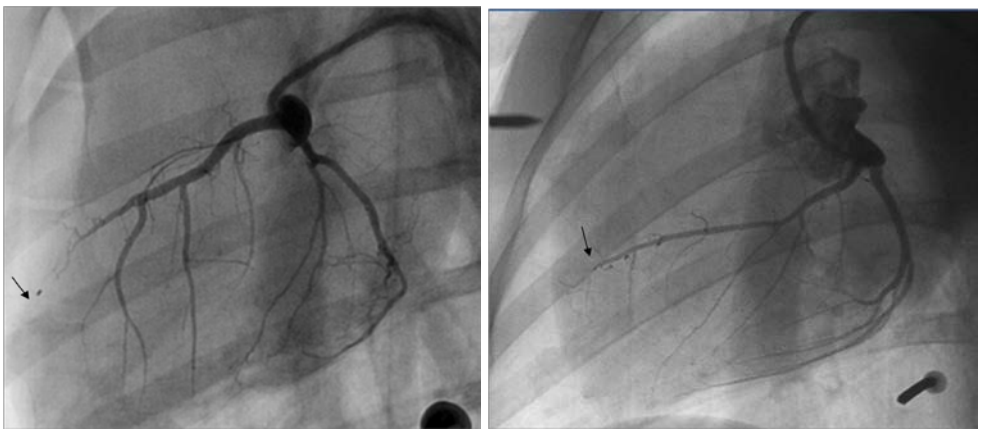
III. In Porcine Model

Tao et al. randomly divided 30 domestic swine into two groups, group A (n=13) and group B (n=17). In group A, The balloon catheter was positioned in the mid-distal segment of left anterior descending (LAD) ,and dilated with rated pressure for 60 min after ischemia precondition, then the micro-embolis was sent to the distal of target vessel; In group B, the micro-embolis was positioned in the distal segment of target vessel directly. Interventional procedure time and model success rate were collected in the two groups. 26 porcine acute myocardial infarction (AMI) models were established successfully. Model success rate of group A was 84.6%, and 88.2% in group B. No statistic significance was found in the two groups. However mean operation time of group B was significantly shorter than that of group A, 28.4±9.4min versus 105.8±27.6min, p<0.001. In addition, 26 AMI models were randomly divided into four groups: CSWT group (n=11), pseudo-CSWT group (n=5), pseudo-operation group (n=5) and blank control group (n=5). Compared with pseudo-CSWT group, the expression of VEGF mRNA was significantly increased in CSWT group with statistic difference (2.90±0.40vs2.12±0.50, P<0.01), especially in the prolonged duration CSWT. The number

of capillaries was significantly higher in CSWT group than that of pseudo-CSWT group (1856±78 vs. 837±54/mm^2, *P<0.0001*). Collateral vessel Rentrop score was significant higher in CSWT group (*2.05±0.11vs0.98±0.09, P=0.03*).Whereas, significant differences were negative between standard and extensive area compared with pseudo-CSWT group, the expression of VEGF mRNA was increased significantly in all CSWT subgroups[15,16]. Sun et al. selected 12 AMI models to detect serum endothelial nitic oxide synthase (eNOS) and expression of eNOS and basic fibroblast growth factor (bFGF) in borderline of infarction. Therapy group was performed CSWT on 1,3,5 days after AMI with low energy(0.09mJ/mm^2) at 200 shoots/spot for 12 spots. Including control group, peripheral blood was extracted at 1,3,5 days, 1,2,3,4 weeks and myocardial tissue was excided after 4 weeks. In both group, serum concentration of eNOS reduced obviously after AMI. In CSWT group, eNOS expression began to rise at 1day of CSWT, and there was a concentration peak after 3 times treatment and declined at 4 weeks. On contrast, eNOS expression in control group kept lower level during 4 weeks ($p<0.01$). In CSWT group, expression of eNOS and bFGF in borderline infarction were obviously higher than control group (eNOS 27.705±4.13 vs 16.448±3.21, bFGF 32.571±4.23 vs 17.858±4.17,$P<0.01$)[17,18,19]. We explore a new method inducing porcine acute myocardial infarction by Balloon plus micro-embolis. In porcine model, CSWT can promote the expression of eNOS and bFGF in serum Prolonged duration CSWT at early stage of AMI can improve angiogenesis of myocardium microenvironment and facilitate myocardial micro-vascular circulation. (Picture3)



Picture 3 : Capillaries density was significantly higher after CSWT compared with pseudo-CSWT group



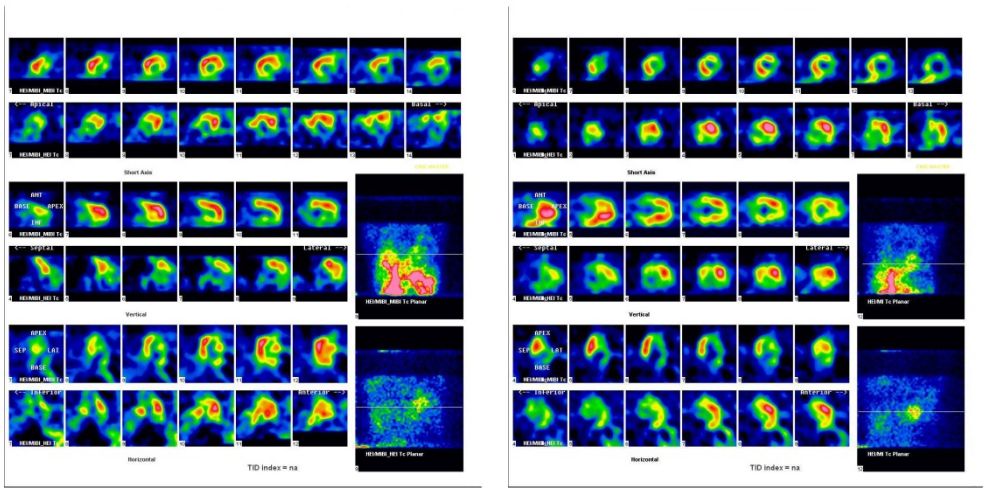
Picture 4 : Collateral vessel Rentrop score was significant higher after CSWT compared with pseudo-CSWT group

IV. CSWT for CAD Patients

Wang et al. initiated CSWT for CAD patients since 2008 in China. Male patients (n=9), aged 50-70 years with CAD diagnosis (5.11±5.46 years) and stent implantation (3.00±2.24 stents) were enrolled. CSWT was carried out each month for 3 months at three week intervals during the first week of the month (1st, 3rd and 5th day) for a total of 9 therapies per patient. Dobutamine stress echocardiography (SE) and radionuclide angiography identified myocardial ischemic segments. The effects of CSWT on myocardial perfusion and systolic function were examined. Other outcome measures included myocardial injury enzyme markers, angina scale, nitroglycerin dosage and cardiopulmonary

fitness assessments. Improved myocardial perfusion and systolic function [stress peak systolic strain rate (PSSR) -1.10 to -1.60 s^{-1}, p=0.002)] were detected in patients following CSWT. Reductions in creatine kinase (CK) (87.89±36.69 to 86.22±35.96 IU/L, p=0.046), creatine kinase MB (CK-MB) (10.89±5.73 to 10.11±5.93 IU/L, p=0.008), aspartate aminotransferase (AST) (IQR 28.00 to 27.00 IU/L, p=0.034) were found. Angina [Canadian Cardiovascular Society (CCS) scale IQR 3.0 to 2.0, p=0.035] and nitroglycerin dose reduction (IQR 3.0 to 1.0 times/wk, p=0.038) were reported. CCS grading of angina and dosage of nitrate esters were significantly reduced in 9 patients after 3 CSWT treatments and regional myocardial systolic function was improved significantly 1 month after treatment. We conclude that CSWT is a non-invasive, effective and safe intervention in the treatment of refractory CAD[20]. (Picture 5)

Picture 5 : PSSR standing for regional systolic function improved significantly after CSWT



Picture 6 : Dual isotope simultaneous acquisition SPECT certified there were improved after 9 times CSWT on myocardial perfusion and metabolism

V. A New Regimen of CSWT

Wang et al. aimed to further evaluated the clinical outcomes of a new CSWT treatment regimen. 55 patients with severe CAD were randomly divided into 3 treatment groups. The control group (n = 14) received only medical therapy. In group A (n = 20), CSWT was performed 3 times within 3 months. In group B (n = 21), patients underwent 3 CSWT sessions/week, and 9 treatment sessions were completed within 1 month. Primary outcome measurement was 6-minute walk test (6MWT). We outlined the including criteria: 1) Coronary angiography (CA) or multi-slice CT coronary angiography (CTCA) suggestive of moderate to severe coronary artery stenosis. 2) Demonstrated cardiac infarction and > 50% stenosis after radioactive and sonographic examinations. 3) Chest tightness, onset of shortness of breath, and poor exercise tolerance after receiving formal drug treatment (with or without stent or bypass graft). 4) Hospitalized more than 2 times within 1 year due to the aforementioned problems. 5) CCS angina grading higher than grade II, and NYHA functional classification of I-III. 6) More than 1 month after AMI and more than 2 weeks after PCI surgery. A history of PCI or CABG was not a contraindication for inclusion. Patients were excluded from the study if they met any of the following criteria. 1) AMI or CABG within the 4 weeks prior to the study. 2) History of heart transplantation. 3) History of metal valve replacement surgery. 4) Intracardiac thrombus. 5) left ventricular ejection fraction (LVEF) < 30% and unstable hemodynamics. 6) Arrhythmia with a rate < 40 bpm or > 120 bpm. 7) Skin ulceration or infection in the treatment area. 8) Severe obstructive lung disease. The treatment protocol of group A followed the recommended protocol developed by Tohoku University of Japan with respect to the shockwave output and the number of shots delivered to each spot and the protocol developed by the University of Essen, Germany[3,11]. In group B, a modified CSWT treatment schedule was adopted. Patients underwent 3 CSWT sessions/week, and the 9 treatment sessions were completed within 1 month. During follow-up, if the patient exhibited no observable lessening of myocardial ischemia, 1-4 treatment courses were repeated. The control group did not undergo CSWT. During the 12-month follow-up, periodic telephone inquiries, out-patient follow-up, and hospitalization were used to adjust the drugs and treat emergencies in addition to the regular 3-month, 6-month, and 12-month follow-ups. Just like our prior study[21], 25 patients had 9 CSWT treatments and two imaging methods were used, PSSR and myocardial

perfusion imaging (MPI) at the 1month follow-up. And in this study, following 12 months of observation, the CSWT treatments using two different regimens both provided satisfactory results that improved CCS grading of angina, dosage of nitrate esters, 6MWT, NYHA functional classification, Seattle Angina Questionnaire (SAQ) score, PSSR after load and resting MPI comparing to pretreatment (month 0) and to the control group. These results suggest a more frequent treatment regimen (one month) can also provide equivalent therapeutic efficacy compared to the regimen of less frequent CSWT treatment (three months). These results are exciting, but the mechanism by which a shorter term, more frequent treatment produces the same effect as a longer term, less frequent treatment is still unclear. We speculate that the mechanism might be related to the cellular and molecular mechanisms of blood vessel formation. In other words, when repeated shock wave stimulations are given within 1 month, the resulting succession of shear force effects will produce a waterfall phenomenon, and a large number of neovascular networks will form in a short period of time, ultimately promoting the establishment of collateral circulation in the ischemic area.

VI. A Randomized, Double-Blind and Placebo-Controlled Study of CSWT

Yang et al. carried out this double-blind and placebo-controlled study on CSWT. 25 patients with old myocardial infarction (OMI) were selected, who were divided into the experimental group (14 patients, the shock wave energy was given in CSWT procedure,) and the control group (11 patients, the shock wave energy was not given in the same procedure). The CSWT procedure was performed for a total of 9 therapies within 3 month. After one month of CSWT, the NYHA, CCS scale, nitroglycerin dosage, scores of myocardial perfusion and myocardial metabolic imaging by Dual-Isotope single photon emission computed tomography (SPECT) in the experimental group were reduced significantly ($P<0.05$), and SAQ scale, 6MWT and LVEF were increased significantly ($P<0.05$) compared with those before CSWT treatment. Whereas, all the parameters were not changed significantly in the controlled group before and after CSWT ($P>0.05$) [22].

VII. CSWT for the Patients with Ischemic Heart Failure

Peng et al. focused on the 50 patients with ischemic heart failure and LVEF<50%, who were randomized to either CSWT group (200 shots/spot at 0.09 mJ/mm^2 for 9 spots, 9 times within 3 month /series, n=25) or control group (exactly same procedures without shock wave energy, n=25). Dual isotope simultaneous acquisition SPECT with 99mTc-sestamibi/18 F-fluorodeoxyglucose (99m Tc-M IBI / 18 F-FDG) and Dobutamine stress echocardiography (DSE) were performed. Follow-ups were completed at 0, 3 and 6 months after therapy. At 1 month follow-up, summed perfusion score (19.40±5.2 vs.22.10±2.10 P =0.006), metabolism score (21.10±5.28 vs. 23.80±3.08 P=0.031), base PSSR (-1.09±0.71 vs. -0.62±0.36 *P* =0.007) and strain PSSR (-1.36±0.23 vs. -0.97±0.40 P <0.001) were improved in CSWT group compared to baseline and to control group. At 3 and 6months follow-up, patients in CSWT group experienced continuous improvement in symptoms: NYHA (2.36±0.50 vs. 1.46±0.21 vs. 1.67±0.52, P=0.008), CCS (2.56±0.07 vs.1.25±0.12 vs. 1.10±0.33, P=0.001), nitroglycerin dosage (3.77±0.55/week vs. 2.18±0.34/week vs. 2.51±0.43/week P=0.006), SAQ (59.01±9.43 vs. 65.0±10.09 vs.66.94±11.22, P=0.031), 6WMT (286.17 ±34.22 vs. 306.04±33.56 vs. 304.78±45.25, *P*=0.027), LVEF (%) (45.02±6.37 vs. 49.30±7.06 vs. 48.70±10.53, *P*=0.022) and LVEDD (mm) (63.10±11.36 vs. 60.13± 7.70 vs.58.10±4.01, *P*=0.033) were improved in CSWT group. Continuous increasing of VEGF (pg/ml) (127.61±31.69 vs.147.29±34.37 vs.159.56±55.36, P=0.022) and decreasing of BNP (pg/ml) (1702.25±122.75 vs. 1492.33±389.55 vs.1334.78± 227.91, P=0.001) were also observed in CSWT group. However, no significant changes were found in the control group ($P>0.05$) [23]. (Picture 6)

VIII. Non-Invasive Nature of CSWT

CSWT can effectively induce angiogenesis by up-regulating the expression of angiogenic factors and depress promoting factors of ventricular reconstruction, It still stimulate the EPCs proliferation, significantly increase the number and function of EPCs, which is certified by regional and global ventricular function improvement[13]. The different shock wave energy promotes the HUVECs proliferation in different degree, the effect of 0.09 mJ/mm^2 energy is the most evident, and it also increases the expression of mRNA and protein of IL-8、ICAM-1 significantly[14]. CSWT can promote the expression of eNOS, bFGF, SDF-1 and its receptor CXCR4[17,18]. CSWT can improve the protein expression of VEGF and it's receptor (VEGFR1/Flt-1 and VEGFR2/KDR). After inhibiting VEGF or VEGFR1/Flt-1 or VEGFR2/KDR, the effect of CSWT in endothelial cell proliferation were weakened, thus VEGF and its receptor may play an important role in the mechanism of angiogenesis of CSWT.

IX. Concluding Remarks

In China, our research team is the one who firstly imported the CSWT device from Switzerland by the end of 2008. Since then we provide scientific basis of CSWT in vitro, animal in vivo and clinical patients for the

first time in China. CSWT is a safe and effective non-invasive intervention in the management of patients with CAD, which can ameliorate symptoms, improve coronary reserve, decrease the incidence of malignant arrhythmias and subsequently improve the patients' quality of life. DSE combined with MPI, and 99mTc-MIBI /18F-FDG- DSA SPECT is a preferable method to locate the viable ischemic myocardial segments and guarantees the accuracy and effect of CSWT. A CSWT treatment regimen of one month duration provided similar therapeutic efficacy compared to a regimen with three months duration. Expanding the range of treatment (25 points therapy) could improve myocardial perfusion, myocardial metabolism and heart function than the conventional treatment protocols (9 points treatment). Indications and contraindications of CSWT in China are concluded, not only for refractory CAD, but also for those chronic pectoris which are reluctant or have no condition to undergo the invasive therapy. The candidates might include patients with ischemic heart failure, patients with permanent heart pacemaker or atrial fibrillation may also benefit from CSWT.

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