Efficacy and Safety of Cardiac Shock Wave Therapy in Patients with Refractory Angina, Ischemic Heart Failure and Acute Myocardial Infarction

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Abstract

Patients with coronary artery disease (CAD) usually suffer from angina and are treated with medications, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). However, a substantial number of CAD patients suffer from disabling angina in spite of having undergone PCI or CABG and continuing on optimal medical treatment. Previous reports have estimated around 5-10% of CAD patients have refractory angina (RA). Several therapeutic interventions have been used in RA patients to relieve their symptoms and improve their quality of life, such as exercise training and enhanced external counterpulsation. In addition, low energy cardiac shock wave therapy (CSWT) could be used to induce shear stress in endothelial cells, producing a complex cascade of short- and long-term reactions leading to angiogenesis; hence CSWT has been confirmed to be an effective, noninvasive, and safe therapeutic option for the treatment of RA.

Ischemic heart failure (HF) is a sequela of CAD and caused by reduced myocardial oxygen supply. Several therapeutic options, such as medical treatment, PCI, and CABG, are available for treating such patients. However, limitations of the therapies persist on account of their varying efficacies. CSWT may reduce ischemia symptoms and improve cardiac function by stimulating angiogenesis and thus it may become a useful therapeutic option for patients with ischemic HF.

Although great advances in emergency systems and primary PCI have markedly reduced the mortality of patients with acute myocardial infarction (AMI), left ventricular remodeling after AMI is still an important challenge in such patients. Similarly, CSWT can induce angiogenesis and therefore may have potential in treating AMI patients in order to reduce left ventricular remodeling.

In this paper, we will review the efficacy and safety of CSWT in CAD patients with RA, in patients with ischemic HF, and in patients with AMI.

Keywords: cardiac shock wave therapy, refractory angina, ischemic heart failure, acute myocardial infarction

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Introduction

Coronary artery disease (CAD) is the most common consequence of cardiovascular atherosclerotic disease and the leading cause of mortality in the developed countries. CAD is frequently caused by lipid-filled plaque due to dyslipidemia resulting in the thickening of the coronary artery wall, which finally results in coronary artery stenosis.[1] Patients with CAD usually suffer from angina and are treated with medications, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). However, a substantial number of CAD patients suffer from disabling angina in spite of having undergone PCI or CABG and continuing on optimal medical treatment.[2] The number of patients with CAD unsuitable for revascularization and with persistent symptoms refractory to medical therapy continues to increase. A report from the ESC joint study group estimates around 5-10% of CAD patients have refractory angina (RA).[3] Several therapeutic interventions have been used in RA patients to relieve their symptoms and improve their quality of life, such as exercise training and enhanced external counterpulsation.[4,5] Furthermore, low-energy cardiac shock wave therapy (CSWT) has also been reported to be an effective and noninvasive therapeutic option for the treatment of RA.[6] CSWT could induce shear stress to endothelial cells and produce a complex cascade of short- and long-term reactions leading to angiogenesis.[7,8]

Ischemic heart failure (HF) is a sequela of CAD and caused by reduced myocardial oxygen supply. Several therapeutic options, such as medical treatment, PCI, and CABG, are applied for treating such patients. However, limitations of the therapies persist due to their varying efficacies. A large number of patients with ischemic HF receiving different treatment interventions still have severe symptoms and high mortality.[9] CSWT is a advanced therapy that can improve myocardial ischemia and cardiac function in CAD patients with refractory angina.[10-12] CSWT may reduce ischemia symptoms and improve cardiac function by stimulating angiogenesis and thus may become a useful therapeutic option for patients with ischemic HF.

Although great advances in emergency systems and primary PCI have markedly reduced the mortality of patients with acute myocardial infarction (AMI),[13] left ventricular (LV) remodeling after AMI is still presents an important challenge in such patients.[14,15] Adverse LV remodeling after AMI is the most common cause of worsening heart function and thus poor prognosis.[16] Correspondingly, CSWT is able to induce angiogenesis[7,8] and improve cardiac function in CAD patients[10-12] and therefore may have potential in treating AMI patients in order to reduce LV remodeling.

In this paper, we will review the efficacy and safety of CSWT in CAD patients with RA, in patients with ischemic HF, and in patients with AMI.

CAD patients with RA

While the present management of CAD has advanced, many patients remain symptomatic. Based on the 2012 guidelines of the Canadian Cardiovascular Society (CCS), RA is defined as "a persistent, painful sensation which cannot be controlled by a mixture therapy of medication, PCI, or CABG".[17] Patients with RA suffer from psychological distress, activity limitation, and unsatisfactory quality of life, and the prevalence of RA is increasing with the improving survival rate in patients with CAD. Hence, it is important to develop effective therapeutic strategies for RA patients. Numerous studies have demonstrated the efficacy of CSWT in patients with RA (Table 1).

Previous animal studies have suggested that CSWT may alleviate angina by promoting angiogenesis and revascularization in treated ischemic myocardium. Encouraged by these promising results, CSWT has been applied in humans. Fukumoto et al. published the first study of CSWT in patients with end-stage CAD

Table 1. The efficacy of CSWT in patients with RA

Reference	Year	Trial type	Treatment/ control (N)	CCS class	SAQ score	NTG use	NYHA class
Fukumoto et al.[10]	2006	Single arm	9/-	Improvement	NA	Decrease	NA
Zuozienė et al.[18]	2012	Single arm	20/-	Improvement	NA	Decrease	NA
Kazmi et al.[19]	2012	Case-control study	43/43	Improvement	NA	NA	Improvement
Slikkerveer et al.[24]	2016	Single arm	15/-	NA	NA	Decrease	Improvement
Alunni et al.[25]	2017	Single arm	72/-	Improvement	NA	Decrease	NA
Slavich et al.[20]	2017	Case-control study	19/4	Improvement	Improvement	NA	NA
Kikuchi et al.[21]	2019	Single arm	50/-	Improvement	NA	Decrease	NA
Duque et al.[22]	2018	Single arm	19/-	Improvement	Improvement	NA	Improvement
Ceccon et al.[23]	2019	Single arm	15/-	Improvement	Improvement	NA	NA

in 2006,[10] which suggested that CWST was an effective, non-invasive treatment for end-stage CAD. In their first published study, they found that CSWT improved symptoms (Canadian Cardiovascular Society [CCS] functional class score, from 2.7 to 1.8, $P < 0.01$) and reduced nitroglycerin use (from 5.4 to 0.3/week, $P < 0.05$). The treatment also improved myocardial perfusion, as assessed by dipyridamole stress thallium scintigraphy (severity score, 25.2% improvement, $P < 0.05$). Myocardial perfusion was improved only in the ischemic area treated with the therapy. These beneficial effects persisted for 12 months. Subsequent single-arm cohort studies and randomized controlled trials have consistently demonstrated that RA patients who underwent 3-month CSWT had a 25-50% reduction in CCS class score,[10,12,18-23] a 25%-50% reduction in New York Heart Association (NYHA) class,[19,22,24] and a 50-100% reduction in nitroglycerin (NTG) usage,[10,18,21,24,25] as compared to the baseline data.

Burneikaitė et al. published a systematic review and meta-analysis of CSWT.[6] They included 1189 CAD patients in 39 reviewed studies, with 1006 patients treated with CSWT, whereby the largest patient sample of their single arm studies consisted of 111 patients. All selected studies demonstrated significant improvement in subjective measures of angina symptoms and/or quality of life, and in the majority of studies LV function and myocardial perfusion improved. In 12 controlled studies including 483 patients (183 controls), CCS angina class, Seattle Angina Questionnaire (SAQ) score and NTG consumption were significantly improved after the treatment. In 593 participants across 22 studies, the exercise capacity was significantly improved after CSWT, as compared with the baseline values (in meta-analysis standardized mean difference = –0.74, $P < 0.001$). They concluded CSWT was a promising non-invasive option for patients with end-stage CAD, but evidence was limited to small sample size single-center studies. Further multi-center, adequately powered, randomized, double blind studies are warranted.

Patients with ischemic HF

Previous animal studies have suggested a beneficial effect of CSWT in ischemic heart failure.[26-28] Several human studies have also demonstrated the efficacy of CSWT in patients with ischemic HF (Table 2). Vasyuk et al.[29] included 24 patients with ischemic HF and LV ejection fraction (LVEF) < 40%. CSWT was performed in 9 sessions with 100 shocks per spot in viable segments detected by dobutamine stress echocardiography. In that study, CSWT significantly decreased New York Heart Association (NYHA) class from 2.2 ± 0.8 to 1.7 ± 0.7 at 6 months (P < 0.01). In addition, a significant increase in LVEF at 6 months after CSWT (from 32.2 ± 6.0% to 37.7 ± 9.5%, P = 0.03) was noted. They concluded a significant clinical improvement accompanied by beneficial changes of LVEF were found after CSWT.

Peng et al.[30] evaluated the efficacy of CSWT in ischemic HF patients in a randomized controlled trial (RCT). They enrolled 50 ischemic HF patients with LVEF < 50%. They also found NYHA class and LVEF showed significant improvements after CSWT (P ≤ 0.001) and concluded CSWT might serve as a new, non-invasive, safe and efficient therapy in patients with ischemic HF.

Wang et al.[31] included 23 ischemic HF patients with LVEF between 20% and 45%. CSWT was performed 3 times per week for 3 weeks. One week after CSWT, NYHA class had decreased from 3.0 to 2.0 (P < 0.001), but LVEF had no significant change. They additionally demonstrated that CSWT resulted in a significant increase in the expression of promoters of neovascularization and a notable decrease in the expression of a mediator of cell apoptosis. Finally, they concluded that CSWT constituted an effective treatment for patients with ischemic HF through the promotion of neovascularization and inhibition of cell apoptosis.

CSWT in AMI

Animal study

Wang et al. evaluated the role of CSWT in pigs with AMI.[32] Their study included 25 pigs with AMI created by coronary embolism. They divided the pigs into 3 groups: an AMI + CSWT group (n = 15), an AMI group without CSWT (n = 5), and a sham + CSWT group (CSWT without AMI, n = 5). They found that compared with the AMI group, the AMI + CSWT group showed significantly ameliorated myocardial fibrosis, in terms of collagen area fraction (27.21 ± 8.13 vs. 10.13 ± 4.96, P < 0.05), and reduced fibrocytes

Table 2. The efficacy of CSWT in ischemic HF

Reference	Inclusion criteria	Number	Trial type	6MWT	NYHA class change	LVEF change
Vasyuk et al.[29]	Ischemic HF and LVEF <40%	24	Single arm	414 m to 538 m at 6 months (P < 0.01)	2.2 to 1.7 at 6 months (P <0.01)	32.2% to 37.7% at 6 months (P = 0.03)
Peng et al.[30]	Ischemic HF and LVEF <50%	50	Case-control study	Improvement in six-minute walk test (P = 0.012)	Improvement in NYHA class at 1 month (P < 0.01)	45.0% to 47.0% at 1 month (P = 0.001)
Wang et al.[31]	Ischemic HF and 20% <LVEF <45%	23	Single arm	NA	3.0 to 2.0 at 1 week (P < 0.001)	No significant change at 1 week

($P < 0.005$). They concluded CSWT ameliorates myocardial fibrosis after AMI in pigs, associated with a decreased amount of fibrocytes.

Abe et al. examined whether CSWT exerts beneficial anti-inflammatory effects in a rat model of AMI.[33] AMI was created by ligating the proximal left anterior descending coronary artery in rats. They randomly divided the rats into 2 groups: AMI with CSWT (n = 20) and AMI without CSWT (n = 20). The energy of CSWT was 0.1 mJ/mm^2, 200 shots, 1 Hz to the whole heart at 1, 3 and 5 days after AMI. Four weeks after AMI, CSWT had significantly ameliorated LV remodeling and fibrosis. Histological examination showed that CSWT significantly suppressed the infiltration of neutrophils and macrophages at days 3 and 6, in addition to enhancing capillary density in the border area. Molecular examinations revealed that CSWT enhanced the expression of endothelial nitric oxide synthase and suppressed the infiltration of transforming growth factor-β1-positive cells early after AMI. CSWT also upregulated anti-inflammatory cytokines and downregulated pro-inflammatory cytokines in general. The authors concluded that low-energy CSWT suppressed post-AMI LV remodeling in rats, which was associated with anti-inflammatory effects, in addition to its angiogenic effects, thus demonstrating a novel aspect of the therapy for AMI.

Human study

Myojo et al. evaluated the efficacy and safety of CSWT in patients post-AMI.[34] Three post-AMI patients were enrolled. They were treated with 9 sessions of CSWT to the ischemic areas for 9 weeks. These post-AMI patients had already undergone revascularization with percutaneous coronary intervention in the acute phase. Although echocardiography revealed no remarkable changes of LVEF and LV filling index, no apparent elevations in CK-MB and troponin T levels during the trial were observed. The authors concluded that CSWT was a safe treatment for post-AMI patients, but that the efficacy of CSWT for post-AMI patients remained to be evaluated in future studies.

Kagaya et al. assessed the efficacy and safety of CSWT in patients with AMI who had undergone primary percutaneous coronary intervention.[35] Low-energy shock waves were applied to the ischemic border zone around the infarcted area at 2, 4, and 6 days after AMI. After completing three sessions of CSWT, the patients were then followed up for 12 months. The study included 17 AMI patients and compared them with historical AMI controls by propensity score matching (n = 25), whereby no procedure-related complications or adverse effects were found. At 6 and 12 months after AMI, LV function as assessed by magnetic resonance imaging showed no signs of deleterious LV remodeling. Comparing the CSWT group with the historical AMI controls at 6 months after AMI, LVEF was significantly higher in the CSWT group than in the historical control group by echocardiography (66 ± 7 vs. $58 \pm 12\%$, $P < 0.05$). The authors concluded that low-energy CSWT is feasible and may ameliorate post-AMI LV remodeling in patients with AMI, when used as an adjunctive therapy to primary percutaneous coronary intervention.

Safety

Wang et al. found that isolated premature ventricular contraction occurred in 6 out of 41 patients during CSWT,[36] but did not cause patient discomfort or change in the patient's blood pressure, heart rate, or oxygen saturation. More importantly, no subsequent arrhythmia occurred during the follow-up period. Several patients felt mild chest pain when the wave energy was increased during CSWT. However, the mild chest pain was relieved soon after the energy was reduced.[36,37] Of course, there remained the hypothetical concern that shock wave exposure could result in coronary plaque rupture, induce apoptosis, or damage the endothelium. However, serial measurement of cardiac biomarkers after CSWT showed no significant changes, as

compared to the placebo group.[36] Ceccon et al. demonstrated CSWT improved myocardial blood flow reserve in treated ischemic segments, as demonstrated by quantitative real-time myocardial perfusion echocardiography.[23] This suggests that CSWT could be focused precisely on the treated ischemic myocardium, while not affecting remote segments. The current studies also confirmed that no patients suffered from procedural complications, arrhythmia, pericardial disease, heart failure, or skin damage.[10,21-23,37]

Conclusion

Several previous single-arm cohort studies or randomized controlled trials have consistently demonstrated that CSWT could relieve symptoms, improve quality of life, and reduce myoischemia in CAD patients with RA. This could furthermore result in a significant reduction in NYHA class and a beneficial change of LVEF in patients with ischemic HF, thereby ameliorating LV remodeling and improving LVEF in patients with AMI. Furthermore, the current studies confirmed that no patients suffered from procedural complications, arrhythmia, pericardial disease, heart failure, or skin damage after CSWT. Therefore, although further large-scale and multi-center clinical trials are needed, CSWT is a promising, effective, safe, and non-invasive therapeutic option for patients with RA, ischemic HF, and AMI.

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