Efficacy of cardiac shock wave therapy in patients with stable angina: The design of randomized, triple blind, sham-procedure controlled study

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Abstract

Objective: Despite revascularization and optimal medical treatment (OMT), patients with angina often have a reduced quality of life due to inadequate relief from symptoms. Recent studies have shown that the application of shock waves may reduce angina symptoms and improve quality of life, exercise capacity, and myocardial perfusion due to the stimulation of angiogenesis. However, there is limited evidence due to small, single-arm, single-center studies of low to moderate quality. The purpose of this study is to evaluate the impact of cardiac shock wave therapy (CSWT) on exercise tolerance and angina symptoms in patients with coronary artery disease and objective evidence of myocardial ischemia who cannot undergo traditional revascularization and experience angina despite OMT in comparison to sham procedure.

Methods: We designed a randomized, triple-blind, placebo-controlled, multicentre trial (NCT02339454) to assess the efficacy of CSWT in addition to OMT in patients with stable angina and myocardial ischemia documented by exercise treadmill test (ETT). All patients were treated with stable doses of standard medical treatment 4 weeks before screening. An increase in the total exercise duration on ETT by ≥90 s from the baseline at the end of the study was set as the primary endpoint. Secondary endpoints included angina class, Seattle angina questionnaire scores, symptoms, and ECG changes during stress test. Patients underwent nine sessions of CSWT or corresponding sham procedure applied to all segments of the left ventricle, within 9 weeks. Endpoint assessments were performed at 6-month follow-up. The imaging substudies assessed the potential of CSWT to reduce stress-induced myocardial ischemia detected by dobutamine stress echocardiography, cardiac single-photon emission computed tomography, and cardiac magnetic resonance imaging.

Results: At two centers, 72 of the 323 screened patients were randomized in two groups (ratio 1:1): active treatment and placebo control. Study patients were predominantly males (70.8%); the mean age of the patients was 68.4±8.3 years. Of these, 44 patients had angina Canadian Cardiovascular Society class III, and 66.7% of the patients had a history of myocardial infarction.

Conclusion: Using sham applicators, blinding study participants, investigators, and endpoints assessors to the study data as well as centralized randomization ensures rigorous methodology and low risk of bias in this large randomized controlled CSWT study.

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Keywords: cardiac shock wave therapy, coronary artery disease, stable angina

Introduction

Coronary artery disease (CAD) is being recognized as a leading reason of adult mortality worldwide. According to the ESC guidelines on the management of stable CAD (1), medical treatment, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) are the main therapeutic options. New pharmacological agents such as ranolazine (2) and ivabradine (3) have been suggested for patients with refractory angina. However, surveys show that despite recommended care, up to 14% of patients may continue to be limited with angina, which can markedly affect their quality of life (4-6).

Alternative techniques to enhance myocardial perfusion and reduce symptoms in patients with refractory angina include enhanced external counterpulsation (EECP) (7) and spinal cord stimulation (SCS) (8), as well as sophisticated modalities such as transmyocardial laser revascularization (9), myocardial or intracoronary application of proteins (10) or genetic vectors en-

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coding proteins with angiogenesis potential (11), and stem cell-based therapies (12). Currently, only EECP treatment has been approved and recommended for the management of Canadian Cardiovascular Society (CCS) class III and IV refractory angina (1, 13). Moreover, other therapies are invasive, expensive, and have not yet been proven to be clinically feasible and effective.

Cardiac shock wave therapy (CSWT) has been newly developed based on the lithotripsy method; it uses noninvasive application of low-intensity shock waves to stimulate angiogenesis (14). Several experimental studies have demonstrated that the application of low-intensity shock waves (SW) might induce the release of angiogenic factors such as endothelial nitric oxide synthase, vascular endothelial growth factor, and proliferating cell antinuclear antigen (14-17). Furthermore, many published clinical studies have demonstrated the efficacy and safety of CSWT in patients with refractory angina (18-26). A recently published meta-analysis of CSWT studies showed significantly decreased nitroglycerine consumption and angina frequency; improved CCS angina class, Seattle angina questionnaire scores, and NYHA class; and increased myocardial perfusion and exercise capacity (27). However, the analysis of methodological quality of the majority of available randomized controlled trials (RCTs) on CSWT demonstrated only low to moderate scientific quality because of the high risk of bias in terms of attribution, sample size calculation, blinding of participants, and outcome assessment (27). These findings indicate the need for an adequately powered study that will eliminate the methodological weaknesses of previous research. Thus, we designed a new RCT with sham applicators aiming to ensure proper procedures of blinding, outcome assessments, data reporting, and interpretation.

Methods

Study design

This study was a randomized, triple-blind, sham procedure-controlled, multicentre trial, which was designed to assess the antianginal efficacy of CSWT in addition to standard optimal medical treatment (OMT) in patients with stable angina. The study protocol was created according to the CONSORT statement recommendations for parallel group randomized trials (28). The study was conducted in Lithuania and Russia in accordance with Good Clinical Practice, Declaration of Helsinki, 2013. This study was approved by two ethical committees (Vilnius Regional Ethics Committee, Approval No. 158200-13-616-187 and Moscow State University of Medicine and Dentistry Local Ethics Committee, Approval No. 10-12); it is registered at ClinicalTrials.gov (NCT02339454).

We hypothesized that CSWT reduced angina symptoms and improved exercise tolerance in patients with stable angina more effectively than OMT alone.

The primary endpoint was the total exercise duration in modified Bruce treadmill test at 6-month follow-up. The secondary endpoints were changes in the following: 1) ST-segment depression during treadmill test, 2) angina symptoms during treadmill test, 3) number of angina attacks per week, 4) number of sublingual nitroglycerine consumption per week, 5) CCS angina functional class, and 6) Seattle angina questionnaire (SAQ) score at 6-month follow-up.

Study population

The study cohort included patients with CAD and exercise-induced angina not controlled by the standard OMT, who fulfilled the inclusion/exclusion criteria and had provided informed consent for participation in the study. Patients were found eligible if there was no technical possibility for further revascularization procedures. Table 1 summarizes the inclusion and exclusion criteria. The duration of follow-up lasted for 6 months after CSWT/placebo treatment initiation. The recruitment commenced in May 2013 and finished in December 2015.

This study consists of four phases: screening for eligibility criteria, randomization, treatment, and follow-up.

Screening

The screening phase included evaluation of symptoms, medical history, physical examination, and vital signs, as well as review and adaptation of medical treatment according to the guidelines. Four-week period was kept to ensure clinical stability and stable doses of medication. During the second part of the screening, patients underwent exercise treadmill test (ETT).

Randomization

After the baseline evaluation, consecutive subjects who met the inclusion criteria were assigned to study group A or B with a 1:1 ratio using a random allocation sequence table. For this trial, a professional statistician generated random allocation sequences for two centers. Using centralized randomization, a password-protected access to the random allocation lists was granted only to one principal investigator (JC) for both the centers. The study investigators who performed patients' screening were blind to the allocation sequence.

Similar to the patients, the investigators (clinicians and data assessors) and statistician were blinded to treatment allocation; therefore, the design was fitted for a triple-blinded study. The randomization code was disclosed after the last visit of the last patient during the primary statistical analysis.

Treatment

All patients were maintained on stable doses of optimal medical therapy (1) for 4 weeks before treatment and during the study period. All patients received antiplatelet therapy with aspirin 75–150 mg per day or clopidogrel 75 mg per day, if aspirin intolerance was present. Few patients received dual antiaggregant therapy. All patients received cholesterol-lowering therapy (atorvastatin in most cases) with a target level of low-density lipoprotein (LDL)<1.8 mmol/L. Anti-ischemic therapy included long-acting beta-blockers, calcium channel blockers, and prolonged nitrates

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Table 1. Inclusion and exclusion criteria

Inclusion criteria	• Male and female patients aged ≥18 years with obstructive coronary artery disease confirmed by angiography, prior MI, prior revascularization (PCI, CABG) and with exercise angina not controlled by the optimal medical therapy; • ST-segment depression ≥1 mm during exercise ECG;
Exclusion criteria	• Angina at rest; • ECG abnormalities at rest: left bundle-branch block, ST-segment depression ≥1 mm at rest, WPW-syndrome; • Planned coronary revascularization procedure (PCI or CABG) within 6 months; • Heart failure (class III or IV NYHA); • Thrombus in LV; • Moderate to severe uncontrolled hypertension (systolic BP>160 mm Hg and/or diastolic BP>100 mm Hg); • Hypotension (systolic BP<100 mm Hg); • Acute coronary syndrome or coronary revascularization procedure within the prior 3 months before enrolment; • Severe concurrent pathology, including terminal illness (cancer); • Contraindications for exercise testing (e.g., acute myocarditis, pericarditis, deep venous thrombosis, severe aortic stenosis); • Conditions which in the investigator's opinion may interfere with the study's execution or due to which the patient should not participate for safety reasons; • Risk of low patient cooperation; • Patient is simultaneously participating in another device or drug study, or has participated in any clinical trial involving an experimental device or drug, including other drugs or devices enhancing cardiac neovascularization, or any cardiac shock wave therapy machine of a competitor company within 3 months of entry into the study.

BP – blood pressure, CABG – coronary artery by-pass grafting, ECG – electrocardiogram, LV – left ventricular, MI – myocardial infarction, NYHA – New York Heart Association, PCI – percutaneous coronary intervention, WPW – Wolf-Parkinson-White syndrome

as first-line treatment and trimetazidine, ivabradine, or ranolazine as second-line treatment, along with angiotensin-converting enzyme inhibitors as standard secondary prevention.

CSWT consisted of nine sessions with three sessions per week and was performed on 1st, 5th, and 9th study week. The treatment intensity was 100 impulses applied to one spot with up to 1200 impulses to the patient per session or corresponding duration of placebo application (Fig. 1). A specific sham applicator whose external appearance and behavior were similar to that of an active applicator was used.

During the 1st, 5th, and 9th study week, SWs (up to 10800 impulses in a patient) were delivered to the basal, middle, and apical segments of the left ventricle, respectively. A 3-week treatment-free interval was kept after the 1st and 5th treatment week (Fig. 1).

SWs were generated by discharging a high-voltage spark under water or electromagnetic impulse. CSWT was performed using a Cardiospec™ device (Medispec Ltd, Germantown, USA) coupled with a cardiac ultrasound imaging system (Vivid i, GE Healthcare, Horten, Norway) to target the treatment area. Low-intensity SW (100 impulses/spot; energy flux, 0.09 mJ/mm^2) were delivered using a special applicator through the anatomical acoustic window to the treatment area under electrocardio-

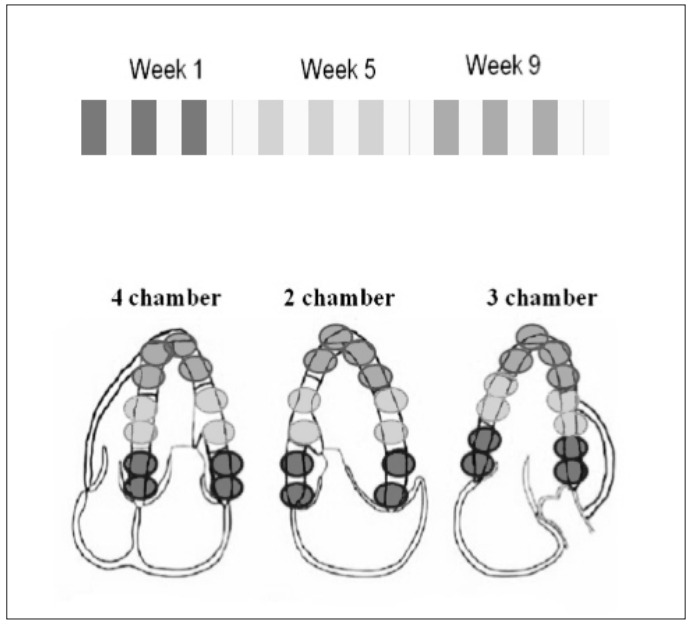

Figure 1. Treatment schedule
During the 1st, 5th, and 9th study weeks, shock waves were delivered to the basal, middle, and apical segments of the left ventricle, respectively (2 zones of waves' application in each wall in apical 4-, 2-, and 3-chamber positions)

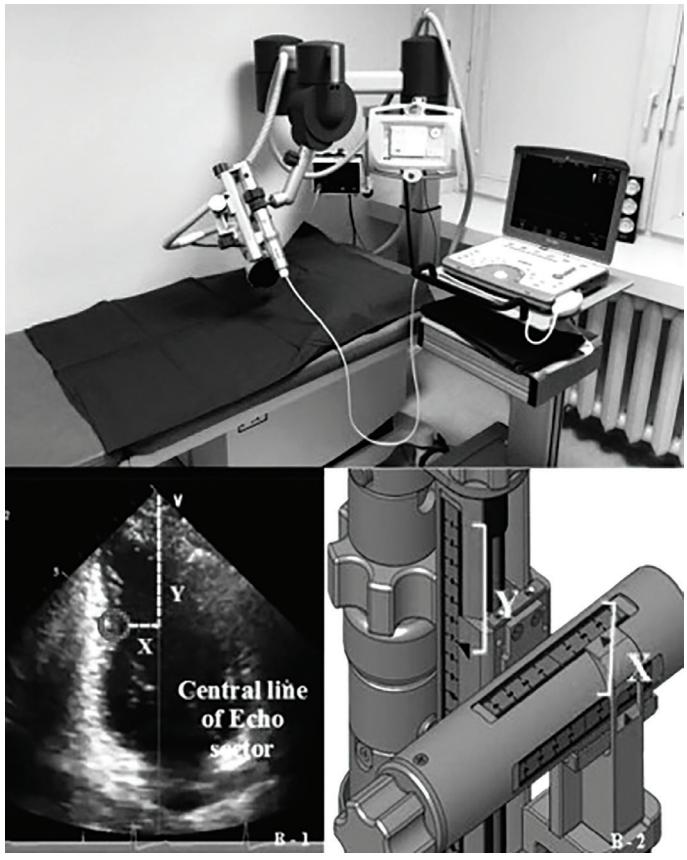

Figure 2. The methodology of shock wave therapy
(a) Shock wave generator system and cardiac imaging system.
(b) Shock wave focal zone alignment: Position of the subsegment on the two-dimensional image determined by X and Y coordinates (1). The shockwave applicator position is identically adjusted along X- and Y-axes corresponding to the X and Y coordinates of the ultrasound image (2)

graphic R-wave gating. The patient was positioned on a device table and connected to the ECG monitor. An ultrasound probe was used to identify the target area. The shock wave applicator was connected with the ultrasound transducer and placed through a membrane in contact with the skin at the target treatment zone, which was visualized on the ultrasound screen (Fig. 2a). For optimal therapy, the treatment area was divided into target zones corresponding to the size of the focal zone of the SW applicator (1-cm diameter circle) (Figure 2b). The distance to these target zones was measured and marked on the ultrasound screen, enabling the operator to see the treated zone in real time. The SW applicator was fixed at the measured distance. An inflatable silicon cushion was filled, and ultrasound gel was used for optimal delivery of shockwaves into the body.

Follow-up visits were performed and outcome measures were assessed at 3 and 6 months after randomization. Table 2 summarizes the follow-up scheme.

Efficacy assessment

All study patients underwent ETT using modified Bruce protocol at baseline and 3 and 6 months after treatment. Beta-blockers were stopped for 48 h and nitrates and other antianginal medicines for 24 h before the ECG stress test in all patients. During the test, 12 ECG leads were continuously monitored, and the blood pressure (BP) was measured at 2-min intervals. The exercise duration in seconds, maximum cardiac workload [expressed by metabolic equivalent (MET)], peak heart rate, and ST-segment depression were recorded. The criteria to stop ECG stress test included ECG changes (≥2 mm ST-segment depression and complex or sustained arrhythmias), severe angina, fatigue, and abnormal BP responses. The ST-segment deviation was measured at 60 ms after J point compared with the resting values during peak exercise and was considered significant if there was ≥1 mm horizontal or down-sloping ST-segment depression in computer-averaged complexes.

The level of angina was classified according to the CCS angina classification. During follow-up visits, patients were asked about the number of angina episodes and sublingual nitroglycerine doses taken in the past week. Quality of life was assessed using SAQ, which is a 19-item self-administered questionnaire that measures five clinically important dimensions of health affected by angina in patients with CAD: physical limitation, angina stability, angina frequency, treatment satisfaction, and quality of life.

Substudy

The substudy, performed only at the Vilnius site, assessed the potential of CSWT to reduce myocardial ischemia determined by dobutamine stress echocardiography (DSE), cardiac single-photon emission computed tomography (SPECT), and cardiac magnetic resonance imaging (CMRI).

For the substudy, patients underwent DSE, SPECT, and cardiac MRI before CSWT and at 6-month follow-up, with DSE performed additionally at 3 months. The analysis of each DSE, SPECT, and CMRI study images was performed by two independent observers who were blinded to the study data. Discordant assessments were jointly reviewed. Myocardial perfusion, regional wall motion, and early and late contrast-enhanced images were performed using the LV 17-segment model (29, 30).

During SPECT and CMRI tests, pharmacologic stress was induced by infusing adenosine at a standard rate of 140 μg/kg/min (maximal total infusion duration of 6 min) (29). All stress tests were performed under continuous monitoring of heart rate and BP.

The segmental wall motion was semi-quantitatively graded as follows: normal; hypokinetic, marked reduction of endocardial motion and thickening; akinetic, defined as the virtual absence of inward motion and thickening; and dyskinetic, corresponding to paradoxic wall motion away from the center of the left ventricle in systole. The sum of all segment scores made up the wall motion score (WMS), divided by the number of interpretable segments made WMSI.

Myocardial perfusion imaging SPECT

A 1-day ECG-gated stress and rest SPECT protocol was used. After 3 min of adenosine infusion, patients were intravenously injected with a body mass index adjusted dose (250–350 MBq) of

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Table 2. Study schedule

	Screening		Randomization	Treatment period			Follow up period	
	-56 to -29 day	-28 to -1 day	0	1 week	5 week	9 week	3 month	6 month
Informed consent	X							
Inclusion/Exclusion criteria	X	X						
Cardiovascular medical history and risk factors	X							
Other medical history and current conditions	X							
CCS class	X	X		X	X	X	X	X
Physical examination	X			X	X	X	X	X
Assignment to study group			X					
SAQ		X					X	X
Echocardiography		X						X
ECG		X						
ECG Treadmill stress test		X						X
Dobutamine stress echocardiography*		X					X	X
Myocardial perfusion imaging SPECT*		X						X
Cardiac MRI*		X						X
Medication review (including nitroglycerin consumption)	X	X		X	X	X	X	X
CSWT/placebo procedure				X		X	X	
AE recording		X		X	X	X	X	X

AE - adverse event, CCS - Canadian Cardiovascular Society angina class, CSWT - cardiac shock wave therapy, ECG – electrocardiogram, DSE - Dobutamine stress echocardiography, MRI - magnetic resonance imaging, SAQ - Seattle Angina Questionnaire, SPECT - single photon emission computed tomography.
* – test was performed only at Vilnius site

technetium 99m (^{99m}Tc)-sestamibi (MIBI). Rest myocardial perfusion imaging (MPI) was performed on the same day 4 h after the stress MPI with identical acquisition protocol. Gated SPECT studies were performed 60 min after ^{99m}Tc-MIBI injection using a dual-head INFINIA GP3 (GE Medical Systems, Waukesha, WI, USA) gamma camera.

SPECT stress tests were performed and digitally recorded at baseline and 6-month follow-up. Gated and nongated SPECT MPI image sets were reconstructed using OSEM iterative reconstruction with the dedicated Xeleris 2.1 workstation using Cedars-Sinai QGS/QPS software package (Cedars-Sinai, Los Angeles, CA, USA). Perfusion defects were scored using a 5-point scoring system. SPECT analysis included summed rest, stress, and difference scores. A summed difference score of 0 was considered as normal, of 1–4 as mild ischemia, of 4–7 as moderate ischemia, and >7 as severe ischemia of myocardium (31).

Dobutamine stress echocardiography

Electrocardiogram and echocardiogram were performed at rest, and intravenous access was secured. Dobutamine was infused at 5, 10, 20, 30, and 40 μg/kg/min for 3 min at each stage. When no end point was reached, atropine (in four divided doses of 0.25 mg, up to a maximum of 1 mg) was added to the continuing 40 μg/kg/min dobutamine infusion.

Transthoracic stress echocardiographic studies were performed using a commercially available ultrasound machine (System Vivid 7 and 9, GE Healthcare, Horten, Norway) with a 1.5–4.6 MHz transducer. From the parasternal window, the long and short axis of LV, and from the apical window, the 4-, 3-, and 2-chamber views were acquired for comparing the four stages of the stress test. The images were stored digitally and analyzed offline using customized software (Echopac PCBT08, GE Healthcare). For DSE evaluation, moderate ischemia was defined as ≥3 segments with stress-induced hypokinesis or akinesis (32).

Speckle tracking images were recorded at baseline and peak dobutamine levels with breath holding. The frame rate of stored apical 2-, 3-, and 4-chamber cine-loops for speckle tracking analysis was in the range of 70–90 frames/second. Graphical displays of deformation parameters (reflecting the average value of displacement markers in each segment) were then automati-

cally generated for six segments in each view. The peak longitudinal systolic strain at rest and during stress was measured using automated vendor-suggested software.

Baseline and 3- and 6-month follow-up studies were digitally recorded. Two experienced independent observers blinded to the study data performed the analysis. DSE analysis included WMS, global myocardial strain analysis, and LV ejection fraction with Simpson's biplane method.

Cardiac magnetic resonance imaging

CMRI was performed using a 1.5 T MR scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany). After acquiring standard cine scans for the assessment of left ventricular function, a turbo gradient echo pulse sequence (Turbo FLASH) was acquired for perfusion imaging. After at least 3 min of adenosine infusion, Turbo FLASH sequence was repeated for stress first-pass perfusion imaging [(intravenous bolus application of 0.15 mmol/kg of gadolinium-based contrast agent (Magnevist)]. After a 10-min waiting period, late gadolinium enhancement (LGE) imaging was done in the identical short-axis geometry with full coverage of the left ventricle.

CMRI examinations were analyzed with Argus software (Siemens Healthcare GmbH, Erlangen, Germany) by two expierenced observers. Short-axis endocardial contours were manually traced in end-diastole (start of R-wave) and end-systole (smallest cavity area). Papillary muscles and trabeculations were included in the LV cavity (according to the ASE criteria). The volumes of LV were automatically computed in milliliters using the modified Simpson's rule by summing the cross-sectional areas contained by the endocardial borders of all short-axis slices included in the analysis. Segmental perfusion was interpreted as normal or abnormal. LGE was assessed on a 5-grade scale as follows: 0=no hyperenhancement, 1=hyperenhancement of 1%–25% of the tissue in each segment, 2=hyperenhancement of 26%–50% of the tissue, 3=hyperenhancement of 51%–75% of the tissue, and 4=hyperenhancement of 76%–100% of the tissue. The LGE-score was obtained by summing the scores of the 17 segments of the LGE images (29, 32).

Statistical analysis

Baseline patient characteristics were descriptively summarized: continuous variables were expressed as mean value±standard deviation (SD), whereas categorical variables were expressed as absolute numbers (percentages). In the first step, the paired parameters were tested for normal distribution with the Shapiro–Wilk test. Chi-square tests or Fisher exact test were used to compare categorical variables. Normally distributed variables were analyzed using parametric test (t-test); not normally distributed variables were analyzed using nonparametric tests (Mann–Whitney U test).

P<0.05 (two-sided) was considered significant. The overall effect of CSWT was evaluated by comparing the average change of variable in the treatment group with the average change of variable in the placebo group. Statistical analyses were performed with SPSS 20.0 (SPSS, Chicago, IL, USA).

Calculation of sample size

For the sample size estimation, a power of 90% and a two-sided type I error of 5% were chosen. On the basis of published data (24), we assumed a SD of 110 s for total exercise duration; this produced 33 patients per group necessary to detect a ≥90 s difference. Estimating withdrawal of 10% of patients after randomization, approximately 73 patients would have to be included in the study.

Results

Baseline patient characteristics

A total of 72 patients who met the inclusion criteria were randomized (Fig. 3). The mean age was 68.4±8.3 years; 61.1% of patients were in CCS class III, 33.3% were in CCS class II, and others in CCS class I. The cardiac risk factor profile was high as each patient had at least two risk factors for cardiovascular disease. History of myocardial infarction was present in 80% of patients in group A and 51.4% of patients in group B (p=0.011). A majority of patients (78%) had multivessel disease, and 96% were not candidates for further revascularization due to the extent and severity of disease, previous interventions, or risk/benefit ratio. There were 58 patients who had previously undergone

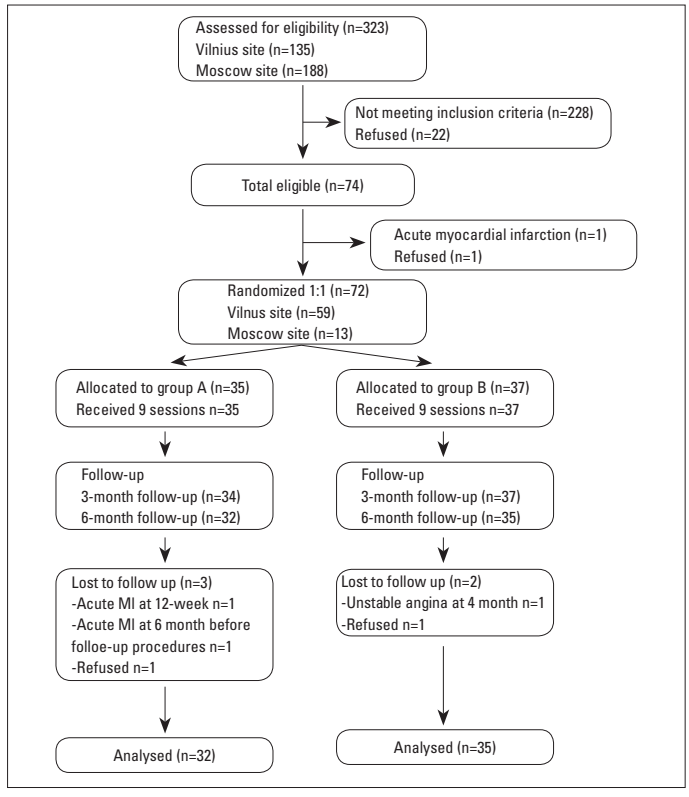

Figure 3. Flow chart of study patients
MI - myocardial infarction

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Table 3. Baseline characteristics of study patients

Variable	Group A (n=35)	Group B (n=37)	*P* value
Demographic characteristics			
Age, years	68.8±8.3	67.6±8.3	0.546
Male sex, n (%)	28 (80)	23 (62.2)	0.099
Cardiovascular risk factors			
Hyperlipidemia, n (%)	30 (85.7)	31 (83.8)	0.824
Hypertension, n (%)	34 (97.1)	36 (96.3)	0.851
Diabetes, n (%)	10 (28.6)	8 (21.6)	0.496
Peripheral vascular disease, n (%)	12 (34.3)	10 (27.0)	0.505
Current smoker, n (%)	6 (17.1)	2 (5.4)	0.117
Positive family history for cardiovascular diseases, n (%)	20 (57.1)	11 (29.7)	0.020
Medical history			
Previous myocardial infarction, n (%)	28 (80)	19 (51.4)	0.011
Previous percutaneous intervention, n (%)	19 (54.3)	19 (51.4)	0.807
Previous CABG, n (%)	20 (57.1)	20 (54.1)	0.799
No revascularization, n (%)	7 (20.0)	7 (18.9)	0.906
Three-vessel disease, n (%)	22 (75.9)		
(n=29)	24 (80)		
(n=30)	0.161		
Two-vessel disease, n (%)	2 (6.9)		
(n=29)	5 (16.7)		
(n=30)			
Paroxysmal atrial fibrillation, n (%)	10 (28.6)	7 (18.9)	0.336
Clinical parameters			
Body mass index, kg/m^2	30.1±3.8	29.7±4.1	0.647
Angina episodes/ week, median (25; 75%)	5.5 (2.3; 13.5)	6 (3; 14)	0.619
Nitroglycerine consumption (times/week), median (25; 75%)	1 (0; 3.8)	2 (0.5; 2.5)	0.250
Left ventricular ejection fraction (echocardiographic), %	56.5±7.1	54.5±9.1	0.284
Systolic blood pressure, mm Hg	129.2±22	125.8±21.7	0.831
Diastolic blood pressure, mm Hg	78.8±11.8	79.1±11.8	0.239
Angina CCS class			
I, n (%)	1 (2.9)	3 (8.1)	0.506
II, n (%)	13 (37.1)	11 (29.7)	
III, n (%)	21 (60.0)	23 (62.3)	
SAQ scores			
Physical limitation, %	53.2±22.6	52.5±21.6	0.915
Angina stability, %	45.3±29.7	39.1±24.1	0.290
Angina frequency, %	58.1±24.8	58.9±31.1	0.776
Treatment satisfaction, %	75.5±17.1	68.3±16.2	0.190
Disease perception, %	55.7±22.4	51.9±20.8	0.662
Medical treatment			
ACE inhibitors/ARB, n (%)	33 (94.3)	36 (97.3)	0.527
Beta-blocker, n (%)	34 (97.1)	35 (94.6)	0.599

Table 3. Cont.

Variable	Group A (n=35)	Group B (n=37)	*P* value
Long acting nitrates, n (%)	16 (45.7)	20 (54.1)	0.479
Calcium channel blocker, n (%)	19 (54.3)	18 (48.7)	0.637
Trimetazidine, n (%)	15 (42.9)	21 (56.8)	0.242
Diuretics, n (%)	18 (51.4)	17 (46.0)	0.649
Statins, n (%)	36 (100)	37 (100)	-
Antiplatelets, n (%)	36 (100)	37 (100)	-
Dual-antiplatelet therapy, n (%)	12 (34.3)	5 (13.5)	0.059
Oral anti-diabetics, n (%)	9 (25.7)	4 (10.8)	0.136

ACE- angiotensin-converting enzyme, ARB- angiotensin II receptor blocker, CABG- coronary artery bypass grafting, CCS- Canadian Cardiovascular Society, MI- myocardial infarction, NYHA- New York Heart Association, PCI- percutaneous coronary intervention, SAQ- Seattle Angina Questionnaire
*-ECG stress test, treadmill, modified Bruce protocol
P<0.05 considered as significant

revascularization (PCI or CABG, or both); seven patients had no revascularization procedure (no technical possibility for further revascularization) in each group. All study patients used statins and antiplatelet drugs; 94.5% and 50.7% of patients used beta-blockers and calcium channel blockers, respectively. The other characteristics (medical history, risk factors, and medications) were similar in both groups (Table 3), except for more frequent positive family history of CAD in group A (p=0.020). The exercise capacity was moderately reduced in both study groups (total exercise duration in minutes was 6.5±2.7 in group A and 6.1±2.3 in group B, p=0.479). There were no significant differences between countries in any baseline characteristics (age, cardiovascular risk factors, medical history, and clinical parameters).

Discussion

Despite major advances in the management of CAD, this condition is recognized to be a leading reason of adult mortality worldwide and is responsible for 20% of deaths each year in Europe (33), with stable angina being the most frequent clinical presentation.

Many patients experience persistent symptoms despite revascularization procedures and modern medical treatment. Thus, there is a crucial need for the development and investigation of novel pharmacological, invasive or noninvasive treatment modalities, aimed at improving care and quality of life for this challenging patient population.

CSWT is a novel approach that is potentially effective for the treatment of patients with refractory angina that reduces symptoms and improves quality of life. SWs belong to acoustic waves that can be transmitted through a liquid medium and focused with a precision of several millimeters to any intended treatment area inside the body. SWs are delivered to the targeted area to potentially induce neovascularization from the healthy area to the ischemic zone through shear stress. The noninvasive nature and lack of significant adverse events make it an attractive option for patients suffering from refractory angina. However, limited information is currently available on the actual efficacy of this new modality.

Recently published systematic review of CSWT studies in stable CAD demonstrated a significant improvement of clinical variables including angina class and quality of life, as well as positive changes in LV function and perfusion. A meta-analysis showed moderate improvement in exercise capacity. Overall, CSWT seems to be a potentially effective, new, and noninvasive option for patients with CAD; however, evidence is limited to small, single-center studies with a high risk of bias due to the absence of credible control and allocation procedures (27). Thus, more data derived from randomized and placebo-controlled trials are required for its widespread use.

The measurement of exercise tolerance by time to ischemic ECG changes or development of symptoms during ETT is a widely used outcome in CAD studies. The subjective physical and emotional impact of angina pectoris is assessed using SAQ (34). SAQ is commonly used for measuring health status in coronary patients, which has been confirmed as a valid, reproducible, and sensitive performance measure for assessing the quality of CAD care (35). Therefore, ETT, CCS score, and SAQ were chosen as efficacy parameters in our study. The advantages of these tests are their simplicity, safety, negligible cost, and wide accessibility.

The novelty and better quality evidence of this study include several aspects. Patients were enrolled to a multicenter, randomized, placebo-controlled trial on the basis of myocardial ischemia proven by several stress tests. A new treatment protocol was produced to facilitate the application of SW to all segments of LV. In previously published studies, SWs were applied only to the ischemic segments of LV. The new protocol aims to extend the indications for widespread use of CSWT that is not based on the results of imaging tests or coronary angiography, which are unavailable sometimes. The application of SW to all segments of LV may provide beneficial therapeutic effects by not only reducing ischemia but also attenuating inflammation and suppressing

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oxidative stress and fibrosis in nonischemic segments as well, potentially preventing LV remodeling.

Therefore, compared with previous randomized CSWT trials, we consider our study to be at a low risk of bias in terms of methodology.

Study limitations

As treatment area needs to be localized, the patients without an adequate echocardiographic window (e.g., overweight, pulmonary disease) cannot receive CSWT. The safety of CSWT use in patients with pacemakers of implantable defibrillators has not been defined yet.

Conclusion

Using sham applicators, blinding study participants, investigators, and endpoints assessors to the study data as well as centralized randomization ensures rigorous methodology and low bias in this large, randomized, controlled CSWT study.

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