The effect of cardiac shock wave therapy on myocardial function and perfusion in the randomized, triple-blind, sham-procedure controlled study

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Abstract

Background: Recent triple-blind sham procedure-controlled study revealed neutral effects of the cardiac shock wave therapy (CSWT) on exercise tolerance and symptoms in patients with stable angina. Current data about the effects of CSWT on global and regional myocardial contractility and perfusion is limited. Hereby we report the results of an imaging sub-study that evaluated the capacity of CSWT to ameliorate myocardial ischemia induced during dobutamine stress echocardiography (DSE) and cardiac single photon emission computed tomography (SPECT).

Methods: Prospective, randomized, triple-blind, sham procedure-controlled study enrolled 72 adult subjects who complied with defined inclusion criteria. The subjects were assigned to the OMT + CSWT and the OMT + sham procedure study groups with 1:1 ratio. Application of the CSWT covered all segments of the left ventricle. Imaging ischemia tests were performed in 59 study patients: DSE and SPECT before the CSWT treatment and after 6 months, with DSE carried out additionally at 3 months after randomization. Co-primary endpoints of the study were: change in wall motion score index (WMSI), representing the stress-induced impairment of regional myocardial function, and change in summed difference score (SDS), representing the amount of perfusion defect.

Results: OMT + CSWT and OMT + sham procedure study groups included 30 and 29 patients, respectively. Regional myocardial contractility during DSE significantly improved at 3 months follow-up in OMT + CSWT group compared to baseline as shown by WMSI at stress (1.4 ± 0.4 vs 1.6 ± 0.4, p = 0.001), but not in OMT + sham procedure group (1.5 ± 0.3 vs 1.6 ± 0.4, p = 0.136). The difference in stress DSE results between both study groups disappeared after 6 months. SPECT results demonstrated a significant reduction of inducible ischemia in OMT + CSWT group compared to OMT + sham procedure group at 6 months follow-up (SDS dropped from 5.4 ± 3.7 to 3.6 ± 3.8 vs 6.4 ± 5.9 to 6.2 ± 5 respectively, p = 0.034).

Conclusions: Cardiac shock wave treatment showed the ability to reduce stress-induced myocardial ischemia, as assessed by wall motion abnormalities and perfusion defects, compared to sham procedure.

(Continued on next page)
Trial registration: Clinicaltrials.gov (NCT02339454). The trial was registered retrospectively on 12 January 2015.

Keywords: Cardiac shock wave therapy, Coronary artery disease, Stable angina, Myocardial perfusion, Dobutamine stress echocardiography, Single photon emission computed tomography

Background
Major advances in medical therapy and revascularization techniques have markedly improved the quality of life of coronary artery disease (CAD) patients. However, despite this progress, up to 14% of patients still face considerable symptomatic burden of refractory angina, which is not amenable to traditional revascularization options [1, 2].

Cardiac shock wave therapy (CSWT) is a newly developed method that utilizes a non-invasive application of low-intensity shock waves (SW), which induce the release of angiogenic factors such as endothelial nitric oxide synthase, vascular endothelial growth factor, and proliferating cell antinuclear antigen [3–5]. A number of published clinical studies showed the efficacy and safety of CSWT in patients with refractory angina [6–14]. Despite encouraging results, evidence supporting the efficacy of CSWT mostly came from small, uncontrolled, low to moderate quality single centre observational studies [15]. Moreover, only limited information about the effects of CSWT on global and regional myocardial contractility and perfusion is available in current literature. In addition to the prospective, randomized, triple blind, sham-procedure controlled trial [16], we performed an imaging sub-study to evaluate the capacity of CSWT to reduce the objective signs of myocardial ischemia, that were determined by dobutamine stress echocardiography (DSE) and SPECT.

Methods
Main study design
A prospective, randomized, triple blind, sham-procedure controlled study was designed to assess the antianginal efficacy of CSWT, on top of standard medical therapy in patients with stable angina. Study protocol was created according to Consolidated Standards of Reporting Trials (CONSORT) statement recommendations for parallel group randomized trials [17] and the study conducted in accordance with Good Clinical Practice, Declaration of Helsinki 2013. The design, methods, and results of the main trial (NCT02339454) were described previously [16, 18].

Briefly, patients diagnosed with angiography confirmed-CAD and exercise induced-angina associated with ST-segment depression ≥1 mm on treadmill electrocardiogram (ECG), and symptoms not controlled by optimal medical treatment (OMT), were enrolled in the study. Exclusion criteria were: angina at rest, acute coronary syndrome or planned coronary revascularization within 6 months, New York Heart Association (NYHA) heart failure class III-IV, thrombus in left ventricle, contraindications for exercise testing, ECG abnormalities at rest. Eligible subjects were assigned to the OMT + CSWT and the OMT + sham procedure study groups with 1:1 ratio. Patients, investigators (clinicians and data assessors), and a statistician were blinded to treatment allocation.

Main study treatment
All patients were maintained on stable doses of medications [19] for 4 weeks before the baseline evaluation and the entire study period. CSWT was performed using Cardiospec device (Medispec Ltd., Germantown, Maryland, USA) coupled with a cardiac ultrasound imaging system (Vivid I; GE Healthcare, Horten, Norway) to target the treatment area under ECG R-wave gating. Treatment consisted of 9 sessions with 3 sessions per week and was performed on the first, fifth, and the ninth study weeks. Treatment intensity was equal to 100 impulses applied to one spot with up to 1200 impulses to the patient per session. During the first, fifth, and the ninth study weeks, SWs were delivered to the basal, middle, and apical segments of the left ventricle (LV), respectively, covering the whole LV [18].

Imaging sub-study design
The imaging sub-study was conducted at Vilnius University Hospital Santaros klinikos (Vilnius, Lithuania) and was approved by Vilnius Regional Ethics Committee (Approval No. 158200–13–616-187). We hypothesized that compared to sham procedure, CSWT on top of the OMT will significantly reduce the stress-induced myocardial ischemia as detected by the ventricular wall motion and perfusion imaging tests.

The co-primary endpoints of the study were the anticipated change of:

1. stress wall motion score index (WMSI), representing the stress-induced impairment of regional myocardial function during DSE;
2. summed difference score (SDS), representing the amount of perfusion defect during SPECT.

The secondary endpoints included the anticipated changes of:

1. stress wall motion score and LVEF during DSE,
2. number of patients with at least moderate stress-induced ischemia,
3. frequency of angina and ST depression during DSE,
4. global and single-view systolic longitudinal strain,
5. stress summed score and total perfusion defect
detected by SPECT.

Each sub-study patient underwent DSE and SPECT be-
fore the CSWT treatment and at 6-months follow-up,
with DSE performed additionally at 3 months. Beta-
blocking medications were discontinued for 48 h, other
antiangiinal medications for 24 h prior to stress tests as
recommended in Stress Echocardiography Expert Consen-
sus Statement [20] and European Association of Nuclear
Medicine procedural guidelines [21]. Analysis of each DSE
and SPECT study images were performed by two inde-
pendent observers blinded to the study data using the LV
17-segment model [22, 25, 26]. Discordant assessments
were jointly reviewed.

Dobutamine stress echocardiography
Dobutamine was infused at 5, 10, 20, 30, and 40 μg/kg/min.
If no end point was reached, atropine (up to 1 mg) was
added to the continuing 40 μg/kg/min dobutamine infusion.

Transthoracic stress echocardiographic studies were
performed with a commercially available ultrasound ma-
chine (Vivid 7 and 9, GE Healthcare, Horten, Norway)
with a 1.5–4.6 MHz transducer. Long and short axes of
the LV from the parasternal window and 4-, 3- and 2-
chamber views from the apical window were acquired for
comparison in four stages of stress test. Images were
stored digitally and analysed off-line using customised
software (Echopac PCBT08, GE Healthcare). Segmental
wall motion was semi-quantitatively graded as follows:
normal = 1; hypokinetic, meaning marked reduction of
endocardial motion and thickening = 2; akinetic defined as
virtual absence of inward motion and thickening = 3; and
dyskinetic, corresponding to paradoxic wall motion away
from the centre of the LV in systole = 4. The sum of all
segment scores generates wall motion score (WMS),
which, when divided by the number of interpretable seg-
ments makes wall motion score index (WMSI).

Test positivity was defined as the occurrence of at least
one of the following conditions: 1) new dyssnergy in a
region with normal resting function (i.e., normokinesis be-
coming hypo-, aki- or dyskinetic), 2) worsening of a resting
dyssnergy (i.e., a hypokinesia becoming aki- or dyskinesia).
For dobutamine stress echocardiography evaluation, mod-
erate ischemia was defined as ≥3 segments with stress in-
duced severe hypokinesis or akinesis [23].

Deformation imaging during DSE
Apical 2-, 3- and 4-chamber cine-loops for speckle track-
ing analysis were recorded at baseline and peak dobuta-
mime levels with breath holding in the range of 70–90
frames/sec. After manual tracing of endocardium borders
of the 2D images, the software automatically tracked myo-
cardial motion, creating 6 regions of interest in each apical
image, with tracking quality labelled as verified or un-
acceptable. In segments with unacceptable tracking, ob-
server readjusted the endocardium trace line until a
verified tracking was achieved. If this was not attainable,
that segment was excluded from the analysis. Peak longi-
tudinal global systolic and single 4-, 3- and 2- chambers
view strains at rest and during stress were measured.

DSE analysis included WMSI, myocardial strain ana-
lysis and LV ejection fraction (EF) measured by Simp-
son’s biplane method.

Myocardial perfusion imaging by SPECT
During SPECT stress was induced by infusion of adeno-
sine at a standard rate of 140 μg/kg/min (maximal infu-
sion duration of 6 min) [24]. A 1-day ECG gated stress
and rest SPECT protocol was used. After 3 min of ad-
enosine infusion patients were injected intravenously
with a body mass index adjusted dose (250–350 MBq) of
technetium 99 m (99mTc)-sestamibi (MIBI). At-rest myo-
cardial perfusion imaging (MPI) was performed at the
same day, 4 h after the stress MPI, with identical acquisi-
tion protocol 60 min after 99mTc-MIBI injection, with a
dual-head INFINIA GP3 (GE Medical Systems, Wauke-
sha, WI, USA) gamma camera.

Gated and non-gated SPECT MPI image sets were re-
constructed using OSEM iterative reconstruction, with the
dedicated Xeleris 2.1 workstation, using Cedars-Sinai
QGS/QPS software package (Cedars-Sinai, Los Angeles,
CA, USA). Each segment was scored separately using a 5-
point model as follows: 0 = normal perfusion, 1 = minimal
perfusion defect, 2 = moderate perfusion defect, 3 = severe
perfusion defect, 4 = no perfusion. The variables included
summed rest score (SRS), summed stress score (SSS),
and summed difference score (SDS: stress minus rest score).
Total perfusion defect (TPD) was calculated by dividing
the summed scores by 68, which is the maximal potential
score (4 × 17) and multiplying by 100. Reversible from
stress to rest perfusion defects were considered to repre-
sent myocardial ischemia [21, 25, 26]. Summed difference
score of 0 corresponds to normal perfusion, 1–4 to mild is-
chemia, 4–7 to moderate ischemia, and more than 7 as se-
vere ischemia [27]. In one patient image quality was not
amenable for interpretation, therefore his test was ex-
cluded from the analysis.

Statistical analysis and sample size calculation
Baseline patients’ characteristics were descriptively summa-
rized: continuous variables were expressed as mean value
± standard deviation (SD), whereas categorical variables
were expressed as absolute number (percentage). 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. Difference between groups for variables with normal distribution was analysed by using parametric t-test, while for not normally distributed variables a non-parametric Mann-Whitney test was used. Wilcoxon signed rank test was used to compare paired data at baseline and follow-up.

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

For the sample size estimation, a power of 90% and a two-sided type I error of 5% were chosen. On the basis of study results [7], assuming a standard deviation of 6.4 for wall motion score, 22 patients per group were necessary to detect $\geq 3$ points difference. Estimating a withdrawal of 10% of patients after randomization, approximately 50 patients were needed to be included in the study. Assuming a standard deviation of 3.8 for summed difference score, 18 patients per group were necessary to detect $\geq 3$ points difference. Estimating withdrawal of 10% of patients after randomization, approximately 40 patients were needed to be included in the study.

**Inter-observer agreement**

Inter-observer agreement of the DSE and SPECT evaluations was assessed by two independent investigators, who had measured the representative parameters of stress tests in 15 and 30 randomly selected patients, respectively. Reproducibility was expressed as the mean difference and the SD of the differences between values of observer 1 and observer 2 [28]. As a measure of reliability, intraclass correlation coefficients (ICC) and their 95% confidence intervals (CI) based on consistency of 2-way mixed effects model were calculated for each parameter using the icc(irr) function of R package (version 3.4.1) [29]. ICC values less than 0.5, 0.5–0.75, 0.75–0.9 and >0.9 indicate poor, moderate, good and values excellent reliability, respectively [30].

**Results**

From June 2013 to December 2015, 72 patients were randomized (1:1) in the main study, of them 59 underwent intervention (Table 2, Fig. 1), as well as the occurrence of stress angina both assessment points only in OMT + CSWT group at any time point (Table 2, Fig. 1). Analysis of the SPECT perfusion defects demonstrated beneficial effects of the CSWT treatment at 6-months follow-up. Significant reduction in the amount of reversible ischemia (decreased SDS) was achieved in the OMT + CSWT group and not the OMT + sham procedure group (Table 2, Fig. 2).

**Co-primary endpoints of the study**

CSWT treatment caused a significant reduction of stress-induced ischemia in contrast to the sham applications at 3 months as demonstrated by the decrease of WMSI at stress (Table 2, Fig. 1) at the first time point of the follow-up. Positive anti-ischemic effect was maintained in the OMT + CSWT group throughout the study, however it also appeared in the OMT + sham procedure group at 6-months follow-up, resulting in no significant difference in the stress regional myocardial function between the groups at the end of the study (Table 2, Fig. 1). Analysis of the SPECT perfusion defects demonstrated beneficial effects of the CSWT treatment at 6-months follow-up. Significant reduction in the amount of reversible ischemia (decreased SDS) was achieved in the OMT + CSWT group and not the OMT + sham procedure group (Table 2, Fig. 2).

**Secondary endpoints of the study**

Changes in WMS were equivalent to the dynamics of WMSI: the former decreased only in the interventional group in a short-term, but at the end of the study reached significant reduction in all study patients. Patients in the OMT + CSWT group demonstrated higher ejection fraction at stress at both follow-up time points as well as an increased rest LVEF at the end of study. In contrast, no increase was reported in the OMT + sham procedure group at any time point (Table 2, Fig. 1b). Number of patients with at least moderate ischemia significantly decreased at both assessment points only in OMT + CSWT group (Table 2, Fig. 1), as well as the occurrence of stress angina and ST depression (Table 2). The ECG changes were remarkably less frequent in the interventional group than in sham procedure group at 3 months.

Reduced baseline global peak systolic strain (PSS) was found in all patients both at rest and during stress (Table 2). CSWT treatment demonstrated a protective effect on myocardial deformation throughout the study period: strain values did not significantly change in the OMT + CSWT group in contrast to the OMT + sham procedure group. At 6-months follow up a significant decrease of rest 2-chamber view PSS ($-15.1 \pm 3.3$ to $-13.3 \pm 2.1$, $p = 0.026$) and of stress 4-chamber view PSS ($-15.3 \pm 4.8$ to $-12.9 \pm 2.5$, $p = 0.002$) was recorded in the latter group. Finally, a
| Variable                                      | OMT + CSWT group (n = 30) | OMT + sham procedure group (n = 29) | P value |
|----------------------------------------------|---------------------------|-------------------------------------|---------|
| **Demographic characteristics**              |                           |                                     |         |
| Age, years                                   | 67.2 ± 7.8                | 69.4 ± 7.8                          | 0.274   |
| Male sex, n (%)                              | 19 (63.3)                 | 26 (89.7)                           | 0.018   |
| **Cardiovascular risk factors**              |                           |                                     |         |
| Hyperlipidaemia, n (%)                       | 30 (100)                  | 29 (100)                            | –       |
| Hypertension, n (%)                          | 29 (96.7)                 | 29 (100)                            | –       |
| Diabetes, n (%)                              | 8 (26.7)                  | 8 (27.6)                            | 0.937   |
| Peripheral vascular disease, n (%)           | 10 (33.3)                 | 12 (41.4)                           | 0.523   |
| Current smoker, n (%)                        | 1 (3.3)                   | 4 (13.8)                            | 0.195   |
| Positive family history for CVD, n (%)       | 10 (33.3)                 | 19 (5.5)                            | 0.013   |
| **Medical history**                          |                           |                                     |         |
| Previous myocardial infarction, n (%)        | 15 (50.0)                 | 23 (79.3)                           | 0.019   |
| Previous percutaneous intervention, n (%)    | 16 (53.3)                 | 15 (51.7)                           | 0.902   |
| Previous CABG, n (%)                         | 20 (66.7)                 | 18 (62.1)                           | 0.712   |
| No revascularization, n (%)                  | 7 (23.3)                  | 7 (24.1)                            | 0.936   |
| Three-vessel disease, n (%)                  | 24 (80.0)                 | 22 (75.9)                           | 0.161   |
| Two-vessel disease, n (%)                    | 5 (16.7)                  | 2 (6.9)                             |         |
| **Clinical parameters**                      |                           |                                     |         |
| Body mass index, kg/m²                       | 30.0 ± 4.3                | 30.3 ± 3.8                          | 0.755   |
| Angina episodes/week, median (25%;75%)       | 5.5 (3.3; 14.8)           | 7 (3.8; 15)                         | 0.500   |
| Nitroglycerine consumption (times/week), median (25%;75%) | 2 (1; 2) | 2 (0; 5) | 0.250   |
| Left ventricular ejection fraction (echocardiographic), % | 54.4 ± 9.5 | 56.0 ± 7.2 | 0.366 |
| Systolic blood pressure, mmHg                | 124.7 ± 20.9              | 128.1 ± 22.1                        | 0.845   |
| Diastolic blood pressure, mmHg               | 81.1 ± 11.3               | 77.0 ± 11.2                         | 0.341   |
| **Angina CCS class**                         |                           |                                     |         |
| II, n (%)                                    | 8 (26.7)                  | 9 (31.0)                            | 0.711   |
| III, n (%)                                   | 22 (73.3)                 | 20 (69.0)                           |         |
| **Medical treatment**                        |                           |                                     |         |
| ACE inhibitors / ARB, n (%)                  | 30 (100)                  | 29 (100)                            | –       |
| Beta-blocker, n (%)                          | 28 (93.1)                 | 27 (93.1)                           | 1       |
| Long acting nitrates, n (%)                  | 19 (63.3)                 | 15 (51.7)                           | 0.367   |
| Calcium channel blocker, n (%)               | 16 (51.3)                 | 15 (51.7)                           | 0.902   |
| Trimetazidine, n (%)                         | 20 (66.7)                 | 15 (51.7)                           | 0.243   |
| Statins, n (%)                               | 30 (100)                  | 29 (100)                            | –       |
| Mean dose of atorvastatin, mg                | 36.2 ± 11.8^a             | 40.3 ± 17.0                         | 0.286   |
| Antiplatelets, n (%)                         | 30 (100)                  | 29 (100)                            | –       |
| Dual-antiplatelet therapy, n (%)             | 4 (13.3)                  | 11 (37.9)                           | 0.031   |
| Oral anti-diabetics, n (%)                   | 4 (13.3)                  | 7 (24.1)                            | 0.287   |
| **ECG Exercise test**                        |                           |                                     |         |
| Exercise duration, sec                       | 350.1 ± 133.1             | 370.4 ± 131.0                       | 0.558   |

*one patient in this group was on fluvastatin 80 mg, not included in mean dose calculations

Table 1 Baseline characteristics of the study patients

ACE inhibitors / ARB, ARB: Angiotensin receptor blockers, CABG: Coronary artery bypass grafting, CCS: Canadian Cardiovascular Society, CSWT: Cardiac shock wave therapy, CVD: Cardiovascular disease, OMT: Optimal medical therapy, SAQ: Seattle Angina Questionnaire

^a one patient in this group was on fluvastatin 80 mg, not included in mean dose calculations
significant reduction of myocardial hypoperfusion assessed by decreased SSS, as well as a reduction in the stress TPD was achieved in the OMT + CSWT group and not the OMT + sham procedure group (Table 2, Fig. 2) at the end of the study.

At 6-months follow-up number of patients with no induced ischemia increased significantly in OMT + CSWT group compared OMT + sham procedure group [8 (30.8%) vs. 2 (8%), \( p = 0.042 \)]. Patients with moderate to severe inducible myocardial ischemia decreased to 12 (46.2%) in OMT + CSWT group and 17 (68%) in OMT + sham procedure group (\( p = 0.296 \)) (Table 2, Fig. 2).

**Summary effect of CSWT treatment**

The summary effect of CSWT compared to sham procedure on endpoint imaging parameters is shown in Fig. 3.

The addition of CSWT to OMT resulted in effective reduction of established ischemia signs compared to OMT alone and more frequent normalization of myocardial perfusion and contraction during stress.

**Reproducibility of DSE and SPECT parameters**
The perfusion scores and rest ultrasound LVEF showed excellent reproducibility, followed by good reproducibility of WMS values (Table 3). Estimation of longitudinal deformation marker was the most variable among study endpoints.

**Discussion**

As a part of the recently published randomized, triple-blind, sham procedure-controlled trial [16], we performed an imaging sub-study that evaluated the capacity of the CSWT to reduce myocardial ischemia determined.
Fig. 1 The dynamics of myocardial function and inducible ischemia evaluated by dobutamine stress echocardiography. a dynamics of wall motion score at baseline, 3 and 6 months of follow up in CSWT and sham procedure group; b changes of LV ejection fraction at baseline, 3 and 6 months of follow up in CSWT and sham procedure group; c distribution of mild, at least moderate or no ischemia at baseline, 3 and 6 months of follow up in CSWT and sham procedure group. CSWT – Cardiac shock wave therapy, LV – left ventricle, OMT – optimal medical therapy. Moderate ischemia defined as ≥3 segments with stress induced severe hypokinesis or akinesis. * - P was paired in the group and considered as significant (P < 0.05)
by DSE and SPECT tests. Current publications provide limited information about the effects of CSWT on global and regional myocardial function and perfusion, therefore our study brings novel high-quality data on the effects of this promising method on objective signs of myocardial ischemia. Both primary sub-study endpoints have changed significantly at the end of the study, though only perfusion score was different in the intervention group.

The analysis of the DSE data revealed that CSWT improved regional myocardial contractility and LV ejection fraction during stress. Due to particular study design (i.e. repetitive DSE testing at 3 and 6 months after the treatment initiation), we were able to demonstrate a remarkable

**Fig. 2** Dynamics of inducible myocardial ischemia evaluated by single photon emission computed tomography. **a** dynamics of perfusion scores at baseline, 3 and 6 months of follow up in CSWT and sham procedure group; **b** distribution of mild, moderate, severe or no ischemia at baseline, 3 and 6 months of follow up in CSWT and sham procedure group. CSWT – Cardiac shock wave therapy, OMT – optimal medical therapy, SSS – summed stress score, SRS – summed rest score, SDS – summed difference score. Moderate ischemia defined as summed difference score (SDS) at least 4. * - P was paired in the group and considered as significant (P < 0.05)
reduction in stress induced ischemia assessed by semi-quantitative WMSI, or WMS, and an improvement of LVEF at 3 months, which was significant only in CSWT + OMT group. This early improvement of myocardial function during stress confirms the beneficial effect of shock acoustic waves, which may be attributed to angiogenetic and vasoactive mechanisms. The positive effect on regional myocardial function was maintained further until the end of study at 6 months after the CSWT initiation, along with markedly higher LVEF not only during stress, but also at rest. This at least partially may be explained by enhanced coronary circulation due to the intervention. To our knowledge, this is the first study that evaluated the effects of CSWT on LVEF during DSE test.

Table 3 Reproducibility of the primary and secondary DSE and SPECT parameters

|                  | Mean difference ± SD | Inter-observer ICC | 95% CI          | P value |
|------------------|----------------------|--------------------|-----------------|---------|
| WMS at stress during DSE | −1.7 ± 4.6          | 0.816              | (0.54, 0.93)    | < 0.001 |
| SDS during SPECT    | 0.73 ± 3.4           | 0.757              | (0.64, 0.84)    | < 0.001 |
| LVEF at stress during DSE, % | 3.8 ± 8.3       | 0.774              | (0.45, 0.92)    | < 0.001 |
| Global PSS stress, % | −2.0 ± 2.6           | 0.602              | (0.13, 0.85)    | 0.009   |
| SSS during SPECT    | 0.01 ± 3.1           | 0.950              | (0.92, 0.97)    | < 0.001 |
| WMS at rest during DSE | −0.2 ± 4.1           | 0.861              | (0.64, 0.95)    | < 0.001 |
| LVEF at rest during DSE, % | 1.3 ± 4.6        | 0.932              | (0.81, 0.98)    | < 0.001 |
| SRS during SPECT    | −0.57 ± 2.9          | 0.942              | (0.91, 0.96)    | < 0.001 |
| Global PSS rest, %  | −1.02 ± 1.8          | 0.625              | (0.14, 0.87)    | 0.008   |

CI confidence interval, ICC interclass correlation coefficient, LV left ventricular, PSS peak systolic strain, SD standard deviation
Importantly, the improvement in imaging endpoints of WMSI/WMS, LVEF and perfusion scores were corroborated by decrease in the number of patients with at least moderate ischemia, ECG changes and angina during stress, which was significant only in CSWT group, except angina at 6 months.

Though blind randomization was performed using random number table, the play of chance a history of myocardial infarction was documented more often in the sham procedure group (23 vs 15); however, it did not produce the difference in rest WMS or LVEF (Table 2). Positive changes of the alleviation of myocardial ischemia after 6 months were also achieved in the control group. We interpret it as the result of the optimization of the medical treatment, which in the course of the trial can frequently be more effective compared to routine practice. The design of the study resulted in repeated appointments between the study patients and a cardiologist, potentially increasing the compliance to prescriptions.

For the assessment of myocardial mechanics at rest and during stress, we utilized not only visual assessment but also innovative markers of deformation imaging. Previous CSWT studies analysed changes of peak systolic strain rate [13, 31]. The results showed significant increase of PSSR at 6 and 12 months follow-up in CSWT group compared with controls, accompanied by significant increase in the amplitude of regional myocardial motion in M-mode [13, 31]. We did not find any previous reports of systolic strain dynamics in CSWT trials. The purpose of inclusion of these objective functional parameters was to register probable subtle differences in contractility in the course of the treatment, which sometimes cannot be seen by the naked eye. We found that the application of SWs to all LV segments had a protective effect on myocardial deformation: peak systolic strain values remained unchanged in the intervention group in contrast to the sham procedure group, where global PSS decreased significantly at the end of the study. This important finding suggests that CSWT might inhibit the progression of systolic dysfunction and ventricular remodelling.

Myocardial perfusion imaging results demonstrated that the adjunct of CSWT to the OMT results in a significant reduction of ischemia as compared to the OMT alone. The complete normalization in perfusion scores was more common in patients assigned to OMT + CSWT group. As a method associated with radiation exposure and being more resource-consuming, SPECT was not repeated at 3 months time-point. Our results are in agreement with previous studies that demonstrated the ability of CSWT to improve myocardial perfusion in patients with refractory angina. Higher microvascular density and upregulation of vascular endothelial grow factor, Fms-related tyrosine kinase 1 and placental grow factor were documented as a result of shock wave application in a rodent model [32]. Alunni et al. demonstrated a significant reduction of mean SSS from 21.3 ± 10.3 to 14.1 ± 10.1 (p = 0.003) compared with baseline, but SPECT was not performed in controls at follow-up [6]. Kazmi et al. reported larger numbers of patients with reduced severity of ischemia at follow-up [11]. However, our study is the first to evaluate the effects of CSWT on local perfusion using SPECT and comparing treatment groups in a triple blind and randomized manner.

The anti-ischemic effect of CSWT was clearly proven by cardiac imaging techniques, as well as by symptoms and ECG changes during stress in the present triple blind, randomized placebo-controlled trial. In our main study [16], which assessed the efficacy of CSWT on exercise duration and angina symptoms in addition to OMT in patients with objective evidence of myocardial ischemia, we revealed a neutral result of CSWT on the exercise duration during treadmill stress test, as well as on angina symptoms, angina class, nitroglycerine consumption and quality of life. Interestingly, recent ORBITA trial failed to show symptomatic benefit of percutaneous coronary intervention for stable angina patients compared to sham treatment [33]. Both groups had significant clinical improvement in angina symptoms and exercise variables. Total exercise duration was selected as primary endpoint similar to our main study and did not differ between groups 6 weeks after intervention. Of note, only peak dobutamine WMSI improved significantly with the intervention, similarly to our study.

Our study had a few limitations. First, no detailed analysis on the CSWT responders and non-responders was performed, and it remains a target for the future studies. Second, some differences in the ultrasound image quality of the enrolled patients, e.g. after CABG, having overweight, could have affected the accuracy of the WMSI analysis. Despite these limitations, it is the only study to date to evaluate the effects of CSWT on myocardial function and perfusion using stress imaging techniques and comparing treatment groups in a blind randomized, placebo-controlled manner.

Conclusions

The results of the prospective randomized imaging substudy suggest that cardiac shock wave therapy effectively improves myocardial function and perfusion in stable angina patients. Target patient population which could mostly benefit from such kind of intervention has yet to be defined.

Abbreviations

CAD: Coronary artery disease; CCS: Canadian Cardiac Society; CSWT: Cardiac shock wave therapy; DSE: Dobutamine stress echo/cardiology; ECG: Electrocardiogram; EF: Ejection fraction; LV: Left ventricle; MPI: Myocardial perfusion imaging; NYHA: New York Heart Association; OMT: Optimal medical treatment; PSS: Peak systolic strain; SDS: Summed difference score; SPECT: Single photon emission computed tomography;
SRs: Summed rest score; SSS: Summed stress score; SW: Shock waves; TPD: Total perfusion defect; WMS: Wall motion score; WMSI: Wall motion score index

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Authors’ contributions
GB, ES, AL and JC conceived and designed the study. GB, DV, KC, GZ, BP, RK, IB, RS, JM and JC collected the data and performed analysis. GB, GJ, ES and JC drafted the manuscript. All authors critically reviewed data analysis and the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and analysed during the current study are available from principal investigator Jelena Čelutkiene and Greta Burneikaite on reasonable request.

Ethics approval and consent to participate
Vilnius Regional Ethics Committee approved the study (Approval No.158000–13–616–187) and written consent was obtained from all patients prior to the enrolment.

Consent for publication
Not applicable.

Competing interests
GB has received investigator fees from Sanofi, Janssen Research, and Daichii Sankyo; has received research support from Medispec (applicants for this study). GB has received consulting fee and research support from Medispec (applicants for this study); has received investigator fees from Servier and Bayer. GZ has received research support from Medispec for Cardiac Shock wave study. BP is a member of a steering committee for Novartis and Janssen Research; has received speaker fees from Remedicra, Astra Zeneca, Pfizer, Bayer and Boehringer -Ingelheim. JC is a member of advisory board for wave study. BP is a member of steering committee for Novartis and Janssen (applicators for this study); has received investigator fees from Servier and Sankyo; has received research support from Medispec (applicators for this study).

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