Author’s response to reviews

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

Authors:

Jelena Celutkiene (jelena.celutkiene@santa.lt)
Greta Burneikaitė (gburneikaite@gmail.com)
Evgeny Shkolnik (evgeny.shkolnik@gmail.com)
Gabrielius Jakutis (jakutis.gabrielius@gmail.com)
Donatas Vajauskas (donatas.vajauskas@santa.lt)
Kamilė Ėrlinskaitė (kamile.ерlinskaite@santa.lt)
Gitana Zuozienė (gitana.zuoziene@santa.lt)
Birutė Petrauskiene (birute.petrauskiene@santa.lt)
Roma Puronaitė (Roma.Puronaite@santa.lt)
Renata Komiagiene (renata.komiagiene@santa.lt)
Irena Butkuviene (irena.butkuviene@santa.lt)
Rima Steponėnienė (rima.steponeniene@santa.lt)
Jonas Misiūra (jonas.misiura@santa.lt)
Aleksandras Laucevičius (aleksandras.laucevicius@mf.vu.lt)

Version: 1 Date: 03 Jun 2019

Author’s response to reviews:

On behalf of the co-authors, we appreciate the opportunity to submit a repetitively revised manuscript. We have addressed all the reviewers’ comments and questions, and we have revised the manuscript accordingly. We have provided a detailed response to each reviewer below. Within the response, the reviewers’ comments are noted in regular type, our responses following in Bold. Additions made to the manuscript text are also noted in the response to the reviewers by bold and underline type. Deletions that we have made in response to reviewers’ comments are
further noted by bold and strikethrough. Page and line numbers refer to the pages in the revised (tracked) manuscript.

Reviewer reports:

Reviewer #1: Aim of the study was to evaluate the capacity of cardiac shock wave treatment to reduce the objective signs of myocardial ischemia, that were determined by dobutamine stress echocardiography and SPECT, in prospective, randomized, triple blind, sham-procedure controlled trial.

The authors concluded that 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.

The study is interesting.

Author Response: We thank the reviewer for the positive evaluation.

There are some criticisms:

1. Did the authors should explain in the discussion section higher incidence of myocardial infarction in OMT + sham procedure group compared to OMT + CSWT

Author Response: Thank You for this important comment. We added the sentence “Though blind randomization was performed using random number table, by 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).” on page 19, lines 44-47 accordingly.

2. In the table 2 the authors reported reduction in WMS, increase in EF, reduction of angina during DSE in both studied group at six months follow-up (same values in OMT + sham procedure and in OMT + CSWT groups). The authors should analyze this important point in the discussion section, and, in particular the additive role of CSWT compared to sham procedure

Author Response: We thank the reviewer for this suggestion. Accordingly, we added on page 19, lines 40-43 “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.”

Also, on page 19, lines 35-39 there is a comment on LVEF: “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.”

3. In the table 2 the authors should add also the LVEF at rest, WMSI at rest and WMS at rest at baseline, at 3- and 6- months

Author Response: We agree with the reviewer and added above mentioned variables in the Table 2, organizing the subsections of primary, secondary endpoints and other test characteristics (pages 15-16).

4. The authors should improve the quality of the figures

Author Response: Addressing this comment we reworked all the figures.

Reviewer #2: The Authors of the present manuscript evaluated the capacity of cardiac shock wave therapy (CSWT) to reduce the objective signs of myocardial ischemia, that were determined by dobutamine stress echocardiography (DSE) and SPECT." They analyzed the data of 59 patients and concluded that: "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".

Interesting study.

Author Response: We thank the reviewer for the positive feedback.

I have the following questions and remarks:
1. The Authors described in the Methods section that "patients diagnosed with angiography confirmed-CAD and exercise induced-angina associated with ST-segment depression ≥1 mm on treadmill electrocardiogram, and symptoms not controlled by optimal medical treatment, were enrolled in the study". Taking into account inclusion criteria defined above it is quite interesting that only 57% of the patients demonstrated ischemia during dobutamine echocardiography and 48% of the patients with SPECT (table 2.). Please, explain!

Author Response: Thank You for this question. The percents mentioned above correspond to the number of patients with at least moderate ischemia; remaining study patients demonstrated mild degree of ischemia. We added to page 10, lines 219-220: “Each sub-study patient had positive either DSE or SPECT, the majority had both tests positive.”

2. Furthermore, angina during dobutamine testing was more frequent the "wall motion positivity", which also needs some explanation (see: the ischemic cascade).

Author Response: We thank the reviewer for this clarification; again, angina was more frequent than at least moderate ischemia (defined as ≥ 3 segments with stress induced severe hypokinesis or akinesis in DSE and as SDS 4-7 in SPECT) but not any wall motion positivity.

3. My third question regarding the testing results is the following: The Authors stated that "Majority of patients (78%) had multivessel disease and 96% were not candidates for further revascularization due to the extent and the severity of the disease or technical considerations". It is therefore surprising that in this population the average WMSI at the baseline testing was only 1.6. Please, give an explanation!

Author Response: Thank You for this question. In the study group 77% of patients had one or multiple previous revascularization, therefore most large vessels amenable for bypass or stenting were fixed earlier, and remaining coronary plaques were non-obstructive. Moreover, 65% of patients suffered from myocardial infarction; mean WMSI of 1.6 can be explained by sufficient amount of viable myocardium and presence of ischemia in the level of small vessels.

4. Only 5 patients demonstrated ischemia during dobutamine testing at the end of the study, however there was only marginal improvement in the WMSI.

Author Response: We thank the reviewer for the careful analysis. Again, there were 8 patients with positive DSE in CSWT group at 6 months, with 5 patients showing at least moderate ischemia. The value of WMSI is averaged from some scar, some ischemic and substantial
number of normokinetic segments in our study. The change of 1 point (for example, improvement from 2 – hypokinetic to 1 – normal) contributes by only 0.06 to mean WMSI; the dynamic could involve just 2 segments per patient. This justifies moderate total change of WMSI.

5. The mechanisms how CSWT can decrease ischemia in the heart should be elaborated in a more detailed fashion in the discussion section. For instances, there are some papers in the literature bolstering this hypothesis (for instances, Zimpfer et al J Thorac Cardiovasc Surg. 2009;137:963-70)

Author Response: Thank You for referral to Zimpfer et al study., which we added to the literature. As You suggested we extended the discussion: “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.” on page 20, lines 71-73.