Author's response to reviews

Title: A Modified Regimen of Extracorporeal Cardiac Shock Wave Therapy for Treatment of Coronary Artery Disease

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Author's response to reviews: see over
Rosa Sicari, MD, PhD
Co-Editor
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Dear Dr. Sicari,

We are submitting a second revision of our manuscript entitled “A Modified Regimen of Extracorporeal Cardiac Shock Wave Therapy for Treatment of Coronary Artery Disease” (Manuscript ID 1932547859709095) and hope that it is now suitable for publication in your journal. All changes made in the revised manuscript were highlighted in red in the revised manuscript. A list of changes made in response to the reviewers can be found below.

We are grateful for the opportunity to submit the revised manuscript, and are looking forward to your next correspondence.

Sincerely,

Tao Guo, M.D.

1. Please better detail the study population under investigation: Are these no option patients? To enter the study these patients had to have a positive test for myocardial ischemia?
   
   **Response:**
   a) Yes. All patients are no option patients.
   b) All included patients in this study had coronary heart disease, and the imaging examination confirmed the presence of ischemic myocardium.

   We have added this information to Methods.

2. How the control group was selected?
   
   **Response:** See reply to the next comment.

3. How was the randomization weighed?
   
   **Response:** We have added the following information about patient selection and randomization to Methods:
   “In this study, patients in the three groups were enrolled by a physician who was familiar with patients’ conditions, and that physician drew lots to divide the patients into different groups. The experimental grouping was blinded to both the physicians who were responsible for treatment
and follow-up and to the patients themselves. The majority of patients with coronary heart disease in this study had severe symptoms so that they had a strong desire to receive CSWT. Therefore, we pre-set a smaller sample size for the control group and the sample size was limited to be no more than 15 patients.”

4. Please provide the end-point analyzed: reduction of ischemia extent?

Response: The end point for local blood flow improvement was an improvement of 1 grade or more in the 4-grade scoring system in one of the myocardial segments, that is, improvement over baseline in either the dobutamine stress or in the unstressed test. We have changed the wording in Methods to try to make this more clear.

“Target myocardium was located and quantified according to the 17-segment Myocardial Scoring and the 4-grade scoring system recommended by American Society of Nuclear Cardiology. [23-25] A one point or more improvement in a segment compared to baseline in the 4-grade scoring system for MPI under either basic or loaded conditions was considered as the criterion for local myocardial blood flow improvement. “

We did not use the “reduction of ischemia extent” method. The reduction of ischemia extents is an integrated evaluation method, including clinical indicators (6MWT, SAQ, dose of nitroglycerin, treadmill) and radiographic parameters (MPI and PSSR). Previously, in this method, the raw data of the above indicators have been analyzed and the final statistical results have been obtained.

5. In the discussion section, please explain why the effect is visible in the long term follow-up. Give more insights on the molecular mechanisms at the basis of the improvements: angiogenesis?

Response: We have added the following suggestion of mechanism and three references to the Discussion:

In our study, the one month treatment had the same efficacy as the 3 month treatment at the 12 month follow-up. These results are exciting, but the mechanism by which a shorter term, more frequent treatment produces the same effect as a longer term, less frequent treatment is still unclear. We speculate that the mechanism might be related to the cellular and molecular mechanisms of blood vessel formation. In other words, when repeated shock wave stimulations are given within 1 month, the resulting succession of shear force effects will produce a waterfall phenomenon, and a large number of neovascular networks will form in a short period of time, ultimately promoting the establishment of collateral circulation in the ischemic area.