

Peer Review File

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Reviewer A:

This reviewer has the following concerns:

Comment 1 :Some linguistic issues

”myocardial hypertrophic”

There least 2 floating sentences as shown below

“Automatically set 12-hour alternating light and dark environment.”

“Relative wall thickness(RWT)=(2×LVPWD)/ LVEDD.”

Reply 1: Thank you very much for pointing out our problem, We have unified the expression of myocardial hypertrophy that appears in the manuscript and modified the two floating sentences mentioned, we have modified the description of the sentence as advised (see Page 4, line 6; Page 7, line 7;Page 8, line 11).

Comment 2: Figure 1. Is the at baseline? Why don't the authors present the strain figs on days 7 and 14?

Reply 2: Thank the reviewer for pointing out this problem. This figure 1 is not a baseline figure. We did not specify the shooting time of this figure. I'm sorry. This figure is the strain diagram of the four groups on the seventh day of administration. As for why we did not paste the strain diagram on the fourteenth day, because we considered that the strain had changed on the seventh day when the EF of the administration group had not decreased. The most meaningful figure was posted at this time. Group A was the normal saline control group, Same as the performance of baseline map in each group. we have modified our figure legend as advised (see Page 16, line 6).

Comment 3 :Fig 4. Based on which groups of rats?

Reply 3: Thank you, teacher, this is based on four groups of rats, so there is a trend, we did not include the data of all rats, each group is randomly selected 5 subjects.

Comment 4 :Table 1 (nicely presented!) needs a footnote with statistical information and significance levels.

Reply 4: Thank you very much for your praise. I have added footnotes with statistical information and significance levels. we have modified our text as advised (see Page 12-13, Table 1)

Comment 5 :Instead of heart mass, it is probably better to use LV mass index (gm/bw). It is assumed that when hypertrophy is induced it is generally concentric hypertrophy. This reviewer is not sure if layer strain could provide any incremental values than endocardial or mid-wall stain. Global circumferential strain should be enough to investigate the proposal of the study.

Reply 5: Thank you very much for the teacher, first of all, because we did not use the left ventricular mass index in rats was left heart especially developed animal, can see clearly the papillary muscle, but can't guarantee every anatomical rats are also removed the same left heart, so in order to more intuitive and more accurate assessment of heart size changes, with the whole quality of the quality of the heart

instead of left heart. And when we take the pathological tissue of the myocardium we can accurately cut the myocardium at the papillary muscle level.

We use circumferential layered strain instead of overall circumferential strain because it is more in line with the physiological and pathological characteristics of hypertrophic myocardium. The subendocardial myocardium is centripetal motion, and it is located at the farthest end of the coronary artery. It lacks collateral circulation and is significantly compressed by the systolic myocardium, so the blood shortage is most significant. Moreover, the contractility of the subendocardial myocardium is higher than that of the epicardial myocardium, but at the same time, because of its relatively high energy demand, Our results also show that the strain change in the subendocardial myocardium is prior to that in the epicardial myocardium.

Comment 6 :If BBR intervention (and outcome) is the principal aim of the study, the conclusion and discussion should focus clearly on this. STI is just one of the three modalities used to investigate the outcome of BBR intervention. A more coherent approach contacting echo, strain, histopathology, and immunohistochemistry is needed to grasp the message of the study.

Reply 6: In part of our experiment, we tried to elucidate the mechanism of berberine in delaying the progression of myocardial fibrosis after the formation of myocardial hypertrophy through pathways. At the same time, our experiment also proved that, compared with the traditional left ventricular ejection fraction parameters, the speckle tracking based layered strain imaging parameters, especially the subendocardial myocardial strain, are closely related to the changes of myocardial interstitial fibrosis. What's new in our experiment is that this is the first study using layered strain to evaluate the changes of myocardial mechanics in the early stage of myocardial hypertrophy in rats, This is also the first study to evaluate the efficacy of drug therapy in rats with myocardial hypertrophy through layered strain. we have modified our text as advised (see Page 28, line 4-10)

Thank you very much for your comments. When we dissect the rat heart, the papillary muscle was selected as the myocardial pathological section. We evaluated the myocardial movement and obtained the strain value at the papillary muscle. The consistency of echo, pathology and immunity is ensured as far as possible. Due to the limitation of experimental conditions, we did not use PCR and other methods to further verify at the molecular level, which is our disadvantage.

Reviewer B:

Comment 1 :The biggest concern is that the conclusion can not be made based on the present results: "Conclusion: Ultrasound layered strain imaging could evaluate the early left ventricular systolic function in isoprenaline induced hypertrophy rat model. Berberine could inhibit oxidative stress through the Rho/ROCK signaling pathway and slow down the progression of myocardial fibrosis after the formation of myocardial hypertrophic. Ultrasound layered strain imaging could evaluate the efficacy of short-term drug intervention.". The authors have to add experiments to connect the logic chain. Results from simple four groups are just phenomenal, not causal. additional experiments are needed.

Reply 1: Thanks for your valuable advice. Due to the limitation of experimental conditions, our research did not involve the molecular level, so we could not reach the current conclusion. This is our shortcoming. We should not draw the current conclusion arbitrarily. We have revised our statement (). In future studies, we will go deeper into the molecular level, increase PCR and Western Blot, and

further explore the specific mechanism. Thank you again, teacher. we have modified our text as advised (see Page 4, line 6-7, Page 29, line 15-16, Page 30, line 20-21)