Author’s response to reviews

Title: Left Ventricular Filling Pressure assessed by Exercise TDI was correlated with Early HFNEF in Patients with Non-obstructive Hypertrophic Cardiomyopathy

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Author’s response to reviews: see over
Response to Reviewers' comments

Dear Dr Xie,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback, and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a more complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,
Xinheng Feng

Reviewer 1

The study was well designed and executed. There is some overlap with previous studies such as (Nagueh Circ 2003;108:395-398) although I believe the measurements following exercise is new.

Response: We thank the Reviewer for his comment.

Naguenh’s study suggested that in patients carrying the HCM gene mutation, Sm and Em were already lower than in controls, even before the onset of myocardial hypertrophy. Upon myocardial hypertrophy onset, Sm and Em declined further. However, there was no difference in E between patients and controls. Therefore, the E/Em ratio (left ventricular filling pressure) was higher in patients than in controls before the onset of myocardial hypertrophy. After myocardial hypertrophy onset, the E/Em ratio became even higher.

Our study is different from Naguenh's study. Our patients were clearly diagnosed with HCM. In addition, we measured and compared TDI before and after exercise, and the results suggested that even among HCM patients, some of them had similar Sm, Em and E/Em compared to controls. These results suggest that the left ventricular diastolic function were relatively normal in subgroup A before and after exercise. In
subgroup B, values before exercise were similar to subgroup A, but the E/Em ratio significantly increased after exercise, suggesting that the left ventricular diastolic function was decreased. In subgroup C, the E/Em ratio before and after exercise were both significantly higher than in controls, suggesting that left ventricular diastolic dysfunction was clinically dominant.

We consider that these three subgroups reflect the variability in the clinical manifestation of HCM patients, describing different stages of clinical development and deterioration of cardiac diastolic function.

The most significant result of the present study was the comparison of the E/Em ratio before and after exercise. We observed that some HCM patients already had reduced left ventricular diastolic function before the onset of clinical symptoms of left ventricular diastolic dysfunction. Therefore, these patients had a high risk of developing into dominant diastolic heart failure, and these high-risk patients might need active intervention and prevention.

The limitations of E/Em in measuring LVFP should be discussed in greater detail.

Response: We added some discussion about these limitations.

Exclusion criteria included LVOT obstruction - it should be noted that this was at rest unless LVOTO looked for during or after exercise.

Response: Patients who had a history of LVOTO diagnosis were excluded. Maybe because of the small sample size, we did not observe any LVOTO after exercise among the included HCM patients.

How many patients were screened and excluded from the study?

Response: Two hundred and sixty-eight patients were screened; 103 patients suffered from atrial fibrillation, 43 refused to participate, 39 patients could not be contacted, 12 patients suffered from left ventricular outflow tract obstruction, 35 suffered from severe mitral valve regurgitation, 5 had a hydropericardium, and 4 patients had limited physical capacities. Therefore, 27 patients were included.

It is stated that “LVEF was calculated by the Devereux formula”. This should read “LV mass was calculated by the Devereux formula”

Response: This was corrected.

Table 2 should include Baseline Sm (and if available Stress Sm) since Sm generally correlate with Em.

Response: This was added.

Figure 1 only shows the patients whose E/Em rose following exertion, a preselected a relatively group. It would be much better to include all individuals in the study in this figure to assess random variation better.

Response: We agree with the Reviewer. However, the purpose of this figure was precisely to display E/Em in that particular subgroup.
In the discussion, it states that TDI can diagnose early HFNEF. I think it would be more honest to say that “E/Em may be rise in a minority patients following exercise in which it is normal at rest. This may indicate a rise in filling pressure during exertion and mild HFNEF”.

**Response:** This was added in the Discussion.

You state that “diastolic dysfunction ….causing… exercise intolerance”. However, it is also possible that the cause of exercise intolerance is secondary to inability of the stroke volume to increase appropriately (eg. Critoph et al. Heart. 2014;100:639-46. Lele et al. Circulation. 1995;92:2886) due to abnormal sarcomeric protein causing abnormal contractility and reduced inotropic reserve.

**Response:** We are sorry, the Critoph’s study was not published at the time we prepared our manuscript. We added some discussion about this point.

It should be emphasised that the difference in Stress E/Em appears mainly driven by the lower Em since mitral E wave peak velocity is not statistically different between the groups.

**Response:** This was added in the Discussion.

**Reviewer #2**

1. **Echographic measurement before exercise -only supine or also upright position in treadmill.**

   **Response:** All echographic measurements were performed in the supine position before and after exercise. This was clarified in the manuscript.

2. **Peak upright exercise -with or without echocardiographic measurements**

   **Response:** It is impossible to perform echocardiography while the subject is moving. Therefore, when the subjects completed CPET on the treadmill, they were rapidly placed in the correct position (supine), and then the echocardiography was performed. In addition, all echocardiographic measurements were performed by experienced echocardiography specialists within one minute after the end of exercise. This was clarified in the manuscript.

3. **Post-exercise recovery phase -which patients' position for echocardiographic measurements. Authors should pointed out that analysis included only HCM patients without LVOT obstruction, however upright position (by LV preload reduction) may provoke obstructive LVOT gradient even only after standing and especially during exercise in upright position.**

   **Response:** We entirely agree with the Reviewer. In the present study, all measurements were performed in the supine position to eliminate the variability associated with position. The standing position can reduce the returned blood volume,
and standing position exercise may more possibly induce LVOTO. Maybe because of the small sample size, no LVOTO was observed in our HCM patients.