Author's response to reviews

Title: Left Ventricular Torsional Dynamics Post Exercise for LV Diastolic Function Assessment

Authors:

Muhammad Asrar ul Haq (hissper@me.com)
Vivek Mutha (v.mutha@nh.org.au)
Tina Lim (t.lin@nh.org.au)
Konstantinos Profitis (k.profitis@nh.org.au)
Zoe Tuer (z.tuer@nh.org.au)
Kwang Lim (k.lim@nh.org.au)
David L Hare (d.hare@nh.org.au)
Chiew Wong (c.wong@nh.org.au)

Version: 2 Date: 5 February 2014

Author's response to reviews: see over
February 5, 14

Editor in Chief
Cardiovascular Ultrasound

Re: MS: 1953254670111247 - Left Ventricular Torsional Dynamics During Exercise for LV Diastolic Function Assessment

Thank you for the opportunity to address the reviewers’ feedback and provide a revised version of this manuscript. In the revised document we have made necessary amendments based on the suggestions and have further improved on the discussion section.

A point-by-point response follows. Please do not hesitate to be in touch should you require any further clarification.

Yours Sincerely

Dr M Asrar ul Haq
REVIEWER 1 (Ivan Stankovic):

Comment 1:
The title of the manuscript is somewhat inaccurate as LV torsion/twist was not investigated during exercise but during early recovery phase. I would suggest using “post exercise torsional mechanics” in the title and throughout the manuscript.

Response:
“during exercise” or “at exercise” has been replaced with “post exercise throughout the manuscript.

Comment 2:
Imaging planes for measuring apical and basal rotation from the parasternal acoustic window should be parallel and perpendicular to the LV axis, i.e. basal and apical images should not be obtained from the same acquisition point, just by changing the probe angulation. This limitation can be circumvented by 3D echocardiography. The authors should describe how the images were obtained in their study.

- In addition, the acquisition of TDI and 2D STE datasets should be better described anyway. I assume that the first paragraph of Measurements section refers to the wall-by-wall acquisition of TDI data for calculating E/e’ ratio.

Response:
The “measurements” section has been updated:
“Parasternal short axis images were analysed at basal (mitral valve level) and apical levels (furthest possible view distal to the papillary muscle level) of the LV using 2D speckle tracking echocardiography by two independent operators in a blinded fashion. Utmost care was taken to acquire the basal and apical images using different planes and not merely changing the angle at the same acquisition point.”

Comment 3:
I would refrain from using E/e’ ratio as a measure of LV filling pressure, but rather as an estimate.

Response:
“measure” in context of LV filling pressure has been substituted with “estimate” throughout the manuscript.

Comment 4:
Study population should be better characterized. Were they apparently healthy or suspected HFPEF patients? How many patients from each group fulfilled metabolic syndrome criteria? What were the reasons for lower exercise capacity of pts from Group 1?

Response:
Updated “study population” section:

**Successive** patients over 18 year of age who were referred for exercise stress echocardiography to investigate for symptoms of dyspnoea or chest pain were evaluated if they completed the test.

Exclusion criteria (extract from the manuscript):
- prior history of myocardial infarction or known coronary artery disease,
- ischaemic ECG changes or anginal symptoms during the test,
- induced or fixed wall motion abnormality on echocardiogram,
- systolic dysfunction defined as ejection fraction (EF) of less than 50%,
- significant valvular heart disease (defined as any valvular disease of more than mild severity)
- conditions requiring electric pacemaker or defibrillator,
- atrial fibrillation (AF),
- inability to walk on treadmill, or
- history of significant respiratory disease (based on previous clinical diagnosis, history of inhalers use, smoking history of more than 10 pack years, or suggestive clinical examination.)
- suboptimal echo images defined as inadequate frame rate, poor tracking at high heart rate, or inability to visualise all 17 segments

**Comment 5:**
Results section could benefit from better organization. Separate paragraph with E/e' data should be provided (baseline and post-exercise values of E/e' across the groups should be added to Table 3 or given in a separate table). Current graphic presentation of these data (graphs without errors bars and separate p-values) are not informative enough. Particularly, was there a correlation between METS and resting E/e’?
Table 2 is redundant and can be omitted.

**Response:**
Thank you. Since a superiority of post exercise E/e’ over resting values has been established in diastology, we focused on post exercise E/e’ values to compare with torsion dynamics. Furthermore the main focus of the study was torsion in diastology, baseline E/e’ measures were considered less relevant given the above. However given the suggestion, baseline values have been described in the results:
“The change in post exercise E/e’ (14.2 ±5.2, 12.8 ±4.8, 11.1 ±3, p<0.05) was statistically significant between the three groups (Figure 2), while the baseline E/e’ between the three groups was not found significant (9.5 ±2.8, 9 ±3.3, 10.1 ±5.2, p=0.8).”

Furthermore:

Discussion section has been updated and organized.

Table 2 has been removed, and table 3 has been labeled as table 2.
**Comment 6:**
A failure of pts with lower exercise capacity to increase the apical rotation post exercise is the salient finding of the study and the discussion should be organized to highlight this point.
Discussion, in its present form, is difficult to follow and at times is misleading. For instance, the authors cannot claim that they demonstrated that “the abnormalities of LV torsion and twist occurred before the reduction in the LVEF...”, as it was not investigated in the current study.
The authors should be more specific about their findings, especially about potential clinical utility of the investigated parameters. Albeit statistically significant, all observed correlations are rather weak (r<0.4) and virtually inapplicable in clinical practice.

**Response:**
Thank you. Discussion section has been updated and organized.
Weak correlation despite statistically significant values has now been acknowledged in the limitations of the study.

**Comment 7:**
Finally, almost identical strength of correlation between METS and post exercise LV torsion and E/e’ (0.34 and -0.33, respectively, p=0.002 for both), suggests that there is no added value of measuring post-exercise torsional mechanic. In fact, according to presented data, one should preferably calculate E/e’ for several reasons (Doppler data required for E/e’ are by far less dependent on image quality, there is no need for post-processing software and time...).

**Response:**
We have acknowledged in the manuscript that this is a research theory and potentially new finding, and does not recommend its clinical application at this stage. Further studies are require to validate this finding of a cross sectional analysis and evaluate its clinical utility. This has now been acknowledged in the manuscript. Furthermore, it may help researchers to have a better insight into mechanics of diastology and open further avenues in future.

**Comment 8:**
All abbreviated terms should be spelled out on its first appearance in the text (e.g. LV in the first line of the Introduction section)

**Response:**
Updated.

**Comment 9:**
Please correct spelling mistakes (an angel [measurements section] to an angle, etc...)

**Response:**
Updated.
Response:
Updated.

REVIEWER 2 (Albert Varga):

Comment 1:
Regarding the patients selection the Authors mentioned some exclusion criteria. What was the initial number of the patient population and how many patients did not meet the inclusion criteria?

Response:
This has been now described in the results section:
“Out of 249 patients screened, 161 were excluded (positive stress test: 53; systolic dysfunction: 44; history of ischaemic heart disease: 37; valvular disease: 11; significant respiratory disease: 7; miscellaneous: 9).”

Comment 2:
On table 1, the Authors presented the clinical characteristics of the patients, divided in 3 subgroups. Not surprisingly, patients suffering of hypertension and diabetes were more frequent in the “underachieving” population. It would be also interesting to see whether the change in the torsion characteristics differed significantly in these groups from the more “healthier” population. I.e., how were the measured parameters influenced by the hypertension and diabetes? The Authors acknowledged the lack of this analysis in last paragraph of the Discussion section, but I would encourage them to perform the subgroup analysis.

Response:
Thank you. We agree with your comment and have performed this analysis. However given the lack of power for the subgroup analysis and statistically non significant results, were not included in context of previously established impact of these groups as referenced in the manuscript. It is acknowledged in the limitations of the study.

Comment 3:
The Authors stated that “the change in post exercise E/e’ (14.2 ±5.2, 12.8 ±4.8, 11.1 ±3, p<0.05) was statistically significant between the three groups based on achieved METS.” Please, provide the resting data, as well.

Response:
Since a superiority of post exercise E/e’ over resting values has been established in diastology, we focused on post exercise E/e’ values to compare with torsion dynamics. Furthermore the main focus of the study was torsion in diastology, baseline E/e’ measures were considered less relevant given the above. However given the suggestion, baseline values have been described in the results:
The change in post exercise E/e’ (14.2 ±5.2, 12.8 ±4.8, 11.1 ±3, p<0.05) was statistically significant between the three groups (Figure 2), while the baseline E/e’ between the three groups was not found significant (9.5 ±2.8, 9 ±3.3, 10.1 ±5.2, p=0.8).

Comment 4:
Although the Authors found significant correlations between many echocardiographical and clinical parameters, however these correlations were in the majority of the cases rather weak. Therefore, appreciating the enthusiasm of the Authors, I would be a bit cautious with the firm statement that “Post-exercise LV torsional dynamics correlate with exercise capacity and may be a useful tool for assessing LV myocardial function in subjects with normal LVEF.” I’m convinced that further, large scale studies should be performed and validate the usefulness of the proposed methodology.

Response:
We agree with the comment fully. This has been further amended in the conclusion.

Comment 5:
To me, the most interesting finding of the present work was that: “The increment between the pre and post exercise apical rotation was not significant in people with lower exercise capacity (group 1) whereas the group 2 & 3 patients who achieved more than 100% of their predicted METS had significantly increased apical rotation”. The Authors discussion was also focused onto this finding and the discussion is less related to the correlations.

Response:
Thank you.

Comment 6:
The statement “While resting LVEF did not predict exercise tolerance in our cohort with no systolic dysfunction or prior diagnosis of heart failure, our study demonstrated that post exercise LV torsional dynamics CAN PREDICT exercise capacity.” should be toned down a little bit. I would say: may be associated with, or could correlate with.

Response:
Thank you. “Can” has been changed to “may” as suggested.

Comment 7:
In the methods section the Authors stated that “Patients were divided into three groups according to the percentage predicted exercise capacity adjusted for age and gender (9, 10) based on the tertiles of achieved metabolic equivalents, METS (#100%, 101-125%, #126%). However, on figures 3 and 4 the correlations were demonstrated using the total achieved METS values. Please, explain!
Response:
Thank you. The error in reporting has been updated. Figure 2 has been deleted.