Author's response to reviews

Title: Additional value of lateral tissue Doppler imaging in the assessment of diastolic dysfunction among subjects with pseudonormal pattern of mitral inflow

Authors:

  Hack-Lyoung Kim Dr (khl2876@gmail.com)
  Joo-Hee Zo Dr (jooheezo@hanmail.net)
  Jae-Bin Seo Dr (cetuximab@naver.com)
  Woo-Young Chung Dr (wychung@paran.com)
  Yong-Jin Kim Dr (kimdamas@snu.ac.kr)
  Sang-Hyun Kim Dr (shkimmd@snu.ac.kr)
  Myung-A Kim Dr (kma@brm.co.kr)
  Dae-Won Sohn Dr (dwsohn@snu.ac.kr)

Version: 2 Date: 19 August 2013

Author's response to reviews: see over
Rosa Sicari, CNR Institute of Clinical Physiology  
Editor-in-Chief of *Cardiovascular Ultrasound*  
Tel: +44 (0) 20 3192 2000  
e-mail: rosas@ifc.cnr.it  
Web: http://www.cardiovascularultrasound.com/  

Dear editor,

We would like to thank you and the reviewers of *Cardiovascular Ultrasound* for taking the time and effort to review our manuscript. Many of the valuable and constructive points that the reviewers pointed out, were well taken by all the authors. After going over the reviewers’ comments, we made revisions and indicated the corrections and changes made in red in the manuscript in hopes of improving our paper.

We hope that our revisions meet the reviewers’ comments. We believe that the comments have significantly improved the quality of our manuscript and hope you will find our revised manuscript acceptable for publication.

Sincerely yours,

Joo-Hee Zo, MD, PhD,  
Department of Internal Medicine, Seoul National University Boramae Medical Center,  
Seoul National University College of Medicine, 39 Boramae-gil, Dongjak-gu, Seoul, 156-707, Korea  
Tel: 82-2-870-2214; Fax: 82-2-870-3866; E-mail: jooheezo@hanmail.net
Response to reviewers’ comments

Based on comments from Reviewer 2, we changed the term “E’” to “e’” and “A’” to “a’”.

Comments from reviewer 1 (Sangchol Lee)

This study deals with a unique group of subjects and tries to overcome the shortcomings of current guidelines for grading diastolic dysfunction with echocardiography. It is relatively well-written, and provides some new insights into echocardiographic data. However, it will need some major revisions for publication.

Major Compulsory Revisions

1. Although the issue of discrepancy between septal and lateral mitral annular TDI imaging is compelling, the study is looking at subjects with ‘pseudonormal’ patterns of mitral inflow velocity data and E’/A’<1 patterns of septal mitral annular DTI. However, even though the term ‘pseudonormalization’ is a generally accepted term for mitral inflow velocity data, the E/A’ ratio it is not well received as a universal parameter for analysis of diastolic function with TDI. Furthermore, the A’ is not usually put into use when assessing diastolic function due to various reasons. As this is so, I recommend the data be re-analyzed by only recruiting the patients with grade II and grade III diastolic dysfunction by the current guidelines (using e’ and E/A) and then categorizing the two groups with high and low lateral E’ velocity.

Response: We appreciate your valuable comments. However, we have some different points of view on your recommendation that our data should be re-analyzed by only recruiting the patients with grade II and III diastolic dysfunction. We think that the recommendation does not seem to be in line with our study object that is to show usefulness of lateral TDI pattern in the assessment of diastolic function among subjects who had E/A > 1 and septal e’/a’ < 1 in whom their diastolic dysfunction severity was not determined. Instead, results from the analyses by your recommendations may cause confusion to readers. Moreover, most of subjects with grade II diastolic dysfunction by guideline have lower lateral e’ (< 10 cm/s), thus categorizing these subjects into subgroups according to lateral e’ value may be inappropriate. Otherwise, we absolutely agree with your comments that e’ is more important parameter than e’/a’

Based on your comments,
we added analyzed data using lateral $e'$ velocity instead of lateral $e'/a'$. As a result, lateral $e'$ velocity is significantly lower in subjects with grade II diastolic dysfunction than that in subjects with normal diastolic function ($7.4 \pm 1.9$ vs. $11.6 \pm 2.0$ cm, $p < 0.001$). Lateral $e'$ velocity was also negatively associated with LAVI even after adjustment of potential confounders including age, sex, body mass index, hypertension and diabetes ($\beta = -0.360, p = 0.011$). These results are represented in the result section marked in red.

2. The multivariate analysis for assessment of independent association of variables does not seem to be appropriate. As the study is focused on the lateral mitral annular DTI data, the analysis should be performed with the lateral DTI data as the dependent variable, not the other way around. Also, the larger LAVI has to be higher independently in the group with lateral annular $E'/A'$. This is related to the above statement, as the group with low lateral annular $E'/A'$ was associated with higher frequency of grade II diastolic dysfunction, and the majority of the subjects with lateral annular $E'/A'>1$ showed normal diastolic function. It is certainly an internal statistical error. Furthermore, the multivariate analysis should include important echocardiographic data such as septal annular $e'$ velocity and $E/e'$ ratio, not only the clinical variables form history.

**Response:** Thank you for your comments. We fully understand your comments. However, we had a different idea on your comments. We wanted to show lateral $e'/a'$ as an independent parameter representing diastolic function in Table 2. Because lateral $e'/a'$ was significantly associated with age, we should have adjusted confounding effect of age and other potential confounders in order to show independent association between lateral $e'/a'$ and LAVI in multivariable model. In this point of view, we think that LAVI, has been known to be one of the most reliable indicator of diastolic function, should be a dependent variable in this analysis. In addition, we did not include other diastolic parameters such as septal annular $e'$ velocity and $E/e'$ ratio in multivariable model because we concerned about multicollinearity problem. Because there is a strong correlations among these parameters with lateral $e'/a'$, variables are not independent each other finally causing multicollinearity problem that makes it difficult to build a good multivariable model. Actually, when we included these parameters in multiple linear regression models, VIF values were $> 4$.

3. Is the LAVI associated with $E'/A'$ velocity in other groups of patients such as the patients who showed $E/A<1$ on mitral inflow pattern and those with septal $E'/A' >=1$? If that is the
case, there is no sense stating that this is significant in the subject group, as it is a consistent finding.

**Response:** We agree with your comments. Based on your comments, we analyzed our data whether there were correlation between lateral e’/a’ and LAVI in subjects with normal diastolic function (n = 263) and grade I diastolic dysfunction (relaxation abnormality) (n = 276). In univariate analysis, there was significant correlation between lateral e’/a’ and LAVI in subjects with normal diastolic function ($r = -0.348, p < 0.001$), however this association was disappeared in multivariable analysis ($\beta = -0.175, p = 0.086$). There were no significant correlations between lateral e’/a’ and LAVI in subjects with grade I diastolic dysfunction in both univariate and multivariable analyses. We added these results in the result section, which marked in red.

**Minor essential revisions**

4. In the methods section in the abstract and in the introduction section, the statement 'pseudonormal pattern of mitral inflow and septal TDI' should be clarified. The statement can be misinterpreted as stating that 'pseudonormalization' is also a term used for septal mitral annular TDI patterns.

**Response:** Thank you for your good comments. We agree with your comments. Our definition of “pseudonormal pattern” may cause confusion or misunderstanding to readers. Therefore, “pseudonormal pattern of mitral inflow” or “E/A $\geq 1$ and septal e’/a’ $< 1$” are used in place of “pseudonormal pattern of mitral inflow and septal TDI”.

5. As stated above, re-analysis of the data is recommended. If done, figure 3 would be essentially irrelevant and unnecessary.

**Response:** We have already mentioned about this point in **Response to reviewer comment 1**.

6. There seem to be many mistakes in spelling and grammar. I suggest the manuscript be reviewed by another expert English editor before submission.

**Response:** Our revised manuscript was edited one more time by another expert.
Comments from reviewer 2 (Maurizio Galderisi)

Interesting study dealing with the value of pulsed Tissue Doppler sampling of the mitral annuls (lateral or septal) in grading LV diastolic dysfunction. The authors find that lateral E’/A’ > 1 is a valuable indicator of early diastolic dysfunction but not of advanced diastolic dysfunction. The study is well designed and developed. The concept of “early diastolic dysfunction” is intriguing and could create new tracks in the clinical setting.

1. It is not clear how the patients were classified to have a pseudonormal pattern. The authors shall better describe it in the “Methods” section.

Response: We agree with your comments. As we described in response 4 to comments from reviewer 1, our definition of “pseudonormal pattern” may cause confusion or misunderstanding to readers. Therefore, “pseudonormal pattern of mitral inflow” or “E/A ≥ 1 and septal e’/a’ < 1” are used in place of “pseudonormal pattern of mitral inflow and septal TDI”. In addition, based on your comments, we added more detailed descriptions why we focused on the study subjects with E/A ≥ 1 and e’/a’ < 1 in the background and method sections marked in red.

2. When analyzing the ROC curves, sensitivity and specificity for detecting left atrial dilation, the cut-off value should be moved from 28 to 34 ml/mm2 according to guidelines (Nagueh SF et al).

Response: We agree with your comments, and we changed Figure 5 as you recommended. This change was also reflected in the result section marked in red.

3. Whenever possible, a multivariable analysis should be performed continuous variables such as blood pressure and fasting glycemia.

Response: We fully agree with your comments. However, measurement of blood pressure and blood test were not a routine part of this study. Unfortunately, it is difficult for us to show the data that you recommended.

4. A recent study highlighted the superiority of E/lateral e’ than E/average e’ in detecting LV filling pressure increase in patients with coronary artery disease (Eur Heart J Cardiovasc Imaging 2013 June). This study should quoted and described in the discussion.

Response: We appreciate your valuable comments. Based on your comments, we carefully
reviewed the articles that you recommended and quoted them in the discussion section marked in red.

5. The discussion is too long and should be shortened.  
   **Response:** Based on your comments, we reduced content in the discussion section.

**Minor comments**  
6. According to ASE/EAE rec (Nagueh S et al) the term “e’” shall be preferred to “E’”.  
   **Response:** Based on your comments, we changed the term “E’” to “e’” and “A’” to “a’”.

7. English language of the manuscripts shall be improved.  
   **Response:** Our revised manuscript was edited one more time by another expert.