Author’s response to reviews

Title: Realization of fully automated quantification of left ventricular volumes and systolic function using transthoracic 3D echocardiography

Authors:
Lina Sun (510551631@qq.com)
Haiyan Feng (letitia@jlu.edu.cn)
Lujia Ni (515633863@qq.com)
Hui Wang (wanghui19620708@aliyun.com)
Dongmei Gao (sunlina@jlu.edu.cn)

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers, comments concerning our manuscript entitled “Realization of fully automated quantification of left ventricular volumes and systolic function using transthoracic 3D echocardiography” (ID: CARU-D-17-00066). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing:

Responds to the reviewers, comments:

Reviewer #1:

1. It is not clear the mean time for measuring left ventricle volumes. Probably this information is in Table 1 as Volume rates. If yes, a unit of measure should be added.

Response: we had recorded the time required for left ventricular measurements with both methods in the experimental stage, but we only showed the rough data in the method part in the original manuscript in Page 8 line 150 and Page 9 line 189(with strikethrough). Obviously, it was not precise and clear enough. Thanks to your suggestion, I realize that the mean time taken for measuring left ventricular parameters in each subject is very important for readers to understand the feasibility of the new method, so we have rewritten this part and the relevant information was
shown in Page 6 line 120 in the method section and Page 12 line 216 in the result section (in red font).

Secondly, I am very sorry for my mistake of writing frame rate for volume rate in Table 1. I have modified the volume rate into frame rate in Table 1 and added Hz as the unit of measure (in red font).

2. Please add any information on the mean frame rate used to acquire the images.

Response: we are very sorry that we miswrote the phrase of frame rate for volume rate, we have modified this error and the data about the mean frame rate with both methods was showed in Table 1 (in red font).

3. How did you evaluate the images, quality?

Response: I am sorry we did not give a detailed classification about the images, quality. Considering your suggestion, we rechecked our cine loops and determined the image quality by a five point scale in which 1, clear display of all 17 segments, well visualization of endocardial trabeculae and clear differentiation from the myocardium in at least 12 segments; 2, visualization of all wall segments and clear differentiation of endocardial trabeculae from the myocardium in 6-12 segments; 3, visualization of all wall segments and clear differentiation of endocardial trabeculae from the myocardium in less than 6 segments; 4, dropout of less than or equal to three segments but visualization of adjacent segments within the same territory; 5, dropout of more than 3 segments. Images in scale 5 were considered poor image quality and excluded from the study. This information was added in the method section in Page 6 line 106 and the relevant data was displayed in the result section in Page 10 line 201 (with red font). The definition of high image quality in Page 8 line 163 and poor image quality in Page 8 line 149 were deleted in the original manuscript (with strikethrough).

4. Please define the feasibility of this method, at least in the patients enrolled that by definition had high image quality. It is important to consider that this method is not feasible in patients with kinetic abnormalities of the apex, in AF patients, and in patients with hypertrophy. Moreover in a >10% patients the automated method required a manual adjustment.

Response: The mechanism of automated 3DE involves an adaptive analytics algorithm that consists of knowledge-based identification of initial global shape and orientation followed by patient specific adaptation.

Automated 3DE is not applicable to patients with severe heart malformation for sure because the software could not locate the heart chamber correctly. But it is rare. In our study, this has only happened once in a patient with Mavan syndrome with a huge left ventricle.
In our study, we also excluded subjects with atrial fibrillation (AF). That is because automated 3DE was unlike manual 3DE that the cardiac cycle analyzed was selected by the Heartmodel software rather than the operator. The cine loops for automated 3DE were acquired by Heartmodel software, while full-volume images were acquired for manual 3DE. So the cine loops for the two methods came from different cardiac cycles, and the measurements cannot be compared to each other in patients with AF. But we should know that the images from Heartmodel software are not only applicable to automated analysis, but also can be analyzed in prototype software QLAB for manual analysis. We have tried both methods on the same Heartmodel image in some AF cases, and it turns out we get close quantitative values. But in patients with AF, we want to get the average value from 3-5 cardiac cycles with different cardiac cycle length. However, as I mentioned, the operator could not choose the cardiac cycles autonomously. So the application of automated 3DE has been limited in patients with AF. According to the information from the manufacturers, the engineers are trying to improve the Heartmodel software. Maybe it can be realized that the operator can store more cardiac cycles and have the interested cardiac cycle analyzed.

Besides, we found manual adjustment was needed in about 13% patients, including patients with kinetic abnormalities of the apex and patients with significant hypertrophy due to hypertrophic cardiomyopathy or severe hypertension. Although we cannot realize fully automated analysis in these patients, the new technology still can be used to these patients and have advantage over both 2D echocardiology and manual 3DE. Firstly, the main advantage of 3DE over 2D echo is to allow accurate measurement of LV volume and EF in patients with abnormal 3D shape of LV as in presence of asymmetric hypertrophy or LV kinetic abnormalities. Secondly, even with manual adjustment, the time required for automated 3DE (3.74±1.62 min) was less than manual 3DE (4.93±2.38 min). The detailed data about the mean time was added in the result section in Page 12 line 216. The reason is as follow: with automated 3DE, the measurements can be done on-line and the steps of finding ED and ES frames and chamber identification and alignment are achieved automated by the Heartmodel software instead of the operator.

To sum up, the automated 3DE performed well in measurements of LV parameters in most patients. Actually, we have applied this new technology to routine examination in our ultrasound room except for patients with severe heart malformation, with AF or with too poor quality image to obtain accurate results. In our manuscript, we have excluded the patients with severe heart malformation or with AF in the method section in Page 7 line 137.

5. The manuscript needed some English editing.

Response: considering your suggestion, we have had the whole manuscript polished by the native English speaking editors at MedSci. The certificate of English editing is in the attachments.

6. Considering this time consuming method, which is the principal utility of this method in the busy clinical practice. Should be interest if the authors made the comparison also with
2D echo’s left ventricle volumes evaluation in order to calculate the variability and the time for reading high quality images.

Response: I am sorry we did not illustrate the mean time for measuring LV parameters with the new technology clearly and it caused misunderstanding that the automated 3DE is a time-consuming method. Actually, the mean time taken by the automated 3DE is only 1.12±0.31 min in most patients without manual adjustment, which is less than the time taken by 2D echo with biplane Sampson’s rule. In about 13% patients who needed manual adjustment, the time taken by automated 3DE is 3.74±1.62 min, which is also acceptable and less than the time taken by manual 3DE. The detailed data about the mean time for LV parameters measurement was added in the result section.

During the experiment, we have also stored cine loops for 2D echo measurements. But according to the literature, it is definite that 3DE has prominent advantage over 2D echo in LV measurements. So we did not include the 2D echo in our manuscript in case the article is too long. If you think it is necessary to make the comparison between automated 3DE with 2D echo, we will add the information about 2D echo in our manuscript in the next revised version.

Special thanks to you for your good comments.

Reviewer #2:

1. Much more is needed in terms of clarity.

   (1) “background” section should not include too long literature discussion and this eventually should be reported in the discussion section.

Response: The authors much appreciated for the reviewer’s suggestions. We have deleted a redundant literature discussion in Page 4 line 77 (with strikethrough) and described briefly the development situation instead of literature discussion in Page5 line88 (in red font).

   (2) The “methods-study design” section is not well structured and should provide clearer information regarding the reproducibility and accuracy protocol.

Response: Considering the reviewer’s suggestion, we have reconstructed the “study design” section and have it amended by the native English speakers. We also added the information about the image quality classification in the “study design” section. I hope the revised version may provide clearer information about the study design, the reproducibility and accuracy protocol.

   (3) The discussion section should be shortened.
Response: Considering your suggestions, we deleted some reduplicative and unnecessary content and references in the discussion section (with strikethrough) and tried to describe the content in clarity and simplicity. We also changed the order of the fifth paragraph about the manual editing to the second paragraph. Besides, we added some discussion about EF classification by automated 3DE without manual adjustment in Page 18 line 332 (in red font). As a result, the discussion was shortened by about 150 words.

2. Data regarding the patient population without the 13 manually adjusted should be reported too.

Response: Considering the reviewer’s suggestion, we have added the data without manual adjustment in the result section in Page 12-15 as follows (in red font): we have added the data in the Table 2, 3 and 4. Besides, we have added a figure (Figure 4) about the correlation and bias and limits of agreement between automated 3DE without manual adjustment and manual 3DE. In order to illustrate the differences of the correlation between two methods with and without manual adjustment, the r-value was shown to 3 decimal places in figures and tables. Besides, we also added discussion about the EF classification using automated 3DE without manual adjustment in the discussion section in Page 18 line 332 (in red font).

3. Discussion page 16 line 281. “timesaving” should be supported by data in the results section.

Response: we had recorded the time required for left ventricular measurements with both methods in the experimental stage, but we only showed the rough data in the method part in the original manuscript in Page 8 line 150 and Page 9 line 189(with strikethrough). Obviously, it was not precise and clear enough. Thanks to your suggestion, the relevant information was added in Page 6 line 120 in the method section and Page 12 line 216 in the result section(in red font).

4. I would suggest to add the Bland-Altman plots showing part of data in Table 2.

Response: In the original manuscript, we illustrated the bias and limits of agreement of EDV, ESV and EF between manual 3DE and automated 3DE with manual adjustments by Bland-Altman plots in Figure 3. In the revised version, we have added a Figure 4 to demonstrate the correlation and bias and limits of agreement between manual 3DE and automated 3DE without manual adjustment.

Special thanks to you for your good comments.