Author’s response to reviews

Title: Assessment of Left Ventricular Diastolic Function After Transcatheter Aortic Valve Implantation in Aortic Stenosis Patients by Echocardiographic According to Different Guidelines

Authors:

yao guo (15211320003@fudan.edu.cn)
minmin sun (703797227@qq.com)
haiyan chen (15385519518@163.com)
dehong kong (641750203@qq.com)
xianhong shu (Yxt091221@126.com)
cuizhen pan (15221061056@163.com)

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Reviewer #1:

First, the main causes of LV diastolic dysfunction in AS is LV hypertrophy and interstitial fibrosis. So you need to compare LV mass index change accordingly between discrepancy groups according to two guidelines. For example, in patients with far improved diastolic function according to 2016 guideline but not in 2009 guideline, please see whether LV mass index change is compatible to their improvement. Because the logic of better 2016 guideline compared to 2009 guideline is just based on higher number of improvement according to reclassification with 2016 guideline. You need to show their relationship with comparator for diastolic functional change such as LV mass index or (NT-pro) BNP.

Response: Thank you for your suggestion and we quiteley agreed with the reviewers. As requested, we have already added a new table (supplementary document: Table 5) to compare LV mass index change in patients with different degree of improvement according to 2009 and 2016 guidelines. We found that in patients with improved diastolic function according to 2016 guideline, LV mass index change was compatible to their improvement.

Secondly, according to 2016 guideline, more patients of pre-operative stage of severe AS were classified as "normal" or "indeterminate" diastolic functional status compared to 2009 guideline. However, all they underwent TAVI procedures due symptomatic severe AS, what is the reason of their symptoms? Is it just from low cardiac output status without diastolic
dysfunction? So, in this cases 2016 guideline, especially for patients with preserved ejection fraction, seems to be too conservative.

Response: Thank you for your suggestion. We retrospected the medical history and found that 9 patients had EF less than 50% preoperatively. All these patients had typical and obvious symptoms such as dyspnea or angina, which two of them had syncope. Expect for these 9 patients, others with diastolic dysfunction also had symptoms. So we quite agreed that the reason of aortic stenosis symptoms is not just the low cardiac output status but also diastolic dysfunction. In our study, according to 2016 guidelines, among 7 patients with normal preoperative diastolic function, 5 did not show significant symptoms. Therefore, for patients with preserved EF and normal diastolic function, symptoms may not be obvious since they are in the early compensatory stage or develop tolerance.

Thirdly, how many patients improved LV ejection fraction form less than 50% to higher than 50% after TAVI? I think it would largely affect the results, because 2016 guideline suggests all the patients with reduced ejection fraction have any diastolic dysfunction. Please describe and see its relationship to discrepant reclassification groups.

Response: Thank you for your question. Of the 35 patients, 9 patients had EF less than 50% preoperatively, and 8 had EF increased to more than 50% at different time points after TAVI (three patients improved in post 3 days, 3 improved in post 1 month, 2 improved in post 6 month). These patients were evaluated separately using two guidelines. Except that there was no difference in two patients, 2009 guidelines have still overestimated diastolic dysfunction grading in 5 patients (from grade III to II, or from grade I to Normal). Besides, there was just one patient be underestimated (from grade I to II). According to the theory that diastolic dysfunction occurred earlier than systolic dysfunction, 2016 guidelines have strictly graded the diastolic function in reduced EF patients (at least grade I). Based on this, the improvement of EF may not significantly affect the 2009 guidelines' tendency to overestimate diastolic dysfunction. We have already put this in the part of Results. (In revised manuscript, page 10, line 226-231)

Fourthly, mitral annular calcification is frequent in severe AS, especially in elderly individuals. It affects accuracy of e' and E/e' as a representative index of LV relaxation and filling pressure. If possible, please show their prevalence and its influence on our study results.

Response: Thank you for your suggestion and we quite agreed with the reviewers. Firstly we retrospected the medical history and found that there were 17 patients with mitral annular calcification (MAC) and the calcification was mainly in posterior leaflet. Although the report did not indicate severity degree, according to 2016 recommendation, in patients with moderate to severe MAC, lateral e' may be decreased due to restriction of the posterior mitral leaflet excursion. Thus, an increase in lateral E/e' occurred. Therefore, separation of the effect of MAC from that of LV diastolic dysfunction on lateral E/e' ratio may not be possible in the individual patient. Since no further study was indicated for the influence of MAC on septal e', we used lateral e', septal e', and average E/e' value to assess diastolic function together, which may reduce
the impact of MAC. We have already put this in the part of Table 2 and Limitation. (In revised manuscript, page 12, line 274-281)

Reviewer #2:

Major aspects

1. Exclusion criteria "patients with uncontrolled atrial fibrillation"

Does this mean the authors included the patients who has paroxysmal atrial fibrillation?

Response: We were sorry for this wrong description. We have already excluded all types of atrial fibrillation, including paroxysmal and persistent atrial fibrillation. We have corrected it as “(2) patients with uncontrolled atrial fibrillation (including paroxysmal and persistent atrial fibrillation)” (In revised manuscript, page 5, line 118-119.)

2. Table 2, diastolic function

Which guideline was used for this calcification, 2009 or 2016?

Response: I am so sorry I can't quite understand you. If “this calcification” means aortic valve calcification, this is related to prosthetic valve selection of TAVI. It seems that none of the two guidelines had mentioned it. We don't know much about the details. If it means mitral annular calcification, the 2016 guidelines excluded patients with heavy mitral annular calcification. In patients with moderate to severe mitral annular calcification, lateral e' may be decreased due to restriction of the posterior mitral leaflet excursion. In our study, although the medical history report did not indicate severity degree, there were 15 patients with mitral annular calcification, and the lesion was mainly in posterior leaflet. Since no further study was indicated for the influence of calcification on septal e', we used lateral e', septal e', and average E/e' value to assess diastolic function together, which may reduce the impact of MAC. We have already put this in the part of Limitation. (In revised manuscript, page 12, line 274-281)

3. Figure 3

The colors of each grade are similar, and it is difficult to distinguish.

There are some patients whose diastolic function was not determinate. Those should be included in this figure.

Response: Thank you for your suggestion. As requested, we have already changed the color of each grade and added the part of indeterminate classification. (In revised Figure 3)
4. Figure 4

For the classification with 2016 guideline, there might be patients with indeterminate diastolic dysfunction and indeterminate grading of LVDF. Describe clearly.

Response: Thank you for pointing out the incomplete description. In Figure 4, we showed different grading results in each patient by using two guidelines, including patients with indeterminate diastolic dysfunction. However, we did not describe the algorithm of indeterminate grade completely in Methods. As requested, we have added the content “If only one parameter was available, grade of diastolic dysfunction should not be reported and likewise if there was discrepancy between the only two available parameters”. (In revised manuscript, page 7, line 170-171)