Author’s response to reviews

Title: Left atrial reservoir strain combined with E/E' as a better single measure to predict elevated LV filling pressures in patients with coronary artery disease

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Authors’ responses to reviewers

First of all, we would like to appreciate the editor and reviewers for their constructive and insightful comments and suggestions, which contribute so much to ameliorate our manuscript.

Here are the detailed responses to their concerns (changes that have been made are outlined in red in revised manuscript).

Responses to Reviewer #1:

Major issues:

- How do you explain the superiority of septal E/E' in your analysis, in contrast to other research and recommendation papers, which always prefer the use of lateral E/E' or medium E/E’?

Response: Thank you for your valuable comment. We agree that lateral E/E' or medium E/E' are preferred in many researches and investigations. In researches with a population of patients with regional wall motion abnormalities, the average of velocity at multiple sites is preferred for better prediction of filling pressures because the difference between the velocities at different mitral annular sites (septal E/E' or lateral E/E’) is generally exaggerated[1-3]. When investigating the population with LVEF less than 50% or even lower, lateral E/E' or medium E/E’ are superior to septal E/E’ for evaluating left ventricular filling pressure[4-8]. And lateral E/E’ or medium E/E' had better correlation with pulmonary capillary wedge pressure (PCWP) or LV pre-A diastolic pressure (Pre-A)[4, 5, 7, 9, 10].

However, on the other hand, abundant evidence demonstrated that septal E/E' had stronger correlation with Left ventricular (LV) end-diastolic pressure (LVEDP) or LV mean diastolic pressure (LVMDP), so in the researches provided LVEDP or LVMDP as an invasive LV filling pressure reference, septal E/E’ always has superiority, which were consistent with our results[1,
7, 11, 12]. In addition, we found that these investigations shared similarities with our research as follows: First, the majority of patients enrolled in these studies had coronary artery disease but without visually abnormal regional wall motion. Second, the population had normal LV systolic function or with preserved LVEF (>50%). Based on above analysis, we suppose that septal E/E' may have superiority to evaluating left ventricular filling pressure in CAD patients with preserved LVEF and normal resting wall motion, particularly when the invasive reference is LVEDP or LVMDP. Besides, some researches prefer septal E/E' because septal annulus moves parallel to the ultrasound beam and is less influenced by the translation movement of the heart[5]. We supposed these may be the reasons why septal E/E' is superior to lateral E/E' or medium E/E' in our article. Thank you for your remarks again.

- The characteristics of the population has to be more clearly explained. Are they stable CAD or acute coronary syndrome patients? I think they are stable CAD subjects, but in this case LA enlargement would have been expected, which is not consistent with your results. On the other hand, if they are acute coronary syndrome patients, I believe it could have been more useful to measure LA strain after a certain period to assess if the ischemic event had led to LA maladaptive remodeling with a rise in LV filling pressures, despite normal ejection fraction. Finally, were the patient symptomatic for angina or similar before being treated?

Response: Thank you for your comment. The population of our study were stable CAD patients with no resting wall-motion abnormalities (WMAs). Patients were considered eligible for inclusion if they had angina, ischemic type chest pain or other symptoms suggestive of myocardial ischemia in our research.

As previous evidence demonstrates[13, 14], LA enlargement is considered a marker of both the severity and chronicity of systolic and diastolic dysfunction, and reflects the effects of a chronic increase in LA pressure. It is often increased in patients in atrial fibrillation, patients with mitral valve disease and so on. In addition, LA volume indexed to body surface area (LAVI) was found to correlate negatively with LV ejection fraction and influenced by the extent of CAD[15, 16]. Since we investigated a population of CAD patients with preserved LVEF (>50%) excluding the patients with distinct regional resting WMAs, patients with significant mitral valve disease or patients in atrial fibrillation, the value of LAVI in our research was slightly lower than that of several previous studies [10, 17-19]. However, Ristow et al. reported a similar result of LA enlargement in CAD patients with preserved LVEF (>50%) to our research (mean LAVI: 32±11 mL/m2 vs. 31.7±5.7 mL/m2) [20]. Therefore, we supposed that LAVI has limitations to detect early LV diastolic alterations in our research probably due to the population of our research (CAD patients with preserved LVEF) and without distinct regional resting WMAs, significant mitral valve disease or atrial fibrillation).

The corresponding description has been revised in red in page 5, line 94-98.

Thanks for your valuable remarks again, which really make our research more precise and rigorous.
- You enrolled patients with coronary artery stenosis &gt; 50%. I suppose these are based on visual assessment. Did you also perform fractional flow reserve (FFR) or instant wave-frame ratio (iFR) in 50-70% stenosis to confirm their hemodynamic relevance?

Response: We are grateful for your comment. The results of coronary angiography were interpreted by an expert interventional cardiologist based on visual assessment blinded to the echocardiographic data in our study.

We agree that it is important to use FFR or iFR to assess the functional coronary artery stenosis and confirm the hemodynamic relevance in 50-70% stenosis, which certainly make studies more rigorous and accurate. But, fractional flow reserve (FFR) or instant wave-frame ratio (iFR) were not available in our study due to the technology were not applied widely and the price was relatively high about 6 years ago. These points have been addressed in the revised manuscript and added to the limitation paragraph.

The corresponding changes have been revised in red in page 5, line 101-102 and page 18-19, 390-393.

- In the exclusion criteria you mentioned "old myocardial infarction''. However, in Table 1, among the main characteristics, there are prior myocardial infarction and revascularizations. Could you precisely explain what you meant for "old''?

Response: Thank you for your comment. The patients with old myocardial infarction within the past three months or patients with distinct regional resting wall-motion abnormalities (WMAs) as seen in old myocardial infarction were excluded in our research. Because the remodeling in the LV after acute myocardial infarction is completed in nearly three months from the beginning of the infarction[21], and meanwhile acute myocardial ischemia would result in LA strain decreasing, but which did not reflect the authentic elevated LV filling pressures[22]. Besides, distinct regional WMAs would damage LV systolic function greatly, and thus the patients with WMAs were not eligible for inclusion in our research for detecting early diastolic dysfunction. The corresponding change is revised in red in page 5, line 104-105 of revised manuscript.

- Was there a second echocardiographer who operated speckle tracking offline analysis? Was he blinded to clinical and basic echocardiographic findings?

Response: Yes, two-dimensional speckle tracking echocardiographic measurements and analyses were performed by a single experienced echocardiographer blinded to clinical information, invasive left ventricular pressure measurements, and conventional transthoracic echocardiographic findings in our research.

We have revised the related content in red in page 9, line 175-178 of revised manuscript.
- The Table 1 needs to be completed with the following variables: baseline blood pressure, use of loop diuretics, E/A ratio (which you mentioned in the Methods section), since LV filling pressures could be conditioned by these elements.

Response: According to the Reviewer’s suggestion, Baseline blood pressure, use of loop diuretics, E/A ratio have been added in Table 1 in red and related description has been marked in red in page 11, line 233-235 and page 11-12, line 238-240.

- Did you measure systolic pulmonary artery pressures (sPAP), mitral regurgitation grade, global longitudinal strain (GLS), LA emptying fraction? If yes, please include them in Table 1. These are indices which could influence LA function and the presence of diastolic dysfunction, so it is crucial to consider them for a complete evaluation of your results.

Response: We are grateful for your comment. According to the your suggestion, the parameters of mitral regurgitation grade, left ventricular global longitudinal strain (LVGLS), LA total emptying fraction, LA active emptying fraction and LA passive emptying fraction have been added in Table 1 and Table 2, which really make our research more rigorous. But sPAP were not available in our study because the patients had no indication for right heart catheterization examination and overt tricuspid regurgitation was not found in most of patients.

The corresponding changes are in red in Table 1, Table 2 and page 6, line 119-128; page 7, line 144-145; page 9, line 173-175; page 12, line 249-250 and page 12, line 255-256.

- In my opinion, a classification of the population based on regionality of coronary disease is needed to better understand your findings. Location of culprit lesion and coronary dominance should be included. In fact, since circumflex coronary artery is usually the major determinant of myocardial oxygenation of the LA, this could be more affected by ischemic damage in patients with circumflex artery culprit lesions than in patients with other vessels culprit lesions (as demonstrated by Lee et al. in Echocardiography. 2015 Jul;32(7):1094-100).

Response: We agree with your opinion, and according to your suggestion, we have included the location of culprit lesion and coronary dominance in Table 1 in red. Revised portion has been marked in red in page 11-12, line 226-240.

The location of culprit lesion had no significant difference between CAD patients in group I (LVEDP≤15 mmHg) and group II(LVEDP>15 mmHg) and the types of coronary dominance were not significantly different between these two groups. Since the population of our research were stable CAD patients with no resting wall-motion abnormalities (WMAs), and about 45.0% of them had a history of prior myocardial infarction more than three months, which were different from patients with acute coronary syndrome, LA function in our population was at a less extent impaired by the acute myocardial ischemia caused by LCx-culprit lesion. Therefore, we supposed that LA dysfunction in our research probably due to chronic myocardial ischemia of stable CAD, which led to remodeling of LV structure, decreased LV relaxation and increased cardiac filling pressures and finally impairing LA function.
Response: Thanks for your kind proposal. We have reminded reader to refer to the NORRE study for normal reference values for diastolic function, and we revised that portion in red in the “Methods” section (page 8, line157-159).

Response: Thank you for your comment. The clinical utility of our findings is to recommend the use of LA strain and the novel parameter (LASr/ E/E’septal) for early and accurate detection of LVDD in stable CAD patients with preserved ejection fraction. The clinical utility of our findings has been revised in “Discussion” section in red in page 17-18, line 364-378:

“LASr provided additional value in predicting elevated LV filling pressures in patients with stable CAD and preserved EF in comparison with conventional echocardiographic parameters in the 2016 guideline, especially when encountered with “indeterminate diastolic dysfunction” or clinical situations in which the acquisition of Doppler parameters is difficult, such as lack of or incomplete tricuspid regurgitation jet, tachycardia obscuring mitral annular tissue Doppler tracing and so on. Furthermore, LA reservoir strain combined with E/E’septal (LASr/ E/E’septal) proved to be a better noninvasive parameter to predict elevated LV filling pressures and identify LVDD earlier and more accurately in patients with stable CAD and preserved EF. However, the routine clinical use of LV filling pressure assessment by LASr/ E/E’septal alone needs further validation in larger samples. In addition, further research is required to explore how best to incorporate LASr and LASr/E/E’septal into multiparametric diagnostic models for CAD patients with preserved LVEF, and to validate the optimal cutoff value for these parameters to differentiate LVDD from the normal.”

We are grateful for your valuable remarks, which make our work more explicit.

Minor issues:

- The article needs further English proofreading.

Response: Thanks for your suggestion. Our article has been further edited by Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of the revised manuscript.
- You used intraclass correlation coefficients to test intra- and inter-observer variability of LA strain values. I suggest the use of a Bland-Altman Plot, which would be interesting for a visual assessment of LA strain feasibility.

Response: We agree with you and have added Bland-Altman plots for the reproducibility assessment of LA strain parameters in Fig.5 and rewritten the related part in red in page 10, line 211-213.

- Please spell the abbreviated terms not only in the abstract, but also in the main text.

Response: We appreciate the kind suggestion. The abbreviations have been carefully checked and added in both the abstract and the main text in the revised manuscript in red.


Response: Thanks for your comment, we have updated above mentioned reference with complete citation in revised manuscript in red. (Page 23, Line 516-518)

- Please correct reference 23 with the correct format for the journal: Am J Cardiol instead of The American Journal of Cardiology.

Response: Thanks for your comment, we have corrected this reference with right format in revised manuscript in red. (Page 24, Line 548-552)

- You used the average LA strain value of four and two- chamber views to calculate LA strain, even if the latest European standardization document (that you cited as reference 21) recommend the use of four chamber alone and to leave the biplane assessment as an option. However, the two methods appear to perform similarly. Why not to add a sub-analysis of both methods to test the feasibility of using 4-chamber view alone, in order to provide further evidence, which could lead to a simplification of LA strain routine assessment?

Response: Thank you for your comment. According to your constructive suggestion, we have added a sub-analysis of LA strain data using both methods in Additional file.

Both methods turned to perform similarly. Compared with the control group, the CAD group had significant lower left atrial reservoir strain of four-chamber view (LASr-4C) and left atrial conduit strain of four-chamber view (LAScd-4C). Compared with group I, group II had significant lower LASr-4C and left atrial contraction strain of four-chamber view (LASct-4C) (Supplementary Table 1). In univariate logistic regression analysis, LASr-4C and LASct-4C
significantly predicted elevated LV filling pressures (Supplementary Table 2). However, in multivariate logistic regression analysis, LASr-4C and LASct-4C showed poorer predictive capacity than LASr. The variables that significantly predicted elevated LV filling pressures in multivariate logistic regression analysis were still LASr and E/E\prime septal. Furthermore, the combination of LASr and E/E\prime septal (LASr/E/E\prime septal) was better in predicting elevated LV filling pressures than each of the above parameters. In receiver operating characteristic curve analysis, LA strain data of using four-chamber alone showed slightly weaker accuracy than LA strain data of biplane method (Supplementary Table 3). The reproducibility of LA strain measurements of biplane method seemed to be better than those of only using four-chamber view (Supplementary Fig. 1).

Therefore, we decided to accept biplane assessment of LA strain in our research, which were also adopted by several previous studies[18, 23, 24] since the latest European standardization document had been published online. Averaging results of four- and two-chamber views may minimize the overall and expected difference [25], we supposed, especially in a population with heart diseases. That may be one of the reasons why certain studies still adopted the biplane method to measure LA strain. Since the sample size in our study was relatively small, further validation of the utility of using only the four-chamber view for LA strain is needed in large populations with various diseases.

We have added this point in “Limitation” section in red: (Page 18, Line 385-390)

“Third, we used the average of the four- and two-chamber views to analyze LA strain, rather than the four-chamber view alone as recommended. However, both methods appeared to perform similarly, which was proved by a sub-analysis (see additional file). Further validation of the utility of using only the four-chamber view for LA strain is needed in larger samples of patients with various diseases.”

Responses to Reviewer #2:

1. Intraclass correlation coefficient is a good parameter for inter- and intra-observer variations. But adding Bland-Altman analysis will help the readers understanding the manuscript.

Response: We absolutely agree with you and have added Bland-Altman analysis for the reproducibility assessment of LA strain parameters in Fig.5 and rewritten the related part in red in page 10, line 211-213.

2. Strain and strain rate for left atrium is not dedicated in the EchoPAC software. According to knowledge, this software uses speckle tracking method for left ventricular deformation and the users apply this method to the analysis of left atrium and other cardiac chambers. Otherwise, the values of strain and strain rate are vendor-dependent. Adding above findings to the study limitation will make this manuscript better.
Response: It is really true as Reviewer suggested that the EchoPAC is not a dedicated software for the analysis of strain and strain rate, and the values of strain and strain rate are vendor-dependent. We are grateful for your constructive suggestion and have added the findings to our study limitation in revised manuscript in red. (Page 19, Line 394-399)

3. Page 12, Line 249. There should the space as "above mentioned"

Response: Thanks to your comment, we have made correction in revised manuscript in red. (Page 14, Line 301)

Other changes:

1. We added an affiliation of corresponding author (Weichun Wu) in revised manuscript. (Page 1, Line 16-17)

2. “Four patients with poor imaging quality in more than one LA segment were excluded (feasibility 93.8%)” was removed to the “Results” section (Page 11, Line 220-222) in revised version in red for better addressed the results of population inclusion.

3. “The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committee of Fuwai Hospital. Informed consent obtained from each patient.” has been deleted from “Methods” section for duplication with the “Ethics approval and consent to participate” section.

4. We added “The ratio of early-diastolic trans-mitral flow velocity to tissue Doppler early-diastolic septal mitral annular velocity (E/E’septal), the ratio of early-diastolic trans-mitral flow velocity to tissue Doppler early-diastolic lateral mitral annular velocity (E/E’lateral), and the ratio of early-diastolic trans-mitral flow velocity to tissue Doppler mean early-diastolic myocardial velocity (E/E’mean) were also calculated” in the “Methods” section (Page 7, Line 139-144).

5. “Interobserver and Intraobserver” was corrected as “Inter-observer and Intra-observer” and marked in red in revised paper.

6. Tricuspid regurgitation peak velocity was added in Table 1 in red and the related description was added in red in page 7, line 134-135:

“Peak velocity of the tricuspid regurgitant jet was determined by continuous wave Doppler”
7. We carefully checked our manuscript and corrected several mistakes in Table 1 in red. “BMI, kg/m2” was corrected as “BMI, kg/m²”. The value of late-diastolic trans-mitral flow velocity (Mitral A) of group II “73.2±17.92” was corrected as “73.2±17.9” in line with the format of the same parameter. “LVMI, kg/m²” was corrected as “LVMI, g/m²”.

8. We added the subtitle “Catheterization Data” in Table 1 for better presentation.

9. We added the result of logistic regression analysis of LA conduit strain in Table 2 for comprehensive understanding of the predictive ability of LA strain.

10. We added funding information in revised manuscript. (Page 21, Line 453-455)

Once again, thank you very much for your constructive and insightful comments and suggestions.

References


