Author’s response to reviews

Title: Going beyond classic echo in aortic stenosis: left atrial mechanics, a new marker of severity

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Author’s response to reviews:

Dear Editor,

First, we would like to thank the valuable and precious criticism and suggestions made by the Reviewers and the Editor. We elaborated a point by point rebuttal, in which we intended to answer all questions raised by the Reviewers and the Editor. To address the flaws identified by the reviewers, we have made a significant effort trying to accomplish the majority of the changes requested. Despite our strong commitment to address all the issues raised by the Reviewers a few could not be satisfied because they would be either out of the scope of this manuscript or imply a significant investment that is not feasible in the present conditions. However, we believe that the lack of response to those few questions does not compromise the quality of manuscript and the significance of the achievements that we present. In this way, the specific answers to Reviewers are:

Reviewer #1:
Good paper dealing with a very interesting and timely issue.

Minor concerns as follows:

1. To better understand the consequences of using GLS to assess AS severity, it would be interesting to add a Net Reclassification analysis (LA-GLS vs. mean gradient).

We thank the reviewer for this insightful comment.

We performed a reclassification analysis according to the different LA-strain parameters and added table 3 with that redistribution.

We also added in the text, Results section, page 9, lines 191-195:

“Table 3 shows a schematic redistribution of AS severity according to different LA strain parameters, in which 5% (LA ɛa) to 30% (global strain) cases of moderate AS have criteria of severity. In classic severe AS, the majority of cases have severity criteria, except when based on LAɛsys, where 69% cases have preserved values of this parameter.”
And in the Discussion section page 11, lines 250-253:

“Strain analysis allowed rearrangement of AS cases according to severity criteria. We could find 5 to 30 \% cases of moderate AS that had severity criteria (Table 3). This distribution in the severe AS cohort was less accurate with a somewhat heterogenous distribution.”

2. To ease reading, please re-arrange Table 2 with higher AUCs on top.
We thank the reviewer for this suggestion. Arrangements have been made to table 2 as requested.

3. Survival and event-free rate analysis.

3A- please disclose in the Methods section stats used (i.e. K-M)
We thank the reviewer for the recommendation.
We added in the Methods section, page 7, lines 154-158:

“ Survival analysis was performed using Kaplan-Meier curves, with the date of entry into the study defined as the date of the diagnosis (first echocardiography). Patients that did not die were censored at the end of the study.
Univariate Cox’s proportional hazards analysis was used to identify independent predictors of outcomes in the overall AS population.”

3B- please provided separated data for HF, death and AVR.
We added table 5 with a detailed description of the results and added in the Results section, pages 9 to 10, lines 208 to 215:

“ Survival and event-free rate analysis
Kaplan-Meier curves are depicted in figure 3. Results of the Cox regression analysis is presented on table 5. Only LA-SRS and GLS were significant predictors of HF (BNP, TAPSE, E/e’ ratio, AF, RV/RA gradient were not). AVR was predicted by mean gradient, AVA, LA \varepsilon_{sys} and LA\varepsilon_{e}. Predictors of death were age, BNP, LA \varepsilon_{e} and GLS. Regarding the combined outcome of HF, death, and AVR, LV-GLS, LA \varepsilon_{sys} and global strain, but not E/e’ ratio, TAPSE or RV/RA gradient, were significantly associated with poor outcomes.”

3C- please add an image with survival curves
We added figure 3 with Kaplan-Meier survival curves regarding the general cohor and according to LA-strain and LV-GLS values.