Author’s response to reviews

Title: Left ventricular markers of global dyssynchrony predict limited exercise capacity in heart failure, but not in patients with HFpEF

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Author’s response to reviews: see over
To: Prof. Eugenio Picano, and
Dr. Rosa Sicari
Editors of Cardiovascular Ultrasound Journal

September 2nd, 2012

Dear Dr Picano and Dr Sicari,

Manuscript ID 1505161178784256 entitled „Left ventricular markers of global dyssynchrony predict limited exercise capacity in heart failure, but not in patients with HfpEF”

Thank you for considering this manuscript for potential publication in the Cardiovascular Ultrasound Journal. We also thank the editors and the reviewers for their insightful comments that enabled us to improve the manuscript. We have considered all raised comments, and have revised the manuscript accordingly. Additional analyses and comments are incorporated in the revised version of the manuscript as recommended. Detailed response (in Italic) to the issues raised by each Reviewer is attached.

We hope the manuscript in its corrected form is acceptable by the Cardiovascular Ultrasound Journal.

Sincerely yours

Michael Henein, MD, PhD
Response to Reviewer 1

Comment 1
Bajraktari et al. have a large experience on evaluation of heart failure patients and have published several articles correlating objective measures of functional capacity (6-min walked distance) with various echocardiographic parameters (Berisha et al. Arq Bras Cardiol. 2009 Feb;92(2):121-34; Daullxhiu et al. J Cardiovasc Med (Hagerstown). 2011 Mar;12(3):223-5. Bajraktari et al. Int J Cardiol. 2011 May 5;148(3):271-5.). Therefore, the main question is whether this article provides any incremental value or new insight into the field.

Response
This study is different from our previous studies in many aspects:
- The number of study patients is much higher compared to previous studies which strengthens the results,
- In previous studies we included only patients with impaired left ventricular EF (EF<45%), but in this study we included unselected patients with HF (including HFpEF patients), accordingly, the findings are for HF patients irrespective of EF
- In a subanalysis we found no predictors for exercise capacity in HFpEF, in contrast to HF with low, suggesting multifactorial causes in the former. This remains to be studied in detail.

Comment 2
There are important inconsistencies in the description of the study population: 50.3% are female or male? The etiology of heart failure described in the results section does not match with the one indicated in the methods section.

Response
In the patients cohort as a whole 50.3% were males.
In the methods section we described the data in both study groups separately: Patients with reduced LV EF had ischemic etiology in 42%, hypertensive in 25%, and unknown etiology in 33%. Patients with preserved LV EF had ischemic etiology in 44% and hypertensive in 56.
Whereas in results section, we described the patients group as a whole: The etiology of heart failure was ischemic in 68 patients (46%), idiopathic in 44 (30%) and hypertensive in 35 (24%) patients.

Comment 3
Based on previous articles and in the current one, have the authors modified the clinical management of the patients? It would be important to know whether a prospective evaluation based on these articles would result in relevant changes in the clinical management and further improvement of the clinical outcome.

Response
*This is an observation study in a limited number of patients, the impact of the needs to re-tested in a larger cohort of patients before it applies clinically.*

Response to Reviewer 2
Comment 1
The authors will specify the HFpEF in the title.

Response
*Thank you. We have replaced abbreviation HFpEF with “heart failure and preserved ejection fraction”.*

Comment 2
Abstract: in the abstract is not specify that the analysis was made in the subgroup with preserved EF.

Response
*We have added in the abstract section: ”and also in two groups according to their EF (Group A: LVEF≥45% and Group B: LVEF<45%)”.*

Comment 3
The authors had to clarify better the real aim of the study.

Response
We have rephrased the aim of the study as follows: ‘The aim of this study was to prospectively examine predictors of functional capacity, assessed by 6-MWT in a consecutive group of patients irrespective of EF. This objective is based on the rationale that HFpEF patients have multi-factorial causes for limited exercise capacity therefore difficult to identify breathlessness related mechanisms using Doppler echocardiography’

Comment 4
Line 18: they stated - the predicting role of echo in assessing limited exercise capacity in pts with HF with preserved EF has not been studied- but in the follow sentence they specify that they studied a group irrespective of EF.

Response
We apologize for any confusion. We have now clarified this statement ‘the predicting role of echo in assessing limited exercise capacity in patients with HF with preserved EF has not been thoroughly investigated’

Comment 5
Methods: please specify how many patients have reduced EF and how many have preserved EF.

Response
We have added sentence for clarification: ”55 patients had LV EF <45 % (HFpEF), and the remaining 92 patients had LV EF ≥45%“. These numbers were in Table 5.

Comment 6
Line 13: what’s the meaning of clear evidence for LV dysfunction by echo.

Response
We apologise for any confusion, we have deleted the following sentence “and had clear evidence for LV dysfunction assessed by a baseline echocardiogram“.

Comment 7
Specify how the authors have divided the pts in decreased and preserved EF.

Response
We classified the patients according to EF: preserved EF: LVEF≥45% and decreased EF: LVEF<45%.

Comment 8
Page 8: in the clinical data smoking and hemoglobin were significantly different in the two groups as showed in table 2.

Response
Thank you. We have corrected that.

Comment 9
Page 9 the authors wrote: ”none of clinical or echocardiographic parameters independently predicted the limited exercise in pts with HFpEF”. Where these data are presented?

Response
This statement was mentioned in the results section in page 10, based on univariate analysis of all variables in patients with HFpEF. In view of the number of busy tables we presented, we elected not to produce another table showing no significant predictors. However, we will be prepared to do so if required.

Comment 10
Page 10, line 4: “In addition, they have demonstrated clear evidence..” Maybe this phrase has to be rewritten in relation with the preview sentence.

Response
We have rephrased the sentence as suggested.

Comment 11
Page 10, Line 7: the significance of this sentence it’s not clear.

Response
We are not clear exactly which sentence the Reviewer is commenting on.

Comment 12
Table 5: the data regarding preserved EF corresponds to those with reduced EF
at least for LA, LVEDD, LVEDS, EF

Response

Thank you. We have corrected this statement

Comment 13
Conclusions: How the authors identify the clinical stability of the population?

Response

Te clinical stability was based on symptomatic stability and absence of signs of decompensation.

Comment 14
The authors do not presented any information regarding the presence of COPD in this population. This disease could be one of the principal causes of limited exercise performance.

Response

Thank you. We had excluded patients with COPD from the study. This was stated clearly in the population section of the methods.