Author’s response to reviews

Title: Association between Left Ventricular Global Longitudinal Strain and Natriuretic Peptides in Outpatients with Chronic Systolic Heart Failure

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Author’s response to reviews: see over
Editor's Comment:

“In addition to the observations of the Referees, I would like to underline that table 3 lacks a clear list of exposure variables in the part concerning the multivariate regression analysis (logistic or linear). In the presentation of tabulated data, it would be appropriate to rebuild the table 3 with an accurate list of the explanatory variables with the respective values of odds ratio or beta coefficient, together with the 95% confidence intervals and p-values, for each of the considered explanatory variables”.

Our response:

Table 3 has been rebuilt. Parameter estimates (odds ratio and beta coefficient, with 95% confidence intervals) have been added for the explanatory variables: age, gender, BMI, atrial fibrillation, creatinine and left atrial volume index.

Please, see the revised and resubmitted Table 3.

Reviewer# 1:

Reviewer's report

The present study proposes an interesting hypothesis by correlating LV GLS with NT-proBNP in patients with heart failure. However, the authors assumed that both parameters are merely surrogates of LV wall stress. The lack of invasive measurements of wall stress (as it should be measured) is an important limitation. In addition, there are other ways of measuring LV wall stress with echocardiography that have not been taken into consideration (Grossman et al J Clin Invest 56: 56, 1975; Reichek et al. Circ 1982). The authors should include that parameter and redo the analysis to investigate the association between GLS, natriuretic peptides and LV wall stress.

Our response:

The point raised by reviewer 1 is interesting. We have, therefore, added LV mass index in the resubmitted Table 2.

Please, see the resubmitted Table 2.

The goal of the present study was to evaluate the associations between natriuretic peptides and GLS, but not to evaluate natriuretic peptides and GLS as estimates for wall stress. If this should be
done, we think it should be done in an invasive study against intracardiac pressures (gold standard). We have mentioned this in the discussion paragraph in the revised draft at page 9:

“It should be noted that both both GLS and natriuretic peptides may be indirect measures of myocardial wall stress and future studies should evaluate the relationship between wall stress based on invasive measures and GLS and plasma concentrations of NP’s before any firm conclusions can be made”.

In the last line in the introduction the word “wall stress” has been removed and has been changed

From:

“In the present study we, therefore, tested the hypothesis that impaired LV GLS is associated with increased plasma concentrations of NT-proBNP and midregional pro-atrial natriuretic peptide (MR-proANP) in chronic systolic HF patients and that LV GLS, therefore, reflects wall stress in this chronic disease”.

To (Page 4):

“In the present study we, therefore, tested the hypothesis that impaired LV GLS is associated with increased plasma concentrations of NT-proBNP and pro-atrial natriuretic peptide (proANP) in chronic systolic HF patients and that LV GLS”.

The following lines have been added at page 5:

Two dimensional parasternal view were used to measure LV dimension and wall thickness. LV mass were calculated from the linear dimensions and reported indexed to body surface area.

The following line have been added at page 7

LV mass index was significantly higher in patients with a GLS above the median (P=0.019).

The following line has been removed from the conclusions at page 10:
“Thus, LV GLS may be a new echocardiographic tool to estimate wall stress in stable chronic systolic HF”

Other comments:

1.-what are the clinical implications of the present findings?

Our response:

We have improved the perspectives of our findings in the end of the discussion at page 10 and implemented the following lines:

GLS of the LV is, therefore, both associated with other structural abnormalities of the heart and neurohormonal activity. GLS is easy to obtain and should be used in future studies for risk stratification and clinical/scientific scenarios where GLS might be more useful than NP’s should be identified.

2.-what is the inter and intraobserver reproducibility of the measurements?

Our response:

Reproducibility of the GLS measures has been tested by two co-authors. This has been added to Methods.

Implemented at Page 5.

Reproducibility were tested in 25 random selected patients for both inter- or intra observer variation. No significant bias was found (intra observational: mean diff: -0.08% +/- 1.16%, P=0.703; inter observational: mean diff: 0.19% +/-1.9%, P=0.422).

3.-please include the measurement of LV wall stress as previously described (Grossman et al J Clin Invest 56: 56, 1975; Reichek et al. Circ 1982).

This comment has been addressed in the answer to Reviewers Report. Please see the answer above.

4.-what is the heart failure etiology?
Our response:

The etiology of HF has been stressed in Results, and is also presented in table 1.

Implemented at Page 6

Ischemic heart disease determined by coronary angiography was present in 58% of the patients, and 38% of all patients had atrial fibrillation.

5.-please add the units of GLS anytime in the main text.

Our response:

Units of GLS have been added where GLS-values is presented in the text.

6.-what do the authors mean by GLS below the median or above the median? The non-expert reader may understand that patients below the median are worse than their counterparts while below the median indeed means more preserved since it is more negative. Is this assumption correct? Please clarify.

Our Response

The reviewer has understood the phrasing correct. It has been rewritten and hopefully clarified what is meant by below and above median GLS.

Implemented at Page 3

GLS is reported as a negative value in percentages. A value closer to zero is a sign of impaired function of the LV.

Implemented at Page 7

Baseline characteristic are presented in Table 1 according to LV GLS below (more negative) or above (more positive = impaired) median LV GLS.

Reviewer #2:

Reviewer's report:

General comments: This prospective study investigates the association between left ventricular global longitudinal strain (GLS) and natriuretic peptides in patients with heart failure. It includes successful measurements of GLS in 117 out of 149 patients. The results is interesting with a
significant association between plasma measurements and GLS. The study seems well performed with relevant methodology.

Major Compulsory Revisions:

The novelty of this study is a question that is difficult to assess from the written report. The authors have several statements on this in the Introduction and the Discussion sections, however the reader is not directly informed on earlier work in the field that shows this association. I feel this should be made more clear and that more references should also be included (Nahum et al. 2010, Uraizee et al. 2013)

Our response:

We agree in the point rasied by Reviewer 2 and have included more references at .

Page 3

Only few data exist on the relationship between LV GLS and NT-proBNP in patients with HF, suggesting association between impaired LV GLS and increased NT-proBNP(15). Among patients suspected of HF LV GLS has been reported to be a strong predictor of NT-proBNP (16). In asymptomatic patients with echocardiographic verified diastolic dysfunction GLS rate showed the strongest correlation to increased NT-proBNP(17).

Page 8

This is supported by Nahum et al. who examined 125 patients with chronic systolic HF and found not only prognostic value of GLS, but also an association between both GLS and NT-proBNP and strain rate and NT-proBNP[15].

Minor Essential Revisions:

Page 3/line 53-54. Segmental strain by speckle tracking is a measure of regional myocardial function and global strain is a measure of global chamber function. This sentence should be rewritten.

Our response

The original sentence at page 3 has been rewritten and changed from:
“Left ventricular (LV) global longitudinal strain (GLS) is a novel echocardiographic method for evaluating both regional and global myocardial function of the LV “.

To:

Left ventricular (LV) global longitudinal strain (GLS) is a novel echocardiographic method to evaluate LV function. It is more sensitive to LV dysfunction than conventional methods, and it allows for both regional and global assessment of the LV.

Page 3/line 55. The question of what is normal longitudinal strain is an interesting one. The authors use a review from 2013 for setting the limit for normal strain to -16%. A meta-analysis of normal subjects set an average normal GLS to -19.7% with a variation for the included studies from -15.9 to -22.1% (Yingchoncharoen et al. 2013). Please comment.

Our response

Page3/line 55 – The original sentence has been rewritten and we have included a wider normal area for GLS and added a new reference. The lines at page 3 has been changed

From:

“In healthy adults the normal value LV GLS has been reported to be -16, a value above (more positive) is a sign of impaired function of the LV ”

To (page3):

The normal range has been explored in some studies and it is reported to be in the area from -15.9% to -22.1%. The variation may be due to age, blood pressure and technical circumstances.

Page 5/line 98-99. Which formulae was used for calculating LV mass?

Our response

LV mass index was calculated using the Echopac software from the linear dimensions of the LV in the parasternal view and indexed to body surface area (automatically calculated from height and weight).

We have stated that in the revised version at page 5:

Two dimensional parasternal view were used to measure LV dimension and wall thickness. LV mass were calculated automatically by EchoPac Software from the linear dimensions and reported indexed to body surface area.
Page 5/line 110-111. Speckle tracking echocardiography, why was a visual definition of the aortic valve closure used and not a pulsed wave Doppler recording in the aortic annulus? A visual definition depends on the framerate of the B-mode recording. What was the framerate for the B-mode measurement used for speckle tracking in these patients?

Our response:

The original sentence has been rewritten, clarifying the circumstances of automatic and visual definition of the aortic valve closure.

The two following lines have been inserted at page 5:

In the echocardiographic examination we aimed for a frame rate 40-80 frames/sec in all images for strain analyze.

Aortic valve closure were automated in the analyse and then confirmed visually, when uncertain it was identified with continuous wave doppler in the aortic annulus.

Page 6/line 132-133. The 2 first sentences in the Statistics section should be moved to the start of the Results section.

Our response

The first mentioned sentence has been moved to the Results paragraph at page 7, and the second have been rewritten in the statistics paragraph at page 6.

Page 6:

Baseline clinical data, biochemical data and echocardiographic measures are presented as percentages for dichotomous variables and interquartile range (25%-75%) for continuous variables

Page 7:

Baseline characteristic are presented in Table 1 according to LV GLS below (more negative) or above (more positive = impaired) median LV GLS.

Page 10/line 223-224. Angle is here better than angel! Speckle tracking echocardiography is to some degree also dependent on angle (see Forsha et a. in press) and therefore this sentence should be rewritten although speckle tracking techniques is much less angle dependent compared to doppler based strain methods.

Our response
The challenge of GLS is that it requires good imaging quality of all three apical standard projections and sinus rhythm is preferable. GLS is that is only slightly angle dependent. The calculation of LV GLS is automatic after setting the region of interest and intra- and interobserver variation is low.

Page 10/line 224-225. Even if the calculation of GLS is automatic it still depends on a good image quality to obtain low intra- and interobserver variability. This aspect should be discussed.

Our response

The strength and limitations of GLS has been discussed in the methodological considerations of the study. Please see the answer for the previous comment.

References. Chech the style of the BMC journals carefully: no full stop for journal abbreviations.

Our response

References – BMC style have been corrected

Figure 1 and 2. Some mode details included in the figure legends would be an improvement.

Minor adjustments have been made in the legends in Figure 1 and 2.

Please see the resubmitted Figure 1 and 2.