Author’s response to reviews

Title: Global longitudinal strain is a hallmark of cardiac damage in mitral regurgitation. The Italian arm of the European registry of mitral regurgitation (EuMiClip)

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Version: 1  Date: 05 Nov 2019

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Reply to Reviewers

Reviewer #1:

An interesting study with clinically-relevant findings confirming usefulness of GLS to detect early signs of cardiac damage in a wide spectrum of pathologies. Well written manuscript.

My only suggestion is including the figure illustrating the relationship between GLS and pulmonary artery pressure.

We acknowledge the nice suggestion of this reviewer. A new figure (now Figure 2) showing the univariate relations of LVEF and GLS with pulmonary artery systolic pressure in both the pooled population and in the subgroup with moderate to severe MR has been added accordingly.
This relationship forms the basis of authors’ conclusion. Such figure seems more important to reader than figures illustrating the relationship between GLS and LVEF, which has been already established in numerous studies. On top of that, the strength of linear correlation between GLS and LVEF is a finding with question able implications - LVEF represents a relative change in volumes, whereas GLS represents relative change in length, and from a mathematical point of view these parameters are not bound to correlate in linear fashion (we have discussed this in detail in a paper "Should we search for linear correlations between global strain parameters and ejection fraction?" published in Eur Heart J Cardiovasc Imaging. in 2014).

We understand the concerns of this reviewer about the non linear relationship between GLS and LVEF. Accordingly, in the new draft of the paper, at page 9, of the “Discussion (lines 14-16), we state that “since LVEF and GLS represent a relative change in volume and length respectively, from a pure mathematicalviewpointitislargelyexpectablethatthesetwoparameters do not correlate in linear fashion” and quote the reference ‘#31 in the reference list’.

However, we would keep Figure 2, which is very meaningful for explaining our results. By this figure, we highlight that a certain number of patients were above the upper or below the lower limits of the 95% confidence interval (CI) in patients with mild MR whereas only 2 patients were below the 95% CI in moderate to severe MR (highlighted in the figure reported below). As you can see in the figure enclosed below, this an indirect demonstration of the linear relation of GLS and EF.

Therefore, these findings indirectly support and even reinforce the hypothesis risen by the reviewer. In fact, the relation between these two variables is even less consistent in presence of mild MR, a condition in which the burden of the loading changes is less evident and becomes more significant in patients with severe MR, a setting in which the impact of load changes is maximal. We deal with this issue at page 9 (lines 14-16) of the “Discussion”.

Another figure, which seems non-crucial to the manuscript is the one illustrating mean values of GLS and LVEF according to MR etiology. It seems obvious that secondary MR is associated with LV dysfunction, whereas patients with primary MR will have better LV function parameters.

According to the indications of this reviewer, the top part of Figure 1 “MR according to etiology” has been eliminated. In addition, also Table 3 have been eliminated and results of the Table moved on the "Results" (page 7, lines 2-5).

Reviewer #2:

In this Paper the authors analyse differences between GLS and LVEF in detecting myocardial damage in inpatients with different etiology and mechanism of MR.

There are some points that the authors should deeper discuss and address:
1. The pooled population is too heterogeneous; 'primary' and 'secondary' MR are distinctly different diseases. They are almost entirely different in their etiologies, in their pathophysiology and in their therapies. It's very important to highlight key distinctions between the two diseases and it's not easy to make common considerations.

We deal with this issue in the “Limitations” section of the Discussion (page 11, lines 12-15), where we state "'primary' and 'secondary' MR are distinctly different diseases in their etiologies, pathophysiology and in therapies and it is not easy to make common considerations between these two clinical conditions."

2. As we can see from literature, baseline resting left ventricular global longitudinal strain could provide incremental prognostic utility in asymptomatic patients with ≥3+ primary MR and preserved left ventricular ejection fraction. It could also aid in helping determine the timing of surgery. In this study the authors describe in the mild MR subgroup, which mainly consists of primary etiology, a substantially greater number of individuals with reduced GLS, in comparison with LVEF. These findings could support the ability of GLS to detect subclinical cardiac involvement, however we'd need to understand why GLS is low in this subpopulation, if cardiac damage and mitral regurgitation are two different diseases or should other risk factors have a role in this. Furthermore, this consideration could call into question the use of GLS as a parameter for the choice of cardiac surgery in patients with significant mitral regurgitation and preserved LVEF. Please discuss this point.

We thank you this reviewer for rising a such appropriate observation. Accordingly, in the new draft of the manuscript we state “Although we cannot know if GLS reduction in this our subpopulation occurs because MR itself or the concomitance of other cardiovascular risk factors, this finding strongly, albeit indirectly, supports the ability of GLS to detect early, subclinical abnormalities of LV systolic function in mild MR, not identifiable by LVEF itself.”(“Discussion”, page 9, last four lines).

3. Currently, the definition of "normal" LV-GLS values in subjects free of cardiovascular disease remains to be fully elucidated. In literature, there are studies that describe the higher-than-normal LV-GLS values in chronic severe MR, as the pathophysiological state (reduced afterload and increased preload) results in a state of hypernormal LV function. This finding also suggests that LV-GLS is likely load-dependent and might have to be corrected for LV volumes. Please highlight this point.

We appreciate the caution of this reviewer on this delicate point. Accordingly, in the new draft of the manuscript we deal with this issue in the "Limitations” section of the Discussion (page 11 last four lines and page 12 first four lines), where we state “Finally, although the last chamber quantification recommendations propose possible reference normal values of GLS, the definition of "normal" GLS in subjects without cardiovascular disease remains to be elucidated. Some studies have described the higher-than-normal values of GLS in chronic severe MR, as the pathological condition (reduced afterload and increased preload) induces a state of hypernormal LV function. These findings also suggest that GLS is a load-dependent and should
be therefore corrected for LV volumes. Accordingly, in the present study we could not indicate a clear cut-off point of GLS to be considered as definitively normal in the setting of MR.”