Author’s response to reviews

Title: The assessment of pressure-volume relationship during exercise stress echocardiography predicts left ventricular remodeling and eccentric hypertrophy in patients with chronic heart failure

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Exercise stress echocardiography and myocardial contractility predict left ventricular remodeling and eccentric hypertrophy in patients with chronic heart failure

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Cardiovascular Ultrasound

First of all, I would like to thank you the Editor and the reviewers for their efforts in revising the manuscript, that contribute so much to ameliorate it.

Here are the detailed responses to their concerns (changes that have been made are outlined in red).
Reviewer #1:

My concern is with the methodology. The outcome measure in this work is LV remodelling, defined on the basis of LV volumes and RWT. These measurements were performed by echocardiography, and the magnitude of changes in these parameters at follow-up is small enough to fall into the intra- and inter-observer margin of error for echocardiographic measurements (there is a huge literature supporting this statement - see the Pelikka paper form 2018 in Ann Int Med for the largest patient population - in the STITCH trial - looked at from the point of view of reproducibility of LV metrics). Who performed the scans? The same person each time? What is the intra- and inter-observer variability coefficient for the laboratory? These are essential questions that need clear answers before this paper can be published.

These points have been addressed in the manuscript, and added to the limitation paragraph.

I am also puzzled by the fact that most patients 'got better' (i.e. had a decrease in LVEDV for instance) during just 6/12 of follow-up. How did this happen? Was their treatment optimised during this time? Were some of them revascularised in the mean time? Do the author mean to imply that this is explained by the 'natural history' of heart failure? If these trends were to continue across time the patients with favourable remodelling would end up normalising their LVEDV in another 12 months, and we all know that does not happen. Why choose the 6/12 cut-off for follow-up? Unless there has been some intervention, then one This touches upon another topic, which is inclusion criteria: Were these patients stable? Why was LVEF <45% (rather than 40%, or 50%) used as the inclusion criterion? Why did these patients have an echocardiogram? Was it clinically indicated or purely for research? Also, the patient population is heterogeneous. Is it certain that none had an MI during the preceding year? LV remodelling can continue for more than 1 year after the event (see, for instance, https://www.ncbi.nlm.nih.gov/pubmed/20865262).

All patients were stabilized and the cut-off for LVEF was 50%. 25% of patients manifested a >10% increase in LVESV at follow-up echo examination, whereas 41% exhibited reverse remodeling (RR), defined as a decrease in LVESV ≥10%. As far as RR is concerned, our findings concur with the results of other studies that have been performed either in patients with dilated cardiomyopathy (Merlo et al, JACC 2011;29:1468), in which RR was observed in 37%, or after acute myocardial infarction (Spinelli et al, IJC Cardiovascular Imaging 2013;29:787), in which RR was noted in 33%, or in patients who underwent cardiac resynchronization therapy in which RR was reported in more than 40% (Waring et al. JACC 2016).

A number of factors may account for the magnitude of reduction in volumes and improvement in LVEF observed in our study. First, the optimization of medical therapy, including ACE inhibitors and beta-blockers. Second, interventions, including resynchronization therapy, correction of mitral regurgitation and myocardial revascularization (these data have been added in the Results section). Third, the heterogeneity of the time enrollment with respect to the index event does not permit to foresee possible further achievements in volume reduction with continuation of the follow-up.

I would also suggest referencing the consensus paper on LV remodelling (2000 - see https://www.sciencedirect.com/science/article/pii/S0735109799006300 ) rather than the 1995 paper by Jay Cohn (who is the 1st author of the consensu paper too).

This change has been done.
Reviewer #2:

Congratulations for this interesting study, well-written methodologically and clinically important. Please check and correct:

1. the lacking correct odds ratio in abstract for ESPVR

This error has been corrected.

2. the lacking word "diminished" or "worsened" before phrase "indices of systolic function" in Results section, second paragraph, although choosen option o naming LV EF /CPOM and ESPVR as indices of disfunction is possible but a bit not clear at first

This error has been corrected.

Finally the title has been changed to:

The assessment of pressure-volume relationship during exercise stress echocardiography predicts left ventricular remodeling and eccentric hypertrophy in patients with chronic heart failure