Author's response to reviews

Title: The prognostic value of mechanical left ventricular dyssynchrony in patients with acute coronary syndrome.

Authors:

Carl Westholm (carl.westholm@karolinska.se)
Jonas Johnsson (jonas.johnson@sth.kth.se)
tomas Jernberg (tomas.jernberg@karolinska.se)
Reidar Winter (reidar.winter@karolinska.se)

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Author's response to reviews: see over
Dear Sirs

Thank you for considering our manuscript "The prognostic value of left mechanical left ventricular dyssynchrony in patients with acute coronary syndrome" MS:1998975958105349 for publication and the invitation to resubmit a revised version. According to comments from the reviewers, we have now revised our manuscript and we have submitted a detailed list of changes made and our responses to the comments from the reviewers. All authors have approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language except as an abstract. None of the authors have any potential conflict of interest relative to this manuscript.

Reviewer's report
Title: The prognostic value of mechanical left ventricular dyssynchrony in patients with acute coronary syndrome.
Version: 1 Date: 18 August 2013
Reviewer: Ivan Stankovic
Reviewer's report:
Using conventional dyssynchrony parameters, Westholm et al. investigated the role of LV dyssynchrony in patients with ACS and concluded that it had no incremental prognostic value in comparison to LVEF. Their conclusion is not that surprising as the authors stated in the discussion section.

Conventional dyssynchrony parameters assess the dispersion of myocardial peak velocities or strains and may reach the cutoffs for dyssynchrony even in the absence of conduction delays. In patients with ACS, ischemia-induced regional heterogeneity of contraction would result in the detection of “dyssynchrony” by parameters based on myocardial strain. Similarly, when akinetic LV segments are pulled from actively contracting segments, velocity-based parameters may also detect “dyssynchrony”.

Therefore, in patients with ACS and regional LV dysfunction, conventional dyssynchrony parameters are most likely reflective of the extent and localization of dysfunctional myocardium only. The extent of LV dysfunction can be more easily (and reproducibly) assessed by LVEF and it is not surprising that conventional dyssynchrony parameters do not have incremental value in this setting.

Major Compulsory Revisions
1. Most of speculations above have already been raised in the discussion section, but in order to support them, the authors should make an effort to quantify the extent and localization of the LV dysfunction (e.g. WMSI, anteroseptal versus inferoposterior LV asynergy, etc…) and relate them to the dyssynchrony parameters.

In order to quantify the extent of LV dysfunction we have added information about EF and WMSI in table 1.
We agree that the information regarding localization of the dysfunction and hypokinesia’s most likely relates to the dyssynchrony parameters. However that this is not within the scope of this present study as we have focused on timing and dyssynchrony as a global parameter for the function of the left ventricle and not regional dysfunction regardless of timing as WMSI is. Furthermore, we do not have that information which would require new analysis of all the 227 patients’ echocardiographic images which would be extremely time consuming.
2. The values of global strain, PSI and WMSI should be reported and their predictive value tested. Instead of MPI, another time-to-peak velocity parameter(s) should be tested and compared.

In table 2a, 2b and 3 we have added the parameters Global strain, PSI and WMSI (page 7 and 9). We keep EF and still focus on that conventional parameter, not because we think it is better than the other but just because it is the most widely spread parameter and is included in almost every echocardiographic report all around the world. (page 11) We already have the parameter Septal-lateral delay which is a Time-to-peak velocity parameter. We choose that parameter and Time-to-peak Strain as two established dysynchrony parameters and introduced MPI SD/delta and PSI SD/Delta as new parameters. Of course the Standard deviation of Time-to-peak Velocity from 12 segments would be interesting to test but unfortunately we do not have the time-to-peak velocity information from more than the septal and lateral wall. New parameters for describing dysynchrony are introduced every year and at the time we analyzed these images we made this selection.

3. The occurrence of new MI should be removed from the composite end-point unless the authors provide the evidence from the literature that the coronary plaque rupture can be predicted by assessing LV dyssynchrony.

We have added a new combined endpoint without the occurrence of new MI,(page 6 and table 2b) however the combined endpoint including new MI was a prespecified endpoint in this study why we cannot just remove it at this stage from a pure research ethical and methodological point of view. We still think that the occurrence of a new MI is a very important endpoint in an acute coronary syndrome population regardless of what parameters we examine It is not that we believe that dysynchrony, or, whatever echocardiographic parameter, can predict plaque rupture but these results and previous experience makes it reasonable to believe that there are confounding factors explaining the association between dysynchrony and the risk of new MI. We have also added some comments in the manuscript regarding this (page 10-12) and also presented new MI as an isolated endpoint to support this assumption (table 2b).

4. The difference between AUC curves should be formally tested (there are methods offered by commercially available software).

We have tested all our AUC-values according to Hanley and McNeil and added that information and a reference in the manuscript (page 9 and10).

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics i

Reviewer's report
Title: The prognostic value of mechanical left ventricular dyssynchrony in patients with acute coronary syndrome.
Version: 1 Date: 18 August 2013
Reviewer: victoria delgado
Reviewer's report:
The present study evaluated the prognostic value of several echocardiographic LV dyssynchrony parameters in 227 patients with acute coronary syndrome. The authors showed that, based on ROC curve analysis, the area under the curve of LVEF was larger than for any other LV dyssynchrony parameter. However, it is not demonstrated that LVEF has incremental prognostic value than LV dyssynchrony parameters since the authors have not demonstrated that this difference is statistically significant and in any case it would be more correct to provide the Harrell’s C statistic of a Cox regression model including each tested parameter or the net reclassification improvement index.

As mentioned above, the differences in AUC-values are not significant. We have added ROC-analysis with combined parameters such as EF*PSI_SD and ED* Time-to-peak Strain SD without getting a higher AUC-value than either of the parameters alone indicating no incremental value of the dyssynchrony parameters in addition toEF, and vice versa (page 11). In the previous version of the manuscript we were unclear regarding how we performed the Cox regression analysis, we have clarified that now (please see #2 below) and hope that it also supports our conclusion about the
prognostic value of our parameters. The aim of this study was to investigate whether dyssynchrony parameters had any incremental value to that of conventional parameters, not the other way around.

Other comments:

1.- Please provide more details of the study population: how many did undergo coronary angiography and received complete revascularization? What were the values of troponin or CK? What was the treatment at discharge? What was the heart rate during the echocardiogram?

In table 1 we have added max troponins and intervention with coronary angiography, PCI and or CABG during admission. We have also added the medical treatment at discharge.

2.- The Cox-regression model may be not correct since the authors included all the LV dyssynchrony parameters which may be interrelated. I would recommend creating a baseline model with well-known prognosticators such as age, gender, location of myocardial infarction, multivessel disease, levels of troponin, diabetes and renal dysfunction. After that please include separately each parameter to be tested and calculate the Harrell’s C statistic for each model. That would give the authors an approximation of how powerful is LVEF relative to LV dyssynchrony parameters.

Unfortunately we were rather unclear in the previous version of the manuscript regarding how we performed our Cox regression analysis (page 10). We did not test all the echocardiographic parameters at the same time but one by one in two models. One univariate without adjustment and model 2 where we adjust for risk factors and tested the echocardiographic parameters one by one. To the risk factors we have now added level of troponins and kreas clearance as can be seen in table 4. We have also clarified in the text and table legend how we performed the analysis. Our number of events (82) does not allow us to test more than 8 parameters which in this case will be 7 risk factors and one echocardiographic parameter. The result, however, is the same as before, only EF Simpson is independent when all the dyssynchrony parameters are not, and therefore further statistical analyses regarding predictive value are of no use.(page 11)

3.- Please provide a figure of how to assess LV dyssynchrony based on speckle tracking.

We have added figure 2 that shows how we assess Time to peak strain from 2d images.

4.- Please pay attention to spelling mistakes (for example the first one in the abstract and introduction: echohcardiography.

We have corrected spelling mistakes.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: nothing to disclose

Sincerely

Carl Westholm
Departement of cardiology, Karolinska University Hospital, Huddinge, Institution of medicine (H7)
Huddinge; Karolinska institutet; 141 86 Stockholm, Sweden. Carl.westholm@karolinska.se fax:+46-8-58586710