Author’s response to reviews

Title: Index of contractile asymmetry improves patient selection for CRT: A proof-of-concept study

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Author’s response to reviews:

Reviewer #1:

I admire the authors’ effort. The problem of prediction CRT responders has an incremental value. The way the paper is written makes it difficult to understand, especially in methodology section.

- Figure 2 does not help to understand the way of transformation the data.

In order to improve the presentation of the methodology used in this article, the following paragraph in the Methods section was rewritten (page 6):

“In case of an almost symmetric LV contraction, such resulting table would contain uniform values relatively close to zero. On the other hand, an asymmetric contraction would result in greater strain rate differences of the two opposing walls. Hence, in case of LBBB, an early contraction in one wall (negative strain rate value) and a simultaneous stretch in opposite wall (positive strain rate value) is expected to lead to high absolute values when these symmetrical
numbers are subtracted from each other. Subsequently, when the latter wall is activated and the former wall is stretched, high difference values with the opposite sign would be generated. To quantify these asymmetrical counteractions during systole, a standard deviation (SD) of such strain rate differences in the CAMM-plot-derived difference table was calculated both in standard apical views and in each of the remaining 180 views (Fig. 2). This value was called index of contractile asymmetry (ICA).”

Also, Figure 2 has been modified considerably. We hope it now reflects the process of calculating ICA by presenting it in a more structured manner. The figure legend has also been rewritten to guide the reader through the steps of the algorithm.

- Figure 3 and 4 makes it difficult to evaluate which wall is represented in the define sector.

Thank you for your feedback. Figure 3 has been modified to reflect the positions of the LV sectors within the LV. Position of the RV has also been taken into account to improve the visual representation. We hope this also helps to put the results presented in Figure 4 into context.

- The lack of data about the scar location is the major limitation. Also we do not know the data about the period from ACS to the implantation of CRT. If it is a long period and we have the data from echo and strain we may try to establish the scar location. The value of strain and the thickness of the myocardium have a good diagnostic value.

Strain analysis has now been performed, and GLS is presented in the revised version of the manuscript. We agree with the Reviewer that location and extent of the myocardial scar would be of major interest, especially taking the position of the LV lead into account. Meanwhile, as the LV lead position was only available in 21 cases, we chose to remove this analysis as per next comment from Reviewer #1. Therefore, we believe, that both LV lead position and the myocardial scar should definitely be assessed in future work on ICA. In the same context, we would like to point out that ICA4 was able to predict response to CRT both in patients with ischemic and non-ischemic cardiomyopathy as described in the revised version of the manuscript (Results section, page 9):

“In the subgroup of patients with ischemic cardiomyopathy, baseline ICA4 had an AUC of 0.82 (95% CI 0.7-0.94), and in non-ischemic cardiomyopathy AUC was 0.83 (95% CI 0.64-1).”

Also, the following was added to the Results section (page 10):

“Stratified by etiology of cardiomyopathy, relative reduction of ICA4 was greater both in responders with ischemic (-36 ± 26% vs. 6 ± 47%, p=0.006) and non-ischemic (-43 ± 21% vs. -12 ± 18%, p=0.005) cardiomyopathy.”

- The authors have data from thoracic CT scans available only for 21 patients (15 responders, 6 non-responders). In my opinion we can not make a conclusion if we have data only for the 6 persons (without data for scar).
Thank you for this comment. Due to limited sample size, the lead position analysis has been removed.

- I would like to ask you what kind of test you performed and the statistical values for the collinearity Baseline ICA4 and relative reduction of ICA4.

As per section Statistical Analysis, collinearity analysis was performed using Pearson’s r.

Reviewer #2: This is an interesting study of original 3D reconstruction of regional SR differences. I have conceptual concerns regarding the use of strain rate values for dyssynchrony evaluation. Since strain rate reflects the deformation rate, and not deformation amount or timing, its value seems questionable compared to mechanical dyssynchrony index or other parameters based on time-to-peak approach. In ischemic cardiomyopathy, dominating in this sample, differences of strain rate may mostly be determined by wall motion abnormalities due to infarcted areas. Greater strain rate difference may show larger zones of preserved contractility - it is not analyzed; in such case whether proposed ICA marker is better than contractility reserve? To make this article convincing in additional value of ICA I suggest a comparison with some time-to-peak modality, better 3D, or contractile reserve (or myocardial work index) including them in multivariate analysis. Also, usual WMSI and strain parameters should be shown.

We appreciate the comments. Therefore, additional analyses have been performed. The manuscript now includes analyses of GLS, mechanical dispersion, and analysis of classical LBBB pattern. The following was added to the Methods section (page 7-8):

“Longitudinal strain analysis based on standard apical views was performed on baseline echocardiograms. Global longitudinal strain (GLS) was calculated as a mean of peak strain values in 16 segments. Mechanical dispersion was calculated as an SD of time to peak of longitudinal strain in 16 segments [14]. Mechanical longitudinal strain dyssynchrony was defined as maximum time to peak delay in basal and midventricular segments in the apical four-chamber view using a cut-off of ≥ 130 ms [6,15]. In addition, pre-implantation echocardiograms were stratified based on presence or absence of classical LBBB pattern [16].”

The following was added to the Results section (page 10):

“Time to Peak Delay and LBBB pattern

Mechanical dyssynchrony based on time to peak delay ≥ 130 ms was present in 46 (69.7%) responders and 16 (69.6%) non-responders (p=0.99). Responders had classical LBBB pattern in 52 (78.8%) cases and non-responders in 11 (47.8%) cases (p=0.008), providing sensitivity 79%, specificity 52%, PPV 83%, NPV 46%, and accuracy 72%.”
The subsection Logistic Regression in the Results section has been rewritten accordingly (page 11). Classical LBBB pattern has been added. Meanwhile, reduction of ICA4 as predictor if response to CRT has been removed (page 11):

“The results of the logistic regression are summarized in Table 2. In a univariable model, CRT response was predicted by baseline ICA4, LBBB pattern, and renal function. In the multivariable models using age, renal function, and either ICA4 or LBBB pattern as predictors, ICA4 ≥ 0.7 s-1 had odds ratio (OR) 10.1 (95% CI 3.2-40), and LBBB pattern had OR 4.44 (95% CI 1.54-13.6). In ROC analysis, the two models had AUC 0.8 (95% CI 0.7-0.91) and 0.72 (95% CI 0.6-0.85), respectively, p=0.18 (Appendix E).”

Table 2 has been modified accordingly. In addition, Appendix E containing ROC analyses of models containing ICA4 and classical LBBB pattern has been added.

Considering the influence of infarcted areas on differences in strain rate, we would like to draw the attention of Reviewer #2 to the fact, that ICA is not based on absolute differences in strain rate of opposing walls, but rather on standard deviation of the differences in strain rate throughout systole (revised Fig. 2). The first sentence of the Discussion section was rewritten (page 11):

“In this study of patients having LBBB and HF, the presence of contractile asymmetry in entire opposing LV walls measured as SD of differences in strain rate throughout systole (ICA) was associated with an increased likelihood of response to CRT.”

This is also elaborated on further in the Discussion section (page 14):

“As per response to Reviewer #1, the above can be supported by the finding, that in ROC analysis, ICA4 was able to predict positive response to CRT both in patients with ischemic and non-ischemic cardiomyopathy.

Another question is a selection bias, as nor image quality neither presence of AFib, no BNP are described.

We appreciate this comment. The following sentence was added to the Methods section (page 8):

“Patients having more than 3 LV segments with inadequate tracking despite manual adjustment were excluded from all STE analyses.”

We also agree that limited clinical data is a limitation of the study, as outlined in the section Study Limitations.
Some figures are of poor quality and too small, thus not suitable for reading - Fig 2, Fig 7.

Thank you for the feedback. Figure 2 has now been redesigned to improve readability as described above. Figure 7 has been removed, as the analysis of lead positions has also been removed from the manuscript as per comment from Reviewer #1 due to limited sample size of patients with thoracic CT.