Author’s response to reviews

Title: The value of left ventricular strain–volume loops in predicting response to cardiac resynchronization therapy

Authors:

Mengruo Zhu (zhumengruo@126.com)
Haiyan Chen (submitsci@163.com)
Zibire Fulati (xinchaoketi@163.com)
Yang Liu (15965813453@163.com)
Yangang Su (1353191982@qq.com)
Xianhong Shu (shu.xianhong@zs-hospital.sh.cn)

Version: 1 Date: 23 Jan 2019

Author’s response to reviews:

January 23, 2019

To: Cardiovascular Ultrasound

Dear Professor Rosa Sicari,

Thank you for your help in our manuscript, entitled: "The value of left ventricular strain–volume loops in predicting response to cardiac resynchronization therapy" (CARU-D-18-00081). Each of the reviewers' comments was carefully considered and the manuscript was revised as suggested. Below you will find the explanation to each of the reviewers' comments and the revision we made.

Reviewer #1:

This manuscript analyses a group of original mechanical parameters that can be improved predictors of CRT response. The parameters were constructed by the correlation between LV volume and principal strain (PS) at all instant of the cardiac cycle, both in global and segmental combinations, evaluated by speckle tracking of 3D echocardiography of the LV. The study is performed on 40 patients and 20 subjects are included as controls.
Overall, the analysis is interesting and the new parameter given by the correlation between MidLateral PS-and Global volume loop (called $R^2$-S/D coupling of MidSeptal PS-Global volume loop) provides better predictive power to CRT outcome. On the other side, also the simple MidLateral PS peak (1st item in table 3 and in table 4) presents a comparable ability to differentiate responder from non-responders at baseline. The new parameter ($R^2$-S/D coupling of MidSeptal PS-Global volume) also performs slightly better than the simple MidLateral PS peak that is number two in performance in univariate logistic regression and not much worse in multivariate. Even the simple GLS value appears to significantly differentiate responder from non-responders at baseline (table 2 and 5).

Main Concerns:

1) The introduction of the new approach seems to work well only in the specific combination MidLateral PS-Global volume and this appears a consequence of the underlying differences in MidLateral contraction in these subjects. Therefore, the results do not provide a conclusive evidence of superiority of this approach to more simple measures. Authors should also test different measures of MidLateral strain (different direction, and synchrony/timing parameters) to confirm the superiority of using the "loop" approach with respect to the many possible strain-based measures.

Thanks for your kind suggestions. Yes, as you said, the simple MidLateral PSpeak and the slope of MidLateral PS-Global volume loop were significantly different between responders and non-responders (coloured in the Table 3) and were also significantly associated with CRT response in the univariate analysis (coloured in the Table 5), which seems like the new approach works well due to the underlying differences in MidLateral contraction in these subjects. However, the MidLateral PSpeak and the slope of MidLateral PS-Global volume loop were not significant in the multivariate analysis (coloured in the Table 5), i.e., they were not independent predictors of CRT response. Therefore, we think the existence of special MidLateral contraction resulted from the septal work efficiency being reduced while lateral function compensatory being improved. As a result of reduced septal work efficiency, compensatory improved lateral function maybe not peculiar to CRT responders but dependent upon the existence of wasted septal work. Lateral functional features can’t be an independent predictor of CRT response in the multivariate analysis. Only the septal functional features, the fundamental cause of the development of dyssynchronous heart failure, may be a useful indicator for the differentiation and prognosis of CRT outcome. We have analyzed this result and present this view in the Discussion section. As suggested in our study, $R^2$-S/D coupling of Midseptal PS–Global volume loop at baseline is proved to have independent predictive value (coloured in the Table 5). Assessment of wasted work in septum at baseline by analyzing strain–volume loop would be helpful to improve patient effective selection for CRT as a non-invasive method. So, we think our results could provide a conclusive evidence of superiority of the "loop" approach to other simple measures because they were not significant in the multivariate analysis.
2) The good results obtained by GLS appears in contradiction with existing results where GLS is definitely not a predictor of response to CRT. This suggests that the dataset may not fully represent the general behavior observable in this type of patients. Authors should better verify the basic results with respect to literature.

Thanks for your kind suggestions. As you can see in the Table 3, the difference of GLS between CRT responders and non-responders did not reach statistical significance. In fact, the failure to demonstrate significant difference between them is likely due to the relatively small study population. GLS can reflect myocardium viability and have been demonstrated to be associated with total LV scar burden assessed by magnetic resonance imaging [1]. Residual viability of LV myocardial is an important determinant to prognosis and lack of response to CRT may be due to the presence of significant amount of myocardial scar or fibrosis deteriorating cardiac function to a degree so that cardiac remodeling could not be reversed by CRT.

GLS was significantly associated with CRT response in the univariate analysis but was no longer statistically significant in the multivariate analysis after adjustment for other factors (coloured in the Table 5), suggesting assessment of GLS at baseline can be helpful for evaluating candidates scheduled for CRT but baseline GLS don’t have independent predictive value for CRT outcome. Similar results were found in previous studies [2]. Because such kind of parameters neglect the dynamics of strain signals and the same values of strain peaks or timings can be observed with different strain curve morphologies [3]. As suggested in Carasso’s study [4], LV segmental strain–time curve morphology is actually highly predictive of response to CRT. It is because the single strain or dyssynchrony parameters have limiting ability to predict CRT response that the LV pressure-strain loop analysis has been put forward [5-7]. However, clinical use of the LV pressure-strain analysis is limited by the challenge to noninvasive acquire instantaneous LV pressure. That's why we are proposing the non-invasive "strain-volume loop" approach the dynamic relationship of myocardial strain with volume load changing across the cardiac cycle, which also have been explained in the Discussion section.


Reviewer #2:

Aim of the study was to investigate the value of LV strain-volume loops in predicting response to cardiac resynchronization therapy.

The authors studied 40 heart failure patients scheduled for cardiac resynchronization therapy.

The authors concluded that analysis of strain-volume loops could provide unique information for predicting response to CRT. Assessment of septal myocardial wasted work at baseline is helpful to improve patient selection for CRT.

The study is interesting.

There are some criticisms:

1. The study population is too small (only 40 HF patients). The authors should add the etiology of HF (ischemic vs non ischemic HF)

Thanks for your kind suggestions. We would like to accept your suggestions and list the small sample size as a limitation.

In addition, we summarized the etiology of HF (ischemic vs non-ischemic) in the Table 1 and compared the different percentage of two groups. All patients received the coronary artery CT angiography or coronary artery angiography within a year before CRT implantation for confirming whether there was coronary artery stenosis. Considering a degree of coronary artery stenosis would result in myocardial ischemia and further lead to decreasing the force of
myocardial contraction, we thought in the presence of one or more major coronary arteries (referring to the left main coronary artery, anterior descending branch, circumflex branch, right coronary artery) stenosis ≥50%, the etiology of heart failure may be attributed to the impact of myocardial ischemia for a long period of time.

2. The LBBB morphology was present in 29/40 (72%) of the patients. The authors should indicate the others morphology. Did the authors include patients with Pace-Maker? QRS morphology may have a role because of electrical dyssynchrony may influence R²-S/D coupling of MidSeptal PS-Global volume loop

Thanks for your kind suggestions. We would like to accept your suggestions and added the electrocardiographic inclusion and exclusion criteria about QRS morphology, diagnostic criteria of LBBB and IVCD et al in the Methods section. We adopted the diagnostic criteria of LBBB by the 2013 ESC guidelines [8] Class 1 Recommendation for CRT, namely a wide QRS duration with QS or rS in V1, broad (frequently notched or slurred) R wave in leads I, aVL, V5 or V6, and absence of q waves in leads V5 and V6. Intraventricular conduction delay (IVCD) was diagnosed as non-specific manner QRS morphology that did not fit the criteria for LBBB and RBBB [9]. The remaining 11 patients of non-LBBB morphology are IVCD and our study didn’t recruit patients with isolated RBBB.

In addition, all HF patients who were enrolled in this study were firstly scheduled for CRT, i.e. no patients with Pace-Maker. We have added this statement in the first sentence, first paragraph of the Study Population, Methods section.


3. In the table 5 the authors should add the traditional predictors of response to CRT, i.e. QRS duration, LVEF, NYHA class.
Thanks for your kind suggestions. We would like to accept your suggestions and the traditional predictors of response to CRT, including gender, NYHA class, etiology of HF, QRS duration, LBBB morphology, LVEF, were also involved in the univariate logistic regression as you can see in the Table 5.

4. In the Methods section (line 55) the authors reported that HF patients scheduled for cardiac resynchronization therapy were symptomatic, in NYHA functional class III or IV despite optimal medical treatment. However, the percentage of therapy used, as reported in the table 1, is sub-optimal: ACEI/ARBs 22 pts (55%), Beta-blockers 19 pts (47%) Diuretics and/or spironolactone 19 pts (47%).

Yes. Thanks for your kind suggestions. Because the optimal medical treatment varies with the individual, not everybody is suitable for the combination of ACEI/ARBs, Beta-blockers and Diuretics and/or spironolactone. For example, the ACEI/ARBs are not recommended for the patients accompanying with renal insufficiency, the Beta-blockers is not recommended for the patients with low heart rate and the Diuretics and/or spironolactone is not recommended for the patients with low blood pressure. So, each patient has indeed received the optimal medical treatment based on his/her individual characteristics, i.e., so-called personalized medicine. But the proportion of taking each medicine could not reach 100%.

5. The authors should add an example of three-dimensional speckle-tracking imaging of responder and nonreponder before CRT and 6-months after CRT.

Thanks for your kind suggestions. We would like to accept your suggestions and added an example of three-dimensional speckle-tracking imaging of responder and non-reponder before CRT and 6-months after CRT, as you can see in the Figure 1.

6. The authors should report the inter- and intra- observer variability of all three-dimensional speckle-tracking imaging measures and the time of off-line analysis.

Thanks for your kind suggestions. We would like to accept your suggestions and added the inter- and intra- observer variability of all three-dimensional speckle-tracking imaging measures in the Method section, as you can see in the Figure 3.

In addition, it took about 3–5 min to perform strain–volume loop analysis off-line for each patient after practice in our study. We added this statement in the third sentence, third paragraph of the discussion section, as you can see according the 'tracked changes'.

Above is the explanation and changes we have made. If you have more suggestions, we would like to accept. Thanks for all you have done for our manuscript. We hope this manuscript can be helpful in clinical practice.
Sincerely,

Xianhong Shu, MD