Author’s response to reviews

Title: Pilot study using 3D-longitudinal strain computation in a multi-parametric approach for best selecting responders to Cardiac Resynchronization Therapy.

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CARU-D-17-00027 / Pilot study using 3D-longitudinal strain computation in a multi-parametric approach for best selecting responders to Cardiac Resynchronization Therapy.

Point-by-point Responses to editor’ and reviewers’ comments

Changes in the revised manuscript are highlight in yellow.

First, we want to deeply thank the editor and the reviewers for having considered our work. This is an important one for us. It was a long work, the software was developed for the purpose of the study. Also, the results are optimistic enough to encourage further works in that field using 2D but also 3D speckle tracking approaches. Therefore, getting this manuscript published could be of great value for our team and for others interesting in 3D speckle and CRT.
Reviewer reports:

Reviewer #1: In this study, septal flash and SDIL,peak were the only dyssynchrony parameters associated with volumetric response in the multivariable model which is interesting.

In my opinion, the most important finding of the current study is that 3D strain-derived parameter could differentiate responders from non-responders among 18 patients without septal flash.

Thanks a lot,

Yes, we agree that is impressive. It was impossible to build a paper only based on such a small population. Here, we are presenting the result of a pilot study and that is true that as mentioned by reviewer 1, the fact that speckle tracking 3D seems to provide an additive value of septal flash is highly valuable from a clinical standpoint. We underscore that in the discussion part of the new manuscript.

Therefore, if these results are confirmed by a validation study, it seems that mechanical dyssynchrony assessment should have 2 steps. As the first step, septal flash should be searched for using a simple visual and/or M-mode approach. If SF is not found, 3D echo should be performed in the next step as an attempt to detect a novel predictor of volumetric response proposed by the authors.

The authors could reshape the discussion section to emphasize these novel findings.

Many Thanks. You are right. We did so in the new manuscript.

Also, Table 5 should include only parameters that were independent predictors of response, especially septal flash alone which is currently missing (from the results section, with Sn and Sp of 79%, SF was equal to, if not better than, SDIL,peak > 1,037%.s-1). Further, since the accuracy of the SDIL,peak > 1,037%.s-1 and septal flash combined was lower than that of SDIL,peak > 1,037%.s-1 alone, it appears that the latter parameter should mainly be assessed in patients without septal flash to improve detection of potential responders. According to Table 5, 5 (28%) patients without SF, who were initially misclassified as non-responders based on the absence of septal flash, were correctly identified as potential responders based on SDIL,peak > 1,037%.s-1, which is impressive. It would be nice to include video examples of patients without septal flash but with SDIL,peak > 1,037%.s-1 in the revised version of the manuscript.

We change the table 5
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Diagnostic accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal flash</td>
<td>79%</td>
<td>79%</td>
<td>90%</td>
<td>61%</td>
<td>0.79</td>
</tr>
<tr>
<td>SDI L, peak &gt; 1.037% s-1</td>
<td>70.6%</td>
<td>7.6%</td>
<td>88.9%</td>
<td>52.4%</td>
<td>0.73</td>
</tr>
<tr>
<td>SDI L, peak &gt; 1.037% s-1 S Septal Flash</td>
<td>55.9%</td>
<td>92.9%</td>
<td>95%</td>
<td>46.4%</td>
<td>0.67</td>
</tr>
<tr>
<td>SDI L, peak &gt; 1.037% s-1 + AV</td>
<td>29.4%</td>
<td>92.9%</td>
<td>90.9%</td>
<td>35.1%</td>
<td>0.48</td>
</tr>
<tr>
<td>SDI L, peak &gt; 1.037% s-1 + IV</td>
<td>67.6%</td>
<td>92.9%</td>
<td>95.8%</td>
<td>54.2%</td>
<td>0.75</td>
</tr>
<tr>
<td>SDI L, peak &gt; 1.037% s-1 + AV + IV</td>
<td>29.4%</td>
<td>92.9%</td>
<td>90.9%</td>
<td>35.1%</td>
<td>0.48</td>
</tr>
<tr>
<td>SDI L, peak &gt; 1.037% s-1 + AV + IV + Septal Flash</td>
<td>23.5%</td>
<td>100%</td>
<td>100%</td>
<td>35%</td>
<td>0.46</td>
</tr>
</tbody>
</table>

- Only patients in sinus rhythm with good image quality were included in this study and also in other studies proposing strain-based methods for the quantification of dyssynchrony. In a real-world scenario, atrial fibrillation is observed in approx. 25% of patients undergoing CRT implantation. Excluding such large proportion of patients is a serious limitation of any method and deserves to be underlined in the respective section of the manuscript.

Thanks, of course we agree. Nevertheless:

- Currently, guidelines do not recommend CRT with a high level of evidence in AFib patients.
Using the single beat 3D acquisition technology, the echo assessment of all the components of mechanical dyssynchrony is (or will be) feasible in atrial fibrillation.

The progress in 3D ultrasound probes (improvement in the volume rates and 3D image definition) will definitely solve that issue of the Atrial fibrillation and the assessment of the 3D strain dataset during a single beat.

Only volumetric response at 6 months following CRT was assessed. However, it has been shown that almost a half of initial volumetric non-responders (after 1 year of CRT) might become responders after a longer period of time which questions this definition of response (Burns KV et al. JACC Heart Failure 2015). This is acceptable for a pilot study, but further validation studies should include harder end-points, especially given the fact that it has already been shown that the correction of septal flash by CRT is associated with improved long-term survival (PREDICT-CRT, EHJ CI 2016).

Thanks for this important comment, we agree that the decrease in LVESvol < 15% at 6-month is an unperfect tool for defining response to CRT. It has been used by many. But as pointed out in Circulation. 2010;121:1985-1991, 17 different primary response criteria were identified from 26 relevant articles. The agreement among these endpoints ranged from 32% to 91%. Agreement between different methods to define response to cardiac resynchronization therapy is poor 75% of the time ... therefore, the next study that we will have to conduct will certainly have to include the LV remodeling, but also the clinical response and that could be done using the endpoint proposed by Packer et al. (Development and Evolution of a Hierarchical Clinical Composite End Point for the Evaluation of Drugs and Devices for Acute and Chronic Heart Failure: A 20-Year Perspective. Packer M. Circulation. 2016 Nov 22;134(21):1664-1678). A sentence is added in the chapter ‘limitations’ of the new manuscript.

If proposed dyssynchrony parameters are the substrate for volumetric response to CRT, it seems logical that they were corrected by CRT. The correction of dyssynchrony by CRT was not assessed in the present study which is, again, acceptable for the pilot study. However, it would be of interest to report what happened to the septal flash (was it corrected or not) in 3 non-responders who had it at the baseline visit.

Low-dose dobutamine challenge might be useful to unmask or potentiate dyssynchrony, SF/ApRock (Parsai et al EHJ 2009, Stankovic et al EHJ 2013) in patients with no dyssynchrony at baseline.
Thanks a lot, we agree but the present manuscript was done with the objective to test the new 3D speckle tracking based tools that we built. We did not want to mimic what has been nicely done by Voigt et al or Parsai et al in the close past.

Minor

ABSTRACT

"All attempts to improve patient selection for cardiac resynchronization therapy (CRT) using echo-derived indices have failed so far"

- This statement probably refers to the catastrophic results of the PROSPECT trial. There are other multi-center dyssynchrony studies since then and this sentence could be softened a bit.

We agree! We soften the statement. Nevertheless, still a long road is in front of us before that we convince the electrophysiologists that we can help substantially.

METHODS

"The morphology was classified as either LBBB or non-LBBB (non-specific intraventricular conduction delay"

- It should be clarified whether only patients with LBBB and non-specific intraventricular conduction delay were included. What about patients with RBBB?

No RBBB was included in the present pilot study. Non-specific intraventricular conduction delays were included. It is clarified in the new version of the manuscript.

"…the main aim during the implantation was to obtain the finest QRS at the end of the procedure"

- I guess the authors had "the narrowest" QRS in mind

Sorry, it is corrected.

Reviewer #2: In this study the authors described LV mechanics using 3D echocardiography integral-derived longitudinal strain parameters in patients eligible for CRT and to test the relevance of this new tool for predicting CRT response
The authors concluded that this new automatic analysis of 3D longitudinal strain curves, using integral-derived parameters, provided original information on LV mechanics by combining timings and LV regional contractility data. This approach could be of value for improving patient selection for CRT.

The study is interesting.

There are some suggestions:

1. The study population is too small (only 48 HF patients) and heterogeneous (31% with ischemic etiology)

Thanks, we agree, but this is a pilot study and before getting support for a largest study we wanted to get these preliminary data published.

2. There are difference in 3D longitudinal strain in ischemic and nonischemic etiology of HF?

3. The scar should influence the 3D longitudinal strain values?

In response to point 2 and 3: the area under the curve allow us to take into account the ischemic segments. The systolic strain in very low and the post-systolic strain often greater, this is taken into account in the automatic computation that we are proposing. Here, the population is rather small so we were advise to not look at subgroups specifically from a methodological standpoint.

4. The authors should comment the time consuming of 3D longitudinal strain compared to 2D strain.

It is a bit longer for the acquisition but afterward, we built a dedicated ‘routine’ that is providing the results as soon as you ask for. We add a sentence in the manuscript.

5. The authors should consider the opportunity to analyze only 18 patients without septal flash and the clinical impact of SDIL peak values and the improvement in the selection of CRT patients.

Actually, the two-step approach underscored by reviewer 1 is closer to what we’re doing in the routine clinical practice. It is convenient to observe a septal flash and to consider it. Published data on septal flash and apical rocking are quite convincing even if a large prospective randomized study is still missing for validating these simple approaches. Our goal is to start with the simple tools and if required to us the computation that we are proposing. We deeply hope that you would agree.