Author's response to reviews

Title: Usefulness of NT-pro BNP monitoring to identify echocardiographic responders following cardiac resynchronization therapy: a randomized prospective study

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Responses to reviewer

In revised version of the manuscript, sections that are modified are highlighted in yellow and those that are deleted in red.

Reviewer #1

“This is an interesting and well written manuscript addressing an important clinical problem. The study provides a wealth of data but some remain hidden in the manuscript. The part dedicated to CRT and MR is far too long.”

We thank the reviewer for these encouraging comments on our work. In revised version of the manuscript, we added results regarding LV contractile reserve (CR) and its impact on NT-pro BNP and changes in NT-pro BNP. Moreover, we included a paragraph in the discussion section specially dedicated to contractile reserve.

We agree with the reviewer that the part dedicated to MR is too long in the manuscript. This is not the main focus of the paper, thus we decided to delete some results and complementary multivariate statistical analysis that were specifically based on MR. We thank the reviewer for this suggestion which clarify the manuscript.

“1. Authors performed stress echocardiography in all their patients but they do not provide how patients with contractile reserve respond to CRT and how the presence of a contractile reserve may have impact on the NT-proBNP values at follow-up. Authors report the correlation but no clear explanation in the results section of the manuscript.”

We assessed the presence of CR using changes in wall motion score index (from rest to dobutamine). As previously used by Ciampi et al., [1], we defined the presence of CR as an improvement ≥ 0.20 in wall motion score index during dobutamine. We added this in the method section of the revised manuscript (page 5, paragraph 2, lines 17-18): “The presence of LV contractile reserve (CR) was defined as an improvement of ≥ 0.20 in WMSI (rest-DSE).”

Using this definition, 30 patients (71%) had CR and these patients were more frequently responders (n=24, 80%) than those without CR (n=5, 42%; p=0.01). These results were added in Table 2. Patients with CR had higher improvement in LV end-systolic volume (-33±5 vs. -6±11ml, p=0.01 and -20±3 vs. 6±5%, p=0.02) following CRT. Moreover, baseline and follow-up NT-pro BNP were statistically not different between patients with or without CR. However there was a significant decrease of NT-pro BNP in patients with CR.

We added a new paragraph in results section providing data regarding CR (page 8, paragraph 2, lines 13-24). We also included in the paragraph “Relations between changes in NT-pro BNP and echocardiographic parameters” the impact of CR on
changes in NT-pro BNP (page 9, paragraph 2, lines 15-16). CR was trendily associated with changes in NT-pro BNP, certainly due to the relative small number of patients included in the study.

“This very same aspect should be discussed in depth in the discussion section of the manuscript.”

We thank the reviewer for this comment that allows us to improve the manuscript. We added in the revised version of the paper a new paragraph in the discussion section (page 12, paragraph 2, lines 13-21).

“These references were cited in the revised manuscript.

“4. Please upload sample cases (movies; there is no space limit)”

We thank the reviewer for this suggestion. We added in the new submission a case representative of our population showing a significant improvement in LV volume following CRT. Baseline and follow-up NT-pro BNP values could be add in the legend. Before CRT implantation, NT-pro BNP level was 1543pg/ml and left ventricular end-systolic volume and ERO were 180cc and 42mm² respectively. After CRT implantation, NT-pro BNP was 1104pg/ml (-24%) and left ventricular end-systolic volume and ERO were 136cc (-28%) and 15mm² (-64%) respectively.
Reviewer #2

“This is an interesting study addressing an important clinical issue.”

We thank the reviewer for this positive comment on our work.

“There are only minor issues that authors should address: The routine use of NT-proBNP has been recently questioned. Please discus”

We agree with the reviewer that routine use of NT-pro BNP may be questioned. Indeed, it seems that only large changes in serial measurement of NT-pro BNP conveys to changes in outcomes. We added in the discussion section of the revised manuscript the following paragraph: “Recently, Miller et al. [2] found in a prospective series of 172 ambulatory heart failure patients that a significant increase in BNP was associated with markedly reduced event-free survival. However, only large decrease in concentrations of natriuretic peptide led to outcome improvement. More modest increases or decreases seem to confer little additional predictive value.” (page 13, paragraph 1, lines 4-7).

“Contractile reserve may be an important parameter to assess. Please address.”

We thank the reviewer for this comment and as specified to the reviewer #1, we added the contractile reserve in the results section and discussed these results (page 8, paragraph 2, lines 13-24) and (page 12, paragraph 2, lines 13-21).

“TDI and derivatives parameters do not seem to work in this set of patients.”

In this study, TDI was used to quantify asynchronism extent and to evaluate longitudinal function as mentioned in the methods section. We added this point in the limitation section of the revised manuscript: “Dyssynchrony was defined by longitudinal TDI using a cut-off value of 50 ms on as inclusion criterion. Combining longitudinal and radial dyssynchrony index as inclusion criterion could have been helpful in choosing a more homogenous population prone to CRT response.” (page 14, paragraph 1, lines 1-3).
Reference List
