Author's response to reviews

Title: Characterization of exercise limitations by evaluating individual cardiac output patterns: a prospective cohort study in patients with chronic heart failure

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Author's response to reviews: see over
Dear Editor,

Hereby we would like to resubmit our manuscript entitled:

“Characterization of exercise limitations by evaluating individual cardiac output patterns: a prospective cohort study in patients with chronic heart failure”

Please find enclosed the revised manuscript and our point-by-point response to the reviewers’ comments. We would like to thank the reviewers who added valuable comments and identified areas of our manuscript that needed clarification, corrections or modifications.

We are at service for any assistance or questions raised during the reviewing process.

Awaiting your appreciated decision,

On behalf of the authors,

R.F. Spee

Veldhoven, The Netherlands
Reviewer: Barbro Kjellström

Major Compulsory Revisions

- **Abstract** – please revise last sentence in the conclusion. The idea of tailored therapy has not been studied

Indeed, the concept of tailored therapy by using hemodynamic patterns has not been studied. The last sentence in the abstract was deleted as suggested.

- **Methods**, line 133 – 134. It is unclear to me what the authors mean by “A central exercise limitation was defined as a plateau or decline in Q from 90-100% of exercise time”. Please be clearer in this description

It should be “a central **hemodynamic** exercise limitation” We postulated that an approach that can be used to characterize exercise limitations is to examine the pattern of the cardiac output (Q) response to symptom-limited exercise, with a failure to augment or a decrease in cardiac output towards peak exercise being indicative of a central exercise limitation. See line 136-139 for the change in the manuscript.

- **Results**, line 160. Is peak VO2 here same as in Table 1 or is Table one max VO2. The SD differ. Please clarify in Table 1 what is measured.

It is indeed the same peak VO2. The SD value in table 1 is changed into 5.9 corresponding to the value mentioned in line 160.

- **Results**, line 173. Do the authors mean “…differ between groups…”

This is correct. As proposed by the reviewer, we changed this sentence
• Table 2 – please add Atrial fibrillation, Resting HR, Mitral regurgitation Rhythm, including atrial fibrillation and resting HR were added to the table as suggested by the reviewer. Mitral regurgitation, categorized as severe, is already part of table 2.

• Table 2 – show percent for gender (e.g. percent male), Etiology, NYHA class to help the author interpret results

This is added as suggested by the reviewer.

• Table 2 – variable Plateau/decrease in VO2. In results only decrease in VO2 is mentioned, please correct one of the places

The variable was corrected in the results section to “plateau/ decrease in VO2” corresponding to table 2.

Minor Essential Revisions

• Methods, first paragraph, first sentence, please add the Netherlands after Maxima Medical Centre

This was added in the text.

• Methods first paragraph, last sentence, please add that “prior to the study” at the end of the sentence

This was added in the text.

• Methods, line 134. Chronotropic incompetence is abbreviated as CI, please avoid this abbreviation in a hemodynamic paper as it is an accepted abbreviation for Cardiac Index and is confusing when reported in results and in discussion.
As suggested by the reviewer we did not use the abbreviation CI for chronotropic incompetence anymore in the revised version.

- **Results line 152, should be Thirty-four**
  Corrected in the manuscript as suggested

- **Discussion, line 192. Do not agree that the results of heart transplant is affected by the results in this study – despite the explanation later on (line 246-8)**
  We agree that this study (reference 8) did not evaluate the outcome after heart transplantation. The results of the study suggested that the cardiac output response to exercise is an important predictor of survival in ambulatory patients being considered for heart transplantation, and may be valuable for the selection of patients. We adjusted the text in the manuscript. See line 203-204.

**Figures 1-2. To make the reported results more visible to the reader I suggest to show four panels;**

1) **Group: Increase in Q – show average and SD on top of individual values for VO2**

2) **Group: Increase in Q – show average and SD on top of individual values for Q**

3) **Group: Plateau/decrease in Q – show average and SD on top of individual values for VO2**

4) **Group: Plateau/decrease in Q – show average and SD on top of individual values for VO2**

We acknowledge the underlying thoughts of the reviewer and adjusted the figures as requested. However, the average values and SD are not well represented on top of all the
individual plots as represented in the figures below. For reasons of visibility, we would like to suggest to keep the figures in their current format.

Suggested figure: 1 Group: Increase in Q – average and SD on top of individual values for VO2
Reviewer's report

Reviewer: Corey Tomczak

- **Line 71:** Briefly elaborate on statement regarding “physiological heterogeneity” sourcing references 6-8. This is important here for the reader to understand the authors’ intent.

  As suggested by the reviewer, we elaborated our intentions. See line 69-77 in the revised manuscript.

- **Lines 109-122:** I appreciate the author's inclusion of their methods here. Unless there is a word count restriction, please elaborate slightly more the calibration procedure. Is the measured arm stabilized or is that associated hand gripping the handlebar of the ergometer? A diagram of the testing protocol may help as its difficult to visualize such testing procedures on an upright ergometer.

  We adjusted the text in the manuscript for reasons of clarity as proposed by the reviewer. See line 114-120.

- As well, this group has published exercise findings to validate the current cardiac output method with Fick (J Appl Physiol 2008). As the authors know from their work, cardiac output was likely overestimated in their 2008 paper in HF patients above 10 l/min. In the current manuscript, it appears cardiac output is above 10 l/min in approximately 1/3 or so of patients. This observation needs to be balanced with their prior 2008 work published in J Appl Physiol so as to be sure overstating the current findings does not occur.
We agree with the reviewer that a slight overestimation of cardiac output values above 10 l/min was reported in our previous validation study. However, this study also demonstrated that there was no overestimation of changes in cardiac output in the higher range. Therefore, we believe that this observation has no influence on the pattern of cardiac output during exercise, in patients with a peak cardiac output below or above 10 L/min.

- More information about patient recruitment is needed. For example, were patients consecutively screened?

See line 92-93 for additional information regarding patient recruitment.

- EF value: how recently determined – on testing day or via patient files?

The EF value was determined by echocardiogram or cardiac MRI in all patients before the study with a maximum of 3 months prior to the hemodynamic exercise test. However, in most cases EF was determined within two weeks.

- Why was non-parametric testing used? Please indicate assumption violations associated with parametric testing that let to using Mann Whitney. Subsequently, I suggest reporting chi-squared (or other) value and the associated degrees of freedom for each test.

We thank the reviewer for this comment. In fact, parametric testing with an independent t-test was used and reported in the Results section for continuous variables after normality of data distribution was confirmed. By accident, we noted in the Method section the Mann Whitney U test from a preliminary version of the manuscript We corrected this accordingly.
The χ² test was used for categorical variables. As suggested by the reviewer, we added the χ² value and degree of freedom in the Results section and table 2.

- **How was LBBB block presence tested statistically? In the same procedure as above?**

  LBBB was tested with the χ² test.

- **Not all Figure data is referenced in the manuscript at all - there are 4 Figures.**

  Please incorporate the Figure data into the results and discussion sections, or eliminate the Figures as they have no context without reference.

  A requested, figure data are incorporated in the results and discussion section.

- **Figure legends do not appear to correspond to actual figures. There are 4 figures labeled 1-4. Legends are labeled 1 and 2 with subfigure labels of ‘a’ and ‘b’.**

  Please correct and clarify.

  This was due to separate uploading of (sub)figures. In the revised version, we combined these 4 figures in 2 figures with subfigures A and B.