Author's response to reviews

Title: hsTnT increase after exercise in patients with pulmonary arterial hypertension

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Author's response to reviews: see over
Dear Dr Shipley,

Thank you for inviting us to re-revise our submission “High-sensitive Troponin T increase after exercise in patients with pulmonary arterial hypertension” (MS: 120894258130009).

We believe we could address all reviewer concerns and have significantly improved the quality of our submission. We hope you will now find our work acceptable for publication in BMC Pulmonary Medicine.

Thank you and we look forward to reading the comments from your reviewers.

Yours sincerely

Dr. M. Vökers
Reviewer #1

This is an interesting paper evaluating the clinical usefulness of hsTnT after exercise in patients with pulmonary arterial hypertension. The authors pointed out that hsTnT levels increase in PAH patients after exercise. The relative small number of patients is one of the limitation of this study so the confirmation of the results requires verification in a larger population sample.

We appreciate the reviewer’s enthusiasm towards our work and have addressed the comments as follows:

Below are some of my major compulsory revisions:
1. Please add to the “results” section the serum level of hsTnT in 3 healthy controls. Why they released this biomarker? Are they really healthy? Please explain this in “discussion” section.

This is a very important question. Low serum concentrations of Troponin T are detectable in healthy subjects with the new hsTnT immunoassay (Giannitsis E and Katus HA, Nat Rev Cardiol. 2012, 9(11): 616-8). To our best knowledge, no cardiac disease was known in the healthy cohort group. Values <14ng/L are not considered as pathological and the mechanism of Troponin T release in those subjects is currently unknown. We modified the discussion as suggested by the reviewer.

In the second paragraph of the Results section, we added the following:

“Whereas hsTnT levels were <14 ng/L (limit of quantification) in these control subjects (3.34 ng/L, 3.96 ng/L and 5.97 ng/L), hsTnT baseline values were >14ng/L and thus pathologically elevated in 4 patients.”

Additionally, we added in the fourth paragraph of the Discussion section:

“However, low serum concentrations of Troponin T are detectable in healthy subjects with the new hsTnT quantitative electrochemiluminescence immunoassay [21], as observed in our control cohort. Although values <14 ng/L are not considered as pathological, the mechanism of Troponin T release in those subjects is currently not known.”

2. What was the exclusion criteria for healthy volunteers? Please explain it in “Methods” section. E.g. systemic hypertension, renal function (did the authors measure GFR?)

The reviewer again asks an important question. Control subjects had no pathological findings in echocardiography, no history of systemic hypertension and all relevant laboratory values (including NT-proBNP and creatinin) were within standard values. We explain this now in the modified Methods section as suggested from the reviewer (second paragraph):

“Twelve healthy volunteers served as a control cohort. Control subjects had no suspicion of any pathological finding in echocardiography at rest, bodyplethysmography and symptom-limited cardiopulmonary exercise testing. Additionally, all relevant laboratory values (including hsTnT, NT-proBNP and creatinin) were within standard values.”
3. In table 1. There are the RHC parameters (e.g. PVR, mean RAP, mPAP). Please add RHC methods to “Methods” section

We apologize for making this unclear. RHC methods are now described in the Methods section, where the following paragraph has been added:

“Right heart catheter was performed with a Swan-Ganz catheter from either the right internal jugular or right femoral vein as reported previously [14]. The zero reference pressure has been estimated in a plane 5 cm dorsally to the sternal angle. PAPm and PCWPm were measured in the supine position at rest. Cardiac output (CO) measurements were obtained using the thermodilution method. CO was calculated as the mean value from 3 measurements with <10% variability of at least 5 measurements. The measurements were made using the mean at end-expiration, and were analyzed by two independent investigators from the raw data.”

4. In “Methods” section the authors described echo, spirometry and plethysmography methodology but there were no results of this examination in „results“ section. Please add this to “results” section.

Again, we apologize for any confusion. We believe that detailed echocardiography; spirometry and body-plethysmography results are not necessary for the interpretation of our study and removed the methods from our revised manuscript. We hope that the reviewer agrees with this point.

5. The authors wrote in “results” section: Detectable hsTnT levels are associated with death and decreased right ventricle function in patients with PAH. Please explain this. How long was follow up. Which RV parameters the authors mean?

Here we cite a previous study, which was also performed, in our department (Filusch A et al., Clin Sci (Lond), 119: 207-213). In this study patients were followed for 12 month and increased hsTnT were associated with decreased right ventricle function measured by right ventricular systolic strain and strain rate. We added the reference into the revised manuscript.

Below are some of my minor compulsory revisions:
1. Are there correlations between #hsTNT and PVR? If yes please add to the “result” section.

This is again an excellent point. We tested the correlations between hsTnT and PVR. However, in our study we could not confirm any correlation between hsTnT and PVR. As suggested by the reviewer, we did not include those data in the revised manuscript.

2. “Background” section: Several follow-up studies confirmed ... The authors listed only one reference. Please complete.

We completed the reference list in the revised manuscript, including the latest study performed by Grünig E et al. (Eur Respir J, 40(1): 84-92). We thank the reviewer for the erudite analyses and hope that we appropriately addressed the questions raised.
Reviewer #2

The study of Mirko Völkers, David Rohde et al aimed to investigate the release of myocardial high sensitive Troponin T (hsTnT) in patients with pulmonary arterial hypertension (PAH) in response to physical exercise. The case-control study aims to test hsTnT as a biomarker potentially helpful to clarify whether physical exercise in PAH patients may be beneficial or not. Indeed as stated by authors in the study background, there are conflicting data about the positive or negative effect of physical exercise in PAH patients. In order to answer to this question, 24 patients with PAH, were studied by means of symptom-limited cardiopulmonary exercise tests. hsTnT was then measured by an automated hsTnT assay (Roche) at four different timepoints (before exercise, after 30, 180 and 300 minutes. In around 80% of PAH patients, hsTnT was detectable before exercise with a close correlation between hsTnT and NT-proBNP. In contrast to NT-proBNP which remained constant after exercise, hsTnT was detectable in all PAH patients after exercise with a 95% increase as compared to baseline values.

The paper is on the whole well written, the method chosen are correct to study the kinetics of hsTnT related to physical exercise in PAH, the results are well presented. However, the main pitfall of the current study is that in both the study background and study discussion, the question raised and the answer given to the reader are both misleading considering the available data. Indeed, to present in the background the conflicting data between clinical studies showing prognostic benefits of physical training programs in PAH and negative findings in experimental models of progressive PAH, leads the reader to think that the current study will answer or clarify the following question: is physical training safe or dangerous in PAH? However, this study is not designed to answer to this tricky question. In fact, in the current study the type of exercise is a symptom limited maximal exercise and not the one usually chosen for physical training programs, which are mainly characterized by long lasting exercises and low levels of intensity. Moreover the demonstration that a slight increase in hsTnT may occur after exercise for reasonable increase in arterial pulmonary pressure and right ventricular overload, may not exclude that the amelioration of vascular resistances or in general haemodynamics after exercise (maybe in the long term, not only after just 300 minutes) will not determine a paradoxical reduction in hsTnT release. Therefore, it is overambitious to state or in a more subtle way, to let the reader think, that physical exercise may be potentially harmful in PAH patients. I believe that just stating in the very last paragraph “This does not reflect controlled exercise and respiratory training used in previous studies. If controlled exercise-training can cause relevant hsTnT release in patients with progressive RV dysfunction remains to be investigated.” is not enough as compensation to the biased view expressed in the whole paper.

The authors are thankful for the constructive critique of reviewer #2 and totally agree with all his points. This study was indeed never designed to answer if exercise is dangerous or beneficial to patients with PAH. We apologize if our manuscript led to the assumption that the authors think that physical exercise is harmful to patients with PAH. We revisited our manuscript and revised carefully the wording to make this point clear. Indeed studies from our own department have clearly shown that controlled exercise is beneficial to patients with PAH. The study was just designed to clear the question whether symptom-limited
maximal exercise results in increased hsTnT release. We believe that we improved in our revised manuscript the background and rational for our study.

In Detail, the following passages were changed in order to address this issue appropriately:

1. Abstract, Conclusions:
   “This might provide new insights into pathophysiology and individual risk assessment in patients with PAH.”

2. Background section, second paragraph:
   “Several follow-up studies confirmed that exercise training improved endurance and peripheral muscle function in patients with PAH and supported the role of exercise training as an adjunct therapeutic regime [3, 4]. Moreover, recent studies with larger patient populations approved safety and efficacy of closely monitored exercise training in various forms of pulmonary hypertension, though Grünig et al. characterized it as potentially harmful due to the risk of adverse events [5].”

3. Discussion section, second paragraph:
   “However, it remains uncertain if over-ambitious exercise training with repeated symptom-limited physical activity can contribute to myocardial damage in PAH patients.”

4. Conclusions section:
   “Exercise testing with assessment of hsTnT might provide new insights into pathophysiology and individual risk assessment in patients with PAH.”

Furthermore, although it is reasonable that the increase in hsTnT in this specific population is engendered by right ventricular overload, it cannot be excluded from the data available or reported by authors, whether comorbid left ventricular systolic or diastolic dysfunction, coronary disease or renal insufficiency may contribute to hsTnT elevation in some patients.

This is a very important issue and the authors totally agree with the reviewer’s concern. The added this point to the Discussion section (third paragraph):
“However, it cannot be excluded from the data raised in this study, whether comorbid left ventricular systolic or diastolic dysfunction or coronary artery disease may have contributed to hsTnT elevation in some PAH patients.”

Please report in table 1 also values of ejection fraction, diastolic function, renal function and specify in how many patients a history of coronary disease is known.

This reviewer asks for important data and we included all data in the revised Table 1.
Creatinin values of the patients included in the study were not elevated in a clinically relevant manner (creatinin mean±SD: 1.12±0.83 mg/dL).
3 out of 24 patients had a history of coronary artery disease (12.5%).
Echocardiographically determined left ventricular ejection fractions were in the low normal range in most patients (EF mean±SD: 55.13±4.34%).
Criteria for diastolic LV-dysfunction were met in 10 out of 24 patients (41.67%).
However, it is known that in later stages of right ventricular dysfunction due to pulmonary hypertension, LV-dysfunction, especially during the diastole, occurs
because of compression by the dilated and stiff right ventricle (paradoxical septum motion, D-shaped LV).

Again, we thank the reviewer for the constructive feedback and believe that the quality of the manuscript has been significantly improved.