Dear editor,

Thank you for considering our manuscript “Impact of training specificity on exercise-induced cardiac troponin elevations in professional athletes”, with Manuscript ID 49375, for publication. We would like to express our gratitude to the reviewers that left many valuable comments that we’ve responded to. We have added a coauthor; Mrs Nicolena Stephensen Nyberg. She is a native English speaker and works as a biomedical scientist at Sundsvall County Hospital. She has contributed as a manuscript writer and has also made suggestions about data analysis. Her e-mail address is nicolena.stephensen.nyberg@rvn.se. Her ORCID ID is https://orcid.org/0000-0001-9467-6340. All authors have reviewed the paper. All changes in the revised manuscript are highlighted in red text. We believe that we have improved the revised version of the manuscript and hope that you can accept it for publication in World Journal of Cardiology.

Best regards,

Anders Henriksson

Author contributions: Wedin JO and Henriksson AE were equally involved in designing the report, collecting and analyzing data, and preparing the manuscript. Wedin JO, Nyberg NS and Henriksson AE reviewed and revised the final version of the manuscript.

Reviewer 02729101

The study is interesting demonstrating that intermittent high-grade efforts but not continuous exercise, despite similar levels of maximal load achieved, may lead to high-sensitivity cardiac troponin T (hs-cTnT) release. As reported in discussion this may lead to misinterpretation of clinical significance of values above 99th percentile in clinical setting. Several papers showed that also a small increase in troponin in cardiovascular stress conditions (eg after non cardiac surgery) are associated with a worse early and long-term prognosis. Release pf hs-cTnT may show similar pathophysiological mechanisms in some of these patients but at present we have no way to differentiate "physiological" from "pathological" hs-cTnT increase.

Response: We appreciate the time and effort the reviewer spent reading our manuscript. Regarding the minor issues on language quality, we have had our manuscript proofread by a native English speaker and changed according to the comments. We are happy with the changes and think they improved the final version. All changes in the revised manuscript are highlighted in red text.

Reviewer 02565578

The Authors report an interesting observation that cTn in the athletes trained for performing intermittent exercise the cTn reaches higher levels after intermittent exercise than after the resistance exercise. A review of the cTn kinetics literature demonstrates a pattern of elevation and peak within the first 4 h after exercise dropping within 24h. In contrast myocardial necrosis demonstrates a later cTn peak with a slower reduction occurring over several days. These data derive mainly from the studies in endurance athletes (see Baker et al. Int J Cardiol Heart Vasc. 2019;22:181-186), such as marathon racers.

Response: We are thankful that the reviewer spent the time and effort to help us improve our manuscript. There were some issues with the language and therefore we have had it proofread by a native English speaker that works in this area. All changes in the revised manuscript are highlighted in red text.

Comment: The Authors do not meaningfully compare their work to the already published data (e.g., the above-mentioned review is not cited). The comparison with one of the published papers should be moved from the Introduction to Discussion section.

Response: In line with the reviewers' comment, we've edited the text and now compare the findings of our study to existing data in the Discussion section. The suggested review article by Baker et al was used for this purpose. We feel that the references in the Introduction are needed to give an adequate background to the subject. If there are still issues with the composition of the Introduction, we can restructure it as requested.

Comment: In the discussion and conclusions, the significance of present findings is not clear, especially since cTn elevation following exercise is considered benign and affected individuals are not counselled nor treated. Would it be advisable to include both types of exercise in the training of professional athletes in order to avoid cTn elevation?

Response: Thank you for this important remark. We cannot give general recommendations based on the findings of the present study involving only 9 participants, it is hypothesis generating for future study design in this research area. Regarding acute chest pain after physical exercise in otherwise healthy athletes the authors have personal clinical experience in this challenging situation. Should it be interpreted as myocarditis or is it safe to let the athlete compete the next day? The long-term effects of exercise-induced hs-cTnT elevations are still not known, but some observational studies suggest the possibility that it can result in cardiac dysfunction (mainly RV dysfunction, e.g. La Gerche et al., Eur Heart J 2012;33:998-1006). This motivates future studies on the mechanism behind suspected exercise-induced myocardial injury. Perhaps other biomarkers need to be incorporated in the interpretation.

The significance of our findings is that the type of exercise (endurance or high-intensity), as well as the type of athlete performing it (e.g. endurance athlete or athletes adapted to perform high-intensity exercise), should be taken into consideration when designing future studies on hs-cTnT release in healthy athletes. We have tried to make this message clear in the Discussion and Conclusions sections. Please see the revised version.

Comment: Some animal experiments have shown that trauma and stress induce the cTnT isoform in skeletal muscle. It can be speculated that chronic skeletal muscle damage could

induce cTnT in a similar way in athletes. The authors should include this concept in the discussion of their results.

Response: We thank the reviewer for this valuable comment and have accordingly incorporated a brief discussion regarding this topic in the revised manuscript. Although we cannot find references that support this concept in animals, several studies on humans with muscular disorders support the reviewers' theory. If the reviewer can suggest studies that show this phenomenon in animals, we will gladly read them and incorporate them in the discussion. As for now, we only comment data derived from human studies and we think it adds value to the discussion on potential mechanisms.

Comment: Data are presented in two tables and one figure. The figure unfortunately cannot be viewed in the present submission, but the two tables report exactly the same data (different p for the comparison between time points in the same exercise and different exercisers) and could be easily combined.

Response: We hope that one figure and three tables can be viewed in the resubmitted revision.

REVIEWER 02636166

Dear Drs. Wedin and Henriksson: This is an interesting paper addressing the impact of training specificity on exercise-induced cardiac troponin elevations in professional athletes. Firstly, this an observational experimental study. Only nine male athletes were included for the investigations. Although the study was well conducted, there were some issues needed to be addressed.

1. First, there were only nine male participants and the topic had better name as a pilot study for male athletes.

Response: We agree with the reviewer and have changed the title according to the suggestion. Please see the revised version. All changes in the revised manuscript is highlighted in red text.

2. The baseline data such as ECG and echo were not provided in the table.

Response: ECG and echocardiography (as well as questionnaire) were used to screen the participating athletes for cardiovascular abnormalities that would disqualify them from strenuous exercise. Thus, these tests were only carried out for the safety of the athletes as a part of a preparticipation screening. All athletes were examined by a cardiologist that cleared them for participating in the study, but that data was not sampled for this study. Therefore, specific measurement like left ventricular systolic and diastolic function or ventricular dimensions cannot be provided.

In the first sentence of the Results section, however, we state that all study participants had normal echocardiographic and electrocardiographic findings and that they were eligible for inclusion.

3. Serial lactate levels and hemodynamic parameters like heart rate and BP should be provided in the table.

Response: As we would like to highlight the change of hs-cTnT, we choose to only present the lactate levels in the Result section but not in a Table. Lactate concentration was mainly analyzed to assure the high-intensity character of the cycle ergometer test (which is preferably a test of continuous character). As we do not compare lactate levels between the tests, we find it more appropriate to only mention the results in the text. If the reviewer still has issues with us presenting lactate levels in the text only, we can add it in a Table.

The hemodynamic parameters for the two tests are also described only in the Results section for the same reason. On the reviewers' request, we've added a table and feel that the results of manuscript became more illustrative.

4. Are there any data for other cardiac enzymes such as CPK and MB-isoforms as well as BNP levels available? If not, please mention them in the future works.

Response: Unfortunately, we did not analyze CK nor BNP in this study. This is a good idea for future work and we will take this into consideration when designing our next study.