Author’s response to reviews

Title: Validity of simplified, calibration-less exercise intensity measurement using resting heart rate during sleep: A method-comparison study with respiratory gas analysis

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Author’s response to reviews:

Dr. Gabriel Trajano
Editor
BMC Sports Science, Medicine and Rehabilitation

Dear Dr. Gabriel Trajano,

Please find attached a revised version of our manuscript entitled "Validity of simplified, calibration-less exercise intensity measurement using resting heart rate during sleep: A method-comparison study with respiratory gas analysis" (SSMR-D-19-00035), which we would like to resubmit for publication in BMC Sports Science, Medicine and Rehabilitation.
We appreciate the reviewers for their insightful comments that have helped us improve the manuscript significantly. Please find our point-by-point responses to the reviewers’ comments below.

Additions/Revisions in the revised manuscript are indicated by yellow highlights in the manuscript file. We hope that the revisions and responses are satisfactory and that our manuscript is now suitable for publication in BMC Sports Science, Medicine and Rehabilitation.

We look forward to hearing from you.

Yours sincerely,

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Point-by-point response to reviewer’s comments

The authors thank all the reviewers for their valuable feedback. The following are our point-by-point responses to reviewer’s comments.

The comments from reviewer #1

Comment #1:

Page 5, Line 20-21: You only very briefly mention the 24/7 measurement model at the end of the background. As the 24/7 model forms part of the title of this manuscript, it would be worth expanding on this.
Response:

Thank you for this comment. We have added text regarding 24/7 measurement:

Page 4, Line 12

This may further enable the 24/7 measurement of exercise intensity.

One of the major effects of physical training in rehabilitation is the improvement of fitness, which is linked with the amount of exercise and exercise intensity[21, 22]. To increase the amount of exercise in daily basis, daily activities apart from the training during rehabilitation would also be important. Therefore, measuring how much exercise is performed in daily life is of great significance. If the amount of exercise can be measured 24 hours a day every day, the relationship between the amount of daily exercise and fitness can be better understood.

Page 4, Line 22

In addition, the feasibility of the 24/7 measurement of exercise intensity with the use of this method was tested in healthy subjects

Comment #2:

Page 5, Line 36: The format for how you present mean/SD demographic data changes. Keep the formatting the same.

Response:

Thank you. We have revised the statement as follows:

Page 5, Line 8

Participants’ height and weight were 166.2 ±8.6 cm and 59.1±10.8 kg, respectively.

Also the sentence on Page 8, Line 15 was changed as follows.

The resting HR during sitting, lying, and sleeping were 85±8, 77±9, and 58±5 per minute, respectively.
Comment #3:

Page 5, Line 51: Were the two exercise tests (Bruce & 6MWT) randomised? Also, was there a rest period between these tests? If so, for how long?

Response:

Thank you for this question.

6MWT was performed first followed by and the Bruce test as the fatigue due to treadmill testing could affect the measurements in the subsequent 6MWT if the treadmill test was performed first. As the exercise intensity in 6MWT would be lower, we decided to do the tests in a fixed order. The examinee took a 15-minute rest before proceeding with the treadmill testing in order to eliminate the influence of 6MWT.

We have changed as follows:

Page 5, Line 21

Then, in the 6MWT, participants were instructed to walk at a comfortable speed for 6 minutes. After a 15-minute rest, treadmill exercise testing with the Bruce protocol was conducted.

Comment #4:

Page 6, Line 4: This comment also relates to your use of the equation on page 7. Did you confirm that the participants reached exhaustion on the treadmill test? If so, how? Were you able to confirm, from the data, that VO2max was attained for each participant? If so, could you please include the method you used for this within the manuscript? It is important that the reader is assured that VO2max, rather than VO2peak, was identified in the data.

Response:

Thank you for your questions. I’m sorry that the explanation regarding the methodology used to determine VO2max was missing. In this experiment, we considered the VO2 to be maximum if the participants satisfied at least three of the following four criteria: 1) maximum voluntary exhaustion as measured by the Borg CR-10 scale; 2) exceeding 90% of predicted HRmax by age; 3) presence of a VO2 plateau (VO2 between two consecutive work rates < 2.1 mL/kg·min-1); and 4) a maximal respiratory exchange ratio (RERmax) > 1.1. [3, 4]

We reviewed each patient’s data and confirmed that all the participants satisfied the third criteria when they stopped the treadmill testing.
We have revised the text in the manuscript as follows;

Page 5, Line 23

In this experiment, we considered the VO2 and HR to be maximum if the participants satisfied at least three of the following four criteria: 1) maximum voluntary exhaustion as measured by the Borg CR-10 scale; 2) presence of an HR plateau (HR between two consecutive work rates ≤ 4 beats·min⁻¹); 3) presence of a VO2 plateau (VO2 between two consecutive work rates < 2.1 mL·kg⁻¹·min⁻¹); and 4) a maximal respiratory exchange ratio (RERmax) > 1.1. [10, 23]

Comment #5:

Page 6, Line 10: I am unable to locate any product information/specifications for the Mobile Aero Monitor. As you are using VO2 reserve as the gold standard, the accuracy of your sitting/laying and maximal exercise VO2 data is important. Commercial VO2 systems significantly vary in reliability and accuracy of measures, often dependent on their components. Are you able to supply a link to the product information (there appears to be no link on the manufacturer's page) in your reviewer response (not the manuscript)?

Response:

Thank you for this question.

Unfortunately, there is no page for product information in English. This device is officially certified as medical device for clinical use in Japan that may guarantee the quality of measurement accuracy. There is one paper written in Japanese with English abstract showing the reliability of this system compared with the other common gas analysis system used in Japan. https://www.jstage.jst.go.jp/article/rika/34/2/34_249/_pdf

There are also several papers that have used this system for gas analysis.[5, 6]

Comment #6:

Page 6, Line 16: Was participant comfort while sleeping with the hitoe system considered during recruitment? For example, were only subject who normally wear clothing in bed selected? There may be potential for sleep disturbance if the individual's sleeping attire/environment is changed.
Response:

Thank you for this question.

In this experiment, all the individuals normally wear clothing in bed and those who were reluctant to wear hitoe wear during night were excluded from the experiment. There was no complaint from the participants regarding sleep disturbance. However, the hitoe wear is relatively tight compared to usual T-shirt, and thus there is still some possibility that the use of wear affected the heart rate measurement during night. We added the following explanation in the limitation section.

Page 5, Line 2

The individuals 1) without any medical history of diseases which could affect cardiorespiratory fitness and movement function, such as heart failure, myocardial infarction, bone fracture, and spinal cord injury and 2) who agreed to wear the measuring devices during the entire 2-day measurement session after checking the fit of the wearable devices.

Page 5, Line 7

The exclusion criteria were 1) existence of sleep disturbance and 2) medication which could potentially affect performance.

Page 11, Line 26

First, the hitoe wear is relatively tight compared to a usual T-shirt as the electrode should be attached on the skin. This may have affected the HR measurement during sleep. The influence of the comfortability of the wear and HR measurement during sleep should be further investigated.

Comment #7:

Page 6, Line 49: Were potential HR measure influences considered and controlled? For example, caffeine, exercise, sleep deprivation.

Response:

Thank you for this question.
We told each examinee not to take caffeine and/or alcohol and not to do high intensity exercises 24 hours before the measurement sessions. None of the participants reported sleep deprivation during the period.

We have revised as follows:

Page5, Line 16

The participants were asked to avoid high intensity exercise and alcohol and caffeine 24 hours before the measurement session.

Page 6, Line 9

None of the participants reported sleep disorder during the measurement.

Comment #8:

Page 6, Line 49: I agree with the practicality of using the Gellish formula for age-predicted heart rate max. However, the HRmax value from the exercise test should be used for the study's %HRR calculations. You should limit as much potential predictive variability as possible. The Gelish formula should be advised for use with general population in a practical setting, however the %HRR values should be derived from rested HR and maximal exercising HR measures.

Response:

Thank you for this comment. I see your point. Therefore, we calculated again with HR max value as you see in the table 1, Fig 1.

We have also revised the methods and results accordingly.

Page 2, Line 16

Results: In the treadmill testing, the mean difference between %VO2R and %HRRsleeping was 1.7% (95% confidence interval [CI], −0.2% to 3.6%). The %HRRsitting and %HRRlying values were 10.8% (95% CI, 8.8% to 12.7%) and 7.7% (95% CI, 5.4% to 9.9%), respectively. In the 6MWT, mean differences between %VO2R and %HRRsitting, %HRRlying and %HRRsleeping were 12.7% (95% CI, 10.0% to 15.5%), 7.0% (95% CI, 4.0% to 10.0%) and -2.9% (95% CI, -5.0% to -0.7%), respectively.
%HRR=(HR-restingHR)/(MaximumHR during treadmill testing - restingHR)

The actual maximum value (HRmax) was obtained during the treadmill exercise testing.

In the treadmill exercise testing, the mean differences between %VO2R and %HRR calculated with HRsitting, HRlying and HRsleeping were 10.8% (95% CI, 8.8% to 12.7%), 7.7% (95% CI, 5.4% to 9.9%), and 1.7% (95% CI, −0.2% to 3.6%), respectively (Figure 1A–C).

The 95% LOAs between %VO2R and %HRRs calculated with HRsitting, HRlying and HRsleeping were −5.4% to 27.0%, −11.4% to 26.8%, and −13.7% to 17.2%, respectively.

[Although the actual maximum VO2 values measured in the treadmill testing were used for %VO2R calculation, estimated maximum value by the participants’ age were employed for the %HRR calculation. Therefore, inaccuracies could present due to the estimated values used for the %HRR values, based on age. This is because the aim of this study was to compare the results of a simplified, time-saving method to measure exercise intensity to those from a gold standard method.]

Comment #9:

Page 7, Line 8: See comment for Page 6, Line 4.
Response

We have revised the method section as shown in the response to comment #4.

Comment #10:

Page 7, Line 15-20: This is more of a consideration. If using the average of the final minute for each stage, check that there is no increase to HR immediately prior to initiating the next stage of the exercise. The HR may increase in anticipation of the increased workload. If this is the case, it may be worth getting a minute average minus the ~15 seconds prior to the next workload increment.

Response:

Thank you for this comment. The review of the data indicated that the HR immediately prior to initiating the next stage possibly reflects the anticipation of the increased workload in several cases, but some of them seemed to start earlier than 15 seconds before the next stage and it was difficult to decide the appropriate timing. Thus, we decided to employ the middle one minute of the three minute-stage for the analysis.

Page 6, Line 23

The %HRR and %VO2R data used for the analyses were averaged %HRR and %VO2R during the middle 1 minute of each 3-minute stage during the treadmill testing …

Comment #11:

Page 8, Line 57 to Page 9, Line 9: As comment earlier, I think there needs to be more information regarding the 24/7 measures. It reads as more of an afterthought. For example, of the three subjects, what type of work did they do? What exactly is meant by 'holidays'? Given the period of time of which this data was collected, and potential implications to research in average HR responses, this could probably be an entirely separate manuscript.

Response

Thank you for your feedback. We have added information for this experiment and prepared independent section for this experiment in the method and result section.
24/7 %HRR measurement session

Participants

In the 24/7 measurement session, three healthy adults (all male, aged 33, 27 and 27, respectively) without any medical history of cardiorespiratory, orthopedic or neurological diseases participated. The occupations of the participants were medical doctor, physical therapist, and occupational therapist.

Procedure

For the 24/7 %HRR measurement session, the hitoe system was used for continuous monitoring of HR. Each participant wore the hitoe wear to monitor HR. For each participant, four pieces of hitoe wear were provided, so that they could wash and change the wear. The participants were told that they can take off the wear or transmitter during bathing or whenever they don’t want to monitor HR. The observation was performed for consecutive 180 days.

Analysis

The %HRR was calculated with HR during sleep as resting HR. The maximum HR was estimated using the Gellish equation (HRmax=206.9-0.67×age)[11].

The daily time course of %HRR was compared between working days and holidays. Working days in this experiment were defined as the days when the subjects were at work at for least 8 hours a day, while holidays were defined as the days on which the participants were completely off duty. Days with less than 8 hours’ work was excluded from the analysis.

The %HRR data was averaged for every 20 seconds, and then the ensemble average, i.e., the average of each time point through all the observation periods, was calculated for the working days and holidays. The paired t-test was used for the comparison between the HR on working days and holidays in each participant.

24/7 measurement session

To confirm the feasibility of the 24/7 measurement of exercise intensity with the wearable system and sleeping HR-based exercise intensity measurement, 24/7 measurement of HR in three
healthy subjects were performed. The results of 24/7 measurement of HR are shown in Figure 2. The data was successfully acquired for 132, 142 and 165 days, respectively (working days: 102, 108, 123 days, holidays: 30, 34, 42 days). The graphs show the ensemble average and standard deviation of the %HRRsleeping values of each participant on working days and holidays. In all participants, the average HR values on working days were significantly higher (P<0.0001) than HR values measured on holidays (17.8 ±14.6 vs 14.6 ±13.9, 14.6 ±14.4 vs 12.9 ±12.6, and 14.5 ±11.8 vs 10.3 ±9.7, respectively. The difference in average HR values were more evident during daytime (9am-5pm; 26.0 ±10.9 vs 21.2 ±12.7 P<0.0001, 23.7 ±11.5 vs 21.7 ±10.2 P<0.0001, 22.3 ±6.8 vs 16.3 ±6.8 P<0.0001, respectively).

Page 9, Line 45: Could you please neaten this equation? Use the Math function in word, for example. I would suggest removing the (=SV*HR) altogether, or including as a footnote or in a separate sentence, for reasons of clarity.

Response:

Thank you for this comment. We have revised as follows:

Page10, Line 11

Based on Fick’s principle,[7] the relationship between VO2 and cardiac output (CO) is described as:

\[ VO2 = CO \times a-vO2diff \] (a-vO2diff :arteriovenous oxygen difference), where CO is calculated using the equation: CO= SV*HR.

The comments from reviewer #2

Comment #1

# Language: some gramatical terms needs to be improved. For example: "lying position" is not a standard term. In that case, supine position would be preferable. There are a lot of terms you repeated several times making the wording hard to follow. Please forward the manuscript for a professional proof-reading translator. It would improve the uptake of the information for readers and also ease the job of the editor and reviewers.

Response:

Thank you for your suggestion.
We have used a professional proof-reading service before the submission but it might be insufficient. After the revision, we have sent the file for proof-reading again for additional English editing. About the wording “lying position”, we followed the reviewer’s recommendation. On the other hand, there was a sentence in which the use of “supine position” may be confusing, thus we just removed “position” in this case. We have made changes as follows:

Page5, Line 19

Before treadmill testing and the 6MWT, resting HR and VO2 in sitting and lying position were measured after a 10-minute interval of sitting.

Page6, Line 7

Sleep time was defined as the time when the participant was in supine position, judged with the accelerometer, between midnight and 5 a.m.

Page10, Line 9

The influence of these factors could be removed during sleep. Second, increased stroke volume (SV) in a supine position may contribute to HR better reflecting the change in oxygen consumption.

Comment #2

# Trial registration: The registration is more than welcome. Even not being a randomized controlled trial, I congratulate you for registering the study. However, please remove the word "Trial" once it induces the reader to think it is an RCT.

Response:

Thank you for this comment. We have changed as follows:

Page 2, Line 13

A 180-day trial of ,24/7 %HRR measurement with three healthy adults was also conducted.

Page 7, Line 16

In the 24/7 measurement session, …
For the 24/7 %HRR measurement session,

24/7 measurement session

Comment #3

# Title and all of the reporting: several terms are lacking in terms of reporting to improve the transparency of your paper. Please use the GRAAS Reporting Guideline for Accuracy Studies (J Clin Epidemiol. 2011;64(1):96-106 PMID: 21130355), that can be found in the EQUATOR Network (www.equator-network.org) website to improve the transparency of your reporting.

Thank you for this comment. We carefully checked the GRAAS checklist and modified the manuscript accordingly. Specially we entirely modified Introduction to clarify what is already known and the rationale for the study. About the changes regarding the sample size calculation was summarized in the response to the comment#4.

Title

Validity of simplified, calibration-less exercise intensity measurement using resting heart rate during sleep: A method-comparison study with respiratory gas analysis

HR is widely used to monitor exercise intensity.[8, 9] In particular, percent HR reserve (%HRR) is frequently used as an index of exercise intensity[10] and has been correlated and in good agreement with %VO2R, although %HRR seems to be slightly lower in low exercise intensities.[9, 10] Both of %VO2R and %HRR are considered suitable measures for exercise prescription.[12, 13] The merit of using HR is its easiness; it can be monitored in various settings and is not limited to specialized settings. An individual’s resting and maximum HR are needed to calculate %HRR, in addition to their HR during exercise. The maximum HR should ideally be measured by exercise testing, but there is an easy alternative method to estimate maximum HR with a simple equation using an individual’s age[13]. On the other hand, the resting HR should actually be measured, and the accuracy of resting HR is important for precise calculation of the exercise intensity. HR can easily be influenced by mental state at the time of measurement and/or
activities immediately before measurement. Therefore, sufficient pre-measurement rest and abstention from exercise is needed to obtain accurate resting HR.[15] However, in usual clinical settings, it may not always be possible to provide sufficient time for a subject for resting HR measurement. One possible solution may be to measure the HR during sleep, which should be lower and more stable than that during the awake condition.[15] Recording HR during sleep may present less measurement errors related to psychological or physical factors, which are difficult to eliminate when the measurements are taken while the individual is awake. In addition, longer periods of HR measurement may improve the accuracy of resting HR measurements. Recent technological development has enabled easy monitoring of HR using wearable devices. For example, wrist-band type measurement devices or smart clothing systems have reportedly enabled the continuous monitoring of HR. [16-18] The use of such technologies also enables the measurement of HR during sleep.[19, 20] If %HRR calculation with the use of HR during sleep as resting HR is validated, daily measurement of exercise intensity would be more feasible in the daily clinic.

This may further enable the 24/7 measurement of exercise intensity. One of the major effects of physical training in rehabilitation is the improvement of fitness, which is linked with the amount of exercise and exercise intensity [21, 22]. To increase the amount of exercise in daily basis, daily activities apart from the training during rehabilitation would also be important. Therefore, measuring how much exercise is performed in daily life is of great significance. If the amount of exercise can be measured 24 hours a day every day, the relationship between the amount of daily exercise and fitness can be better understood.

In this context, this study aimed to examine the validity of %HRR, calculated with a simplified method using resting HR measured during sleep, against %VO2R (the gold standard), in a healthy subject. The measurements were performed during two kinds of exercising; treadmill testing with the Bruce protocol and a 6-minute walk test (6MWT). In addition, the feasibility of the 24/7 measurement of exercise intensity with the use of this method was tested in healthy subjects.

Non-probability sampling procedures were used to recruit a convenience sample of participants. The total number of data points used for Bland-Altman plots were 65 in treadmill testing and 36 in 6MWT.
Comment#4

# Sample size: how did you calculate your sample size? I'm very concerned with this very low sample size and a Bland-Altman plot. A sample size calculation for a Bland-Altman plot is today well disseminated (https://www.ncbi.nlm.nih.gov/pubmed/27838682). This is a thing you as researchers should think about how to solve or at least on how to acknowledge in your discussion. To collect more data could be a deviation from the protocol and then not doable.

Response:

Thank you for this comment.

As you pointed out, the sample size of this study could be insufficient.

The previous studies comparing %HRR and %VO2R show strong correlation between these two values but on the other hand large variety in extent of agreement, which ranges 20-30% at the largest. [3, 22] Considering that the %HRR in this experiment would be in similar levels in terms of agreement with VO2R, we set the maximum allowed difference between the methods of 25%. In this study, the pair with smallest and non-significant difference was the %VO2R and %HRR sleeping in the treadmill testing, whose mean and standard deviation of the difference were 1.7% and 7.7%, respectively. According to the formula provided by Lu et al, the required sample size for an alpha risk of 0.05 and a power of 80% would be 26.

In this study, the number of participants was 12 and for each participant repeated measurement during treadmill testing and 6MWT was performed. In total, the number of data was 64 in treadmill testing and 24 in 6MWT. There is no previous study for sample size calculation for Bland Altman plot with repeated measurements, but if it would be possible to apply the same standard as the independent samples, the number of 64 in treadmill testing may satisfy the requirements. On the other hand, the number of the data of 6MWT was too small. Thus, we have increased the number of data to 36 by adding data of middle 1 minute of the 6MWT, in addition to first and last minutes. There may be still some discussion whether this is really sufficient sample size, because these are from the repeated measurements, and not the individual samples. Even though, the present result would be at least meaningful to indicate the possible superiority of the sleeping HR-based %HRR calculation to that calculated with sitting HR, which is already widely accepted methodology in the clinical practice.

Page 12, Line 5

The sample size of this study may also be considered a limitation. In this study, the number of participants was 12, and for each participant, repeated measurements during treadmill testing and 6MWT were performed. The total number of data points in these experiments with repeated measurement were 64 and 36 in treadmill testing and 6MWT, respectively. The previous studies comparing %HRR and %VO2R show strong correlation between these two values; on the other
hand, they display a large variety in extent of agreement, which ranges from 20 to 30% at its largest.[10, 48] Considering that the %HRR in this experiment would be at similar levels in terms of agreement with VO2R, we set the maximum allowed difference between the methods to 25%. In this study, the pair with smallest difference was the %VO2R and %HRRsleeping in treadmill testing, whose mean and standard deviation of the difference were 1.7% and 7.7%, respectively. According to the formula provided by Lu et al, the required sample size for an alpha risk of 0.05 and a power of 80% would be 26, and our sample size satisfies this requirement.[49] There may be still some discussion whether this is really a sufficient sample size, because the sample size is based on the repeated measurements, and not on the individual samples. There is no preceding study on sample size using Bland Altman plot with repeated measurements. Nonetheless, the present result would be at least meaningful to indicate the possible superiority of the sleeping HR-based %HRR calculation to that calculated with sitting HR, which is the widely accepted methodology in clinical practice.

Comment#5
# "Pseudorandom order": what does that mean?

Response:
Thank you for this question. Sorry for misuse of the word.

What I meant was “random order”

We changed as follows.

Page 5, Line 19

Lying and sitting HR were measured with a 5-minute interval in a random order to eliminate order effect bias.

Comment#6

# Blinding and allocation concealment: is there any type of blinding and allocation concealment? If yes, please state YES or NO.

→NO. There is no blinding and allocation concealment.
Comment#7

# Characteristics of participants and inclusion/exclusion criteria: those informations are poorly reported. You need a Table 1 in which you state all relevant characteristics of participants and, for the eligibility criteria, you should state details that would allow external readers to repeat your study. For example: "participants without diseases" is not sufficient. What diseases?

Response:

Thank you for this comment.

We added the name of diseases as the examples, although we could not cover all the disease that are possibly relevant to the present experiment.

Also we added exclusion criteria in this experiment.

But we couldn’t prepare table 1 for this, because this was a study with heathy subjects and we unfortunately have not detailed information of the participants such as respiratory function and motor function, which could be related to the results of this study. The other information of the healthy subjects that we have seemed not so much relevant to the present study.

Instead, we added some more details about the patients characteristics.

The changes are as follows.

Page 5, Line 2

In the validity study, 12 healthy adults (eight males; mean age, 29 ±5 years) participated. The individuals 1) without any medical history of diseases which could affect cardiorespiratory fitness and movement function, such as heart failure, myocardial infarction, bone fracture, and spinal cord injury and 2) who agreed to wear the measuring devices during the entire 2-day measurement session after checking the fit of the wearable devices.

Page 5, Line 7

The exclusion criteria were 1) existence of sleep disturbance and 2) medication which could potentially affect performance.
Comment#8

# Data sharing statement: very welcome you are willing to share the data with the authors. However, the details are poorly related. Please follow the ICMJE 2017 Statement for Data Sharing in order to give to external authors the necessary details in terms of your data-sharing policy.

Response:

Thank you for this comment. We revised the Data sharing statement as follows;

Page 14, Line 7

Availability of data and material: The data collected and analyzed during the current study are available beginning at 9 months and ending at 24 months following article publication from the corresponding author on reasonable request to researchers who provide a methodologically sound proposal. The available data is the individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).


[7] Fick A. The output of the heart. J Physikalisch-Medicinische Gesellschaft. 1870;2;XVI.


[22] Swain DP, Leutholtz BC. Heart rate reserve is equivalent to% VO2 reserve, not to% VO2max. Medicine and science in sports and exercise. 1997;29(3):410-4.