Author’s response to reviews

Title: A moderate 500-m treadmill walk for estimating peak oxygen uptake in men with NYHA class I-II heart failure and mid-range ventricular dysfunction

Authors:
Gianni Mazzoni (gianni.mazzoni@unife.it)
Biagio Sassone (b.sassone@ausl.fe.it)
Giovanni Pasanisi (g.pasanisi@ausl.fe.it)
Jonathan Myers (DRJ993@aol.com)
Simona Mandini (mndsmn@unife.it)
Stefano Volpato (stefano.volpato@unife.it)
Francesco Conconi (cnf@unife.it)
Giorgio Chiaranda (Giorgio.Chiaranda@regione.emilia-romagna.it)
Giovanni Grazzi (giovanni.grazzi@unife.it)

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Author’s response to reviews:

Reviewer reports:

Dear Reviewers, while re-calculating the Bland Altman analysis for making figure 2 as suggested by Reviewer #3, we found a light error. The data of measured and predicted VO2peak have been corrected.

REVIEWER #1

Quin Denfeld (Reviewer 1): Summary: The purpose of this study was to examine the validity of a 500m moderate treadmill-walking test for estimating peak oxygen consumption in community-dwelling older men with chronic heart failure and reduced LVEF. The rationale is that based on an easily performed submaximal walking test, this measure could be used to estimate peak VO2.
The major finding is that estimated peak VO2 based on the 500m walk test is correlated with measured peak VO2 based on traditional CPEX testing.

Comments and Suggestions for the Author:

Overall, this paper would benefit from a significant re-write to logically present the comparison of these methods to assess peak VO2. While the rationale behind this paper is sound, the paper lacks major details, logical flow, and many undefined terms. There is a strong argument for using the 500m walk test in HF patients in a clinically meaningful way; however, the presentation of the methods and data, as well as the generalizability of the findings, could be significantly improved.

Major recommendations:

Comment #1

* The introduction would benefit from consistency in terms used and definitions for terms, as well as better transitions between key points. Moreover, given the varied measures (6MWT, 1K-TWT, CPEX) already available, it would be helpful to see how the 500m walk test distinctly fits in with these other measures (perhaps in a table).

Reply

We appreciate your suggestions. The introduction has been shortened. The difference between the walking tests commonly used (which are close to maximal and therefore difficult to be used with patients with reduced CRF) and the 500-m test has been considered, although without a more detailed comparison.

Comment #2

* There are a number of inconsistencies regarding the subtype of HF, namely in relation to ejection fraction/ventricular dysfunction. The title uses "mid-range ventricular dysfunction" but the abstract uses "HFrEF." Moreover, there is a note in the discussion regarding the "grey area"
of reduced EF (with an EF range of 40-49%). Given the lack of consensus on the gradations of EF, it would be best to stick with one designation throughout the paper.

Reply

Following your suggestions, the title has been modified as follows: “A moderate 500-m treadmill walk for estimating peak oxygen uptake in men with NYHA class I-II heart failure and reduced left ventricular ejection fraction”. Heart failure with reduced left ventricular ejection fraction (HFrEF) is now used throughout the whole paper.

Comment #3

* Because the purpose of this paper is to address validity, there should be more information regarding the type of validity assessed (criterion, convergent, divergent, etc.).

Reply

The type of validity we assessed is convergent. In fact, both the CPX and the 500-m walking test address peak oxygen uptake.

Comment #4

* The validity of the equation for a 500m walk test using the 1000m walk test should be addressed (i.e. are they considered equivalent?). Moreover, there is likely a major miscalculation of estimated peak VO2 for patients on beta-blockers; if this is not the case, please provide evidence that it doesn't affect the calculation.

Reply

We have applied the equations originally developed and validated for the 1000-m walking test to the 500-m test. As indicate in ref #13, two different equations were developed for patients taking or not taking β-blockers (see Methods).
Comment #5

* For the sample size, the abstract reports 43 subjects, the table reports 39 subjects, but the text notes that 3 subjects did not satisfy the criteria for adequate effort. Was this adequate effort for the CPEX or the 500m treadmill walking test? Was there anything specific about these patients who didn't achieve adequate effort? Also, what happened to the other subject who wasn't included in the analysis?

Reply

Thank you for this comment. Adequate effort is referred to CPX. Three subjects did not achieve adequate effort for premature fatigue, and one because of mask intolerance (i.e. claustrophobic). The Results section has been modified according to your suggestions.

Comment #6

* For the analysis, please clarify why a non-parametric regression analysis was used. Particularly coupled with a paired t test and Pearson correlation coefficient (which both have parametric assumptions). Also, please clarify the progression of the statistics from paired t tests to a Passing and Bablock regression analysis to a Pearson correlation coefficient.

Reply

Data have been analysed following the same procedure described in ref #13. Data were first analysed by D'Agostino-Pearson test for normal distribution. Therefore, the predicting equations validated in ref #13 were applied also in this study using in sequence paired t-test, Pearson product moment correlations, and SEE and Passing and Bablok regression. The non-parametric regression analysis we used enables an objective evaluation of the deviations from linearity.

Comment #7

* Where is the data on the paired t tests?
Reply

Following your suggestions, Results section has been revised.

Comment #8

* Even though some good points are made, the discussion would benefit from a major re-write as there is redundancy as well as confusing points.

Reply

You are right. According to your comment (and also considering similar comments by other reviewers), the Discussion has been re-written and shortened.

Minor recommendations:

Comment #8

* Revise the last conclusion statement in the abstract, especially since lack of women was a limitation of the study.

Reply

Thanks. This is a mistake. The Abstract has been modified.

Comment #9

* Need more data in Table 1, especially pertaining to their HF medical history: NYHA class, time with HF, serum sodium, etc.

Reply

NYHA functional class and serum sodium concentration have been added to Table 1. Patients were referred by their family physician to the exercise-based secondary prevention program at
our Center. Before referral to our Center, patients have been followed by more than one GP and by more than one cardiologist. It is therefore very difficult to reconstruct time with HF.

Comment #10

* Would like to see the data from the 500m walk test presented in a table.

Reply

Following your suggestion, an additional table (Table 3) presenting the data from the 500-m walking test has been added in the revised manuscript.

Comment #11

* The figure needs work: title, caption (including the type of analysis).

Reply

The figure represents a regression diagram with the line of identity for VO2peak measured and estimated from 500-m moderate treadmill-walking test. A figure legend has been added in the revised manuscript.

Comment #12

* Review the abbreviations used throughout the paper (i.e. make sure each one is spelled out first), and ideally minimize unnecessary ones.

Reply

Thank you for your comment. One abbreviation (VT) has been removed from the text and replaced with “ventilatory threshold”. HFrEF (heart failure with reduced ejection fraction), CPX (cardiopulmonary exercise test), and RPE (rate of perceived exertion) are now spelled out first in the background and methods sections of the revised manuscript.
Comment #13

* References #12 and #17 are the same.

Reply

Thank you for this comment. Ref #17 has been removed, and all the references renumbered accordingly.

REVIEWER #2

Oyvind Ellingsen, MD PhD (Reviewer 2): The specific aim of the study was to examine the validity of a 500-m moderate treadmill-walking test for estimating VO2peak in men with HFrEF, exercising at self-paced moderate intensity (Borg 11-13). The potential usefulness of the procedure would be to replace a standard cardiopulmonary exercise test with a simpler and more available procedure for diagnostic, prognostic and monitoring purposes.

GENERAL

Comment #1

1. The study demonstrates excellent validity of the procedure in a small-size (n=39) sample of a well-defined subset of male HFrEF patients aged 35-80, NYHA class I-II. Since there already exist several similar procedures and the novelty may appear incremental, it could perhaps be stated even more specifically what was the expected application of the procedure (Abstract, Introduction), what is the novelty of their findings (Abstract, Discussion/Conclusion), what are the limitations (Discussion/Limitations), what is the potential clinical application (Introduction and Discussion), and what should be the future direction of developing this type of methodology (Discussion).

Reply
Abstract, Introduction, Discussion, Limitations, and Conclusions have been modified according to your suggestions.

SPECIFIC

Comment #2

2. Exactly what was the LVEF criterion for inclusion? Upper (and lower?) limit(s) of LVEF should be given (Abstract, Methods).

Reply

Criterion for inclusion was LVEF \( \leq 45\% \). This is now stated in the methods section in the revised manuscript.

Comment #3

3. The phrase "old men" (Abstract, most sections) does not resonate well with the given range of ages for inclusion (35-80).

Reply

Following your suggestion, “old and older” have been removed and replaced with “adults and elderly” throughout the paper.

Comment #4

4. It would be helpful to include the definition of CPX and RPE when first occurring in the text (Methods).

Reply

Thank you for this comment made also by Reviewer #1. CPX and RPE are now spelled out.
Comment #5

5. In Table 1-2, there seems to be space enough to spell out some of the abbreviations (may be all?), thus facilitating the flow of reading.

Reply

Following your suggestions, some abbreviations have been spelled out in the revised Table 1 and Table 2.

Comment #6

6. The relatively small number of patients (N=39) should be mentioned in limitations.

Reply

This limit has been added to the study limitations in the revised manuscript.

Comment #7

7. What is the precision of the procedure studied? Is there any coefficient of test-retest variation? How well suited is the method to assess small to moderate changes within each patient? This should perhaps be discussed in the perspective of using the estimates for monitoring progress and decline in individual patients (Limitations, Future directions).

Reply

The major findings are the high correlation and concordance between measured and predicted VO2peak values, with the small SEE, and the modest residuals. As stated in the Discussion, these results are in agreement with those obtained by others that have attempted to predict VO2peak using sub-maximal walking protocols, in younger and healthy subjects (ref# 5,7,22). Reproducibility was not assessed in this study. However, we previously demonstrated good cross-validation and reproducibility among cardiac outpatients performing the test over the 1000-
m distance (ref #13). Following your comment, this is now stated in the limits of the study section.

Comment #8

8. The final sentence of the "Study limitations" should be expanded with some more suggestions of future direction of research, e.g., with more details of how "external validation of our findings" could be performed.

Reply

Following your suggestion, the final sentence of the “study limitations” has been expanded.

Comment #9

9. It would be more informative if the "Figure title" could be expanded with some more explanation of what the different lines represent and a brief interpretation of what the data shows. Is there any connection with the analyses of Linear correlation, SEE, Bland-Altman, Passing and Bablok, Normal probability plot of the residuals? Should the regression equations be included?

Reply

Thank you for your comment. Following your suggestions, Figure legend has been clarified, and the regression equation included. Data analysis is presented in the text (Results section).

REviewer #3

Raquel Britto (Reviewer 3): Manuscript Number: BCAR-D-17-00601R1

Title: A moderate 500-m treadmill walk for estimating peak oxygen uptake in men with NYHA class I-II heart failure and mid-range ventricular dysfunction
Review

The manuscript addresses the validation of a 500-m moderate treadmill-walking test for estimating peak oxygen consumption (VO2peak) in community-dwelling old men with chronic heart failure (HF) and reduced left ventricular ejection fraction (LVEF). Basically, considering the limitation of these patients to do the 1-km treadmill walk test (#ref 12, published previously by the same research group), they proposed to use, for this population, half of the distance and evaluate responses and agreement with the VO2peak direct measured.

It is really an important manuscript, presenting a simple and practical tool that could be used in cardiac rehabilitation services to monitoring evaluation of patients with HF and LVEF as well as to prescribe exercise intensity, particularly in low-resource settings. Recently, a statement on cardiac rehabilitation emphasised the need of using simpler exercise tests to improve the admission on cardiac rehabilitation (Grace et al., 2016).


Comments

Comment #1

Introduction

Please, include how this kind of tool is important for low-resource settings. Suggestion of reference - Grace SL et al., 2016 (see above).

Reply

We appreciate this comment. This has been considered in the revised Introduction and in the Discussion. The suggested reference has been quoted (#12).
Methods

Any kind of exclusion criteria? For example: patients with peripheral arterial disease.

Reply

All patients reporting no difficulty climbing one flight of stairs without resting or performing basic activities of daily living at the first examination were included (see Methods section). There were no patients with significant peripheral artery disease (see mean walking speed over a 500-m distance 4.37 km/h). Patients with PAD are referred to another specialized Center at our University of Ferrara.

Comment #3

1st page of Methods: Lines 53 to 58: please, provide reference for "….. and by the attainment of at least two of the three following criteria: heart rate value ≥ 85% of the age-predicted maximum, VO2 plateau approaching maximal exertion, and a respiratory exchange ratio ≥ 1.05."

Reply

The criteria defined as indicators of adequate effort are presented in new references now quoted in the revised manuscript as #19 and #20.

Comment #4

2nd page of Methods: Lines 23 to 25: Who adjusted the walking speed? (patient or researcher?). Was the researcher blinded about the VO2peak directly measured?

Reply
This is now clarified in the revised Methods as follows: “In order to maintain a moderate intensity, walking speed was adjusted by the operator following the patient’s perceived intensity”. Yes, the researcher was blinded about the results of the direct VO2peak measurement.

Comment #5

Lines 32-34 : equation - mean walking speed in m/min? Please inform.

Reply

Walking speed was in km/h. This has been inserted.

Comment #6

3rd page of Methods: Lines 24-26: Please include figure of Bland Altmann analysis. It could be also as Fig. 1B.

Reply

Following your suggestion, the Bland-Altman plot has been included as Figure 2.

Comment #7

As HR on ventilatory threshold (VT) on CPX has been used to prescribe exercise intensity, I would suggest including the correlation of HR on 500m test and HR on VT. I think it is important for practical implementation on cardiac rehabilitation as very well discussed on 2nd page lines 30-33.

Reply

We followed your suggestion, and this correlation has been included in the Discussion.
Discussion

Comment #8

1st page of discussion - Lines 56-58 - after "using sub-maximal walking protocols" INCLUDE ", the majority in healthy subjects" - To emphasizes that one of this is on HF but not with reduced FEV.

Reply

Thank you for this comment. Your suggestions have been included in the revised manuscript.

Comment #9

Discussion 2nd page line 18/19 - there is an extra "s" after "tools"

Reply

The mistake has been deleted.

Comment #10

Include on discussion the application for low-resource settings.

Reply

See reply to your comment #1.

Comment #11

Please check ref #12 and #17 is the same. Also correct the citation in the main text.

Reply

Reference #17 has been removed.
Comment #12

Please check the use of abbreviation (LVEF) and the term left ventricular dysfunction as well as the abbreviation HFrEF and respective term in regard to the first or subsequent appearance. For example - introduction line 50, first appearance (need to use complete term even though it was cited on abstract). Discussion 2nd page line 2, etc.

Reply

The use of abbreviations LVEF and HFrEF has been checked and corrected throughout the paper.

Comment #13

I would suggest instead of using HFrEF substitute to "HF with reduced LVEF".

Reply

As indicated in the response to your previous comment, the use of abbreviations has been checked and corrected. HFrEF is spelled out the first time and subsequently used as indicator of left ventricular dysfunction.

Congratulations on such a practical and important manuscript with easy clinical application.

Raquel Rodrigues Britto

PhD, PT, Federal University of Minas Gerais, Brazil