Author's response to reviews

Title: Efficacy of a whole-body vibration intervention to effect exercise tolerance and functional performance of the lower limbs of people with chronic obstructive pulmonary disease

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Author's response to reviews: see over
To the Editorial Office of BMC Pulmonary Medicine,

Please find our revisions for the paper:

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Thank you to the reviewers for their thoughtful and constructive comments to assist with the improvement of our manuscript and research proposal.

Kind regards,

Trentham Furness

-Responses to reviewer 1

Major Compulsory Revisions
The aim of this study is to evaluate the efficacy of a whole-body vibration intervention in stable COPD patients GOLD stage II. First of all, whole body vibration intervention (WBV) could be an interesting additional tool for rehabilitation programs in COPD patients. It could already be shown that WBV leads to a better muscle function and an increase in oxygen uptake. But to test this hypothesis in COPD patients, a randomized study comparing WBV alone, WBV in combination with exercise training and placebo will be necessary. Moreover maximum oxygen uptake and maximum muscle strength should be measured as outcome parameters as well as evaluation of quality of life to confirm the efficacy of the intervention. The study period of 6 weeks is rather short for significant improvements, so a 12 weeks training period would be better.

We agree with the reviewer that WBV could be an interesting additional tool for rehabilitation programs in COPD patients. The recent findings of Goleckl et al. (2012) reported exactly that after a three-week intervention (without a placebo condition). We agree that a RCT is the most robust research design to test the hypothesis of WBV usefulness and future research should examine that. Our research is a phase II efficacy trial and we propose that a RCT should be conducted after a phase II trial. With our non-randomized cross over design, the participants act as their own control, thus strengthening the study. Furthermore, because efficacy of WBV is yet to be established in the community setting with this population, we prefer a phase II trial. We prefer not to randomize our participants because we want to maximize participant compliance in the WBV group, given that this is a 14-week research intervention. The aim of the research is to establish efficacy of WBV in a community setting, in the actual home of each participant. Participants whom are not involved in PR are our participants of
interest. If WBV can improve or maintain functional performance of the lower limbs of people with COPD in the comfort of their own home, the benefits are salient.

We are unable to measure maximum oxygen uptake or maximal muscle strength with any validity or reliability in the home of each participant. Such equipment is laboratory based and we want to present results that are relevant and feasible to the home setting. For that reason we have used common valid and reliable field tests, for which we established population-specific reliability (ICC > 0.800). We are fundamentally focused on maintaining or improving functional performance of the lower limbs and the ability to complete simulated ADLs.

We agree that an extended research intervention period would be desirable. Ideally if efficacy can be established, participants would incorporate WBV to their habitual physical activity schedule. However, because efficacy of WBV in a community setting is unknown, an extended intervention was not considered. However, significant improvements in functional performance can be seen in as little as three weeks after WBV in healthy community dwelling older adults (e.g., Furness & Maschette, 2009), so perhaps the necessity for an extended period for proof of concept could be challenged.

We agree that quality of life data would be useful, but as the reviewer suggested, six weeks is a short period of time. We have used the SF-36 survey in the past but prefer, at this time, only to focus on efficacy of WBV to improve or maintain functional performance of the lower limbs. We understand that management of health status, as well as exercise tolerance are components of the GOLD mandate, but we prefer at this stage to focus on exercise tolerance (i.e., the ability of the participants to perform simulated ADLs). We would certainly include quality of life data to a RCT, with a longer intervention period in the future. We removed reference to ‘health status’ from the manuscript.

Minor Essential Revisions

Abstract: Definition of gentle exercise?

Background: The effect of strength training alone is well known in patients with COPD. Pulmonary rehabilitation consisting of moderate-intensity endurance training and strength training does not increase the exacerbation rate. Pulmonary rehabilitation reduces the number of hospital days in COPD patients.

We have had much discussion about the use of this word ‘gentle’ because the intensity of WBV in this research protocol is much less than other WBV protocols designed to improve function of the lower limbs. We have decided to remove the word ‘gentle’ from the entire manuscript.

We agree and reported efficacy of aerobic conditioning and resistance training during PR in the manuscript. These two modes of physical activity are well established for people living with COPD. We suggest that compliance to resistance training and aerobic conditioning can be compromised due to exacerbations and find it difficult to accept the assertion that AC and RT do not
increase the exacerbation rate (e.g., Brill et al., 1999; Suzuki et al., 2004; Means, Rodell & O’Sullivan, 2005; Troosters et al., 2005). Regardless, the word gentle was used because gentle WBV is much less physically demanding on the body than RT and AC, thus potentially reducing risk of increased dyspnea, which may lead to physical inactivity (i.e., the dyspnea spiral). We do not suggest that WBV should be considered as a mode of physical activity complicit with PR, we seek to describe effects of WBV independent of PR, and foresee that it could be incorporated to PR in the future as a largely safe, home based mode of physical activity for people living with COPD, if efficacy can be established. It could also be used as a pre-exercise therapy for patients in need of a very low intensity introduction to exercise.

We agree that PR reduces the number of hospital days in COPD patients, yet that is beyond the scope of this research. Our participants will be independent living, and not involved in structured clinical PR.

The manuscript was revised:

Considering the statistical and scientific evidence for efficacy of physical activity to reduce burden of disease, the need for safe and valid exercise interventions for people with COPD is salient. The common modes of physical activity; aerobic conditioning and resistance training can exacerbate the disease and affect program compliance [22,23] and may lead to reduced physical activity because of fear of breathlessness. The clinical and social merit of physical activity that can minimise dyspnoea may provide additional exercise tolerance benefit for people with COPD. Whole body vibration may be such a mode of physical activity, and can be easily completed in the home with little skill demand.

Response to reviewer 2

Major compulsory revision
1) Discussion section, last paragraph: you state that you want to prove safety issues of WBVT in individuals with sub-optimal health conditions. Why are you including COPD-patients with GOLD stage II only? These patients might not be the appropriate cohort to prove safety or exacerbation incidence. Including patients with COPD GOLD stages III to IV might be more appropriate for this purpose.
We agree with the comment of the reviewer that perhaps the participants will not have COPD to a severe level to warrant safeness investigation. We want to recruit a specific sample (i.e., Stage II COPD) because the condition is generally well self managed at home, thus allowing this home based research and reducing the risk of participant withdrawal due perhaps to exacerbations. Furthermore, this is a sample of convenience. In the future we would like to recruit participants of varying COPD severity once we have advanced proof of concept that WBV can comprise part of feasible home based exercise interventions. Therefore, we decided to limit our focus. We will be quantifying dyspnea and SpO2 as our field based safety measures. We do not expect WBV to effect either variables (i.e., elicit hypoxemia). In the home of the individual, we expect that if WBV increases dyspnea to levels similar to RT and AC, then habitual sustainability can be compromised.

The manuscript was revised:

Participants and Recruitment

Community dwelling patients listed on the Department of Respiratory and Sleep Medicine, Monash Medical Centre, Southern Health data-base will be contacted to procure interest in participation and later provide informed voluntary consent. Participants must be over 40 years of age, be fully independent in residence, and have well-managed, stable Stage II COPD according to the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria. A convenient sample of people with stable Stage II COPD will be targeted due to a reduced chance of participant dropout from exacerbations independent of the 14-week intervention. Participants must be free of contraindicators to physical activity as well as contraindicators to WBV (free of self reported; vascular disease, reactive arthritis, vertigo, and risk of thromboembolism [33-35]. The study has the ethical approval of the Monash Medical Centre, Southern Health Human Research Ethics Committee A and the Australian Catholic University Human Research Ethics Committee.
Discussion (last paragraph)

A WBV intervention should be safe and valid before implemented to a sample cohort, regardless of health status. Encouragingly, WBV did not negatively affect people with stable COPD [32], people with cystic fibrosis [29] or heart transplant recipients [39]. Despite current knowledge of WBV, as a standalone community based mode of physical activity, efficacy has not been established for improvement of exercise tolerance and functional performance of the lower limbs of people with COPD. Furthermore, it is unknown if a long-term WBV intervention will elicit exacerbations of COPD, or be well tolerated and complied by people with COPD.

2) Methods section, first paragraph: although it was mentioned that the control phase (second 6 Weeks of Placebo WBV) will mainly be used to receive information on trial compliance, authors should keep in mind that a) a 2 week-period might be to less for “washing out” the exercise effects of WBVT and b) if the second phase is worth the effort conducting it?

We agree with the reviewer that a two-week washout period is not very long. We found it most difficult to find any reference for washout duration in the WBV literature. We used the washout design of Erskine et al. (2007) although a washout period of one-week has been used (Cardinale et al., 2006). In our unpublished research we found detraining after a similar period (approx. 16 days) after WBV for healthy older adults (Furness MExSci by research, thesis available at ADT).

We feel it would be extremely difficult to publish a Phase III trial without a control/placebo intervention and WBV. However, this is a Phase II trial with a strong focus on prioritizing safety of the participants. To this end, the effect of WBV should be known (i.e., compared with placebo) before WBV may become a larger RCT using this mode of physical activity for people with COPD. The research design had ethical approval from both Southern Health and ACU and is registered with ANZCTR.

The manuscript was modified:

Interventions
Across the 14-week duration of the study, participants will be first allocated to a six-week WBV intervention, a two-week washout period [36], and a six-week PLACEBO intervention.

Participants and Recruitment

The study has the ethical approval of the Monash Medical Centre, Southern Health Human Research Ethics Committee A and the Australian Catholic University Human Research Ethics Committee. The trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000508875).

3) Participants and recruitment section: please specify your contraindications for WBVT

The manuscript was modified:

Participants must be free of contraindicators to physical activity as well as contraindicators to WBV (free of self reported; vascular disease, reactive arthritis, vertigo, and risk of thromboembolism [33-35].

4) Sample size section: sample size calculation was performed by using the 5 chair stands test but your primary dependent variable as an outcome parameter will be perceived dyspnoea on the Borg CR-10 scale. Is this an appropriate approach?

The manuscript was modified:

Sample size

It is expected that WBV will not change dyspnoea from baseline. To allow sample size calculation therefore, data of functional performance variables were considered
primary and used to estimate sample size. The selected dependent variables were sourced from a previous study of WBV and healthy community dwelling older adults [23]. Sample size needed for a one tailed paired $t$-test with $\alpha = 0.05$ and $n = 14$ with power $= 0.90$ was $n = 16$ for the 5 chair stands test $n < 10$ for the timed up and go test. To allow for an anticipated participant drop out of at least 20%, a total of 20 participants will be included in the study.

Minor essential revision

1) There is a contradiction in the abstract (background section): whole-body vibration training (WBVT) is applicable to improve muscular function, but only if provided as high-intensity WBVT – not as a gentle (=low-intensity) WBVT as it is written in this section! Moreover the intensity of 25 Hz at which you are planning to perform your exercise training on a side-alternating vibration platform is also regarded as high-intensity vibration. This is confusing for the reader!

The word gentle was removed from the manuscript. As a mode of physical activity, WBV at the intensity we are proposing is considered low. Stochastic resonance WBV, for example, uses low frequency (e.g., 2-5Hz) but may not be considered as a mode of physical activity. WBV for bone health has been high (ultra low amplitude and very high Hz) and high but derived from a different source (6 mm amplitude and 50 Hz). Inconsistent methods and nomenclature persist among the WBV literature (Lorenzen et al., 2009).

The manuscript was modified:

**Background:** Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterised by dyspnoea, excessive sputum production, chronic cough, bronchitis and emphysema. Functionally, exercise tolerance is poor for people with COPD and is linked to difficulty in performing daily tasks. More specifically, exercise difficulties are due partly to dyspnoea and lower limb skeletal muscle dysfunction. The benefit of exercise that does not exacerbate the disease while improving exercise tolerance is salient. Whole-body vibration is a mode of physical activity known to improve muscular function of the lower limbs, yet efficacy has not
been investigated for a whole-body vibration intervention conducted in a community setting for people with COPD.

2) Participants and recruitment section: Authors want to include only COPD-patients in GOLD stage II. These patients usually suffer only mild impairments in exercise capacity. Probably the improvements yielded by WBVT might be very low in this particular population. Have you thought about including also patients with severe COPD?

We agree with the comment of the reviewer, however we chose to opt for a “least harm” homogeneous sample of people with COPD to complete this first study. Therefore we will limit our inclusion criteria to stage II COPD. We are not aiming to quantify exercise capacity, only functional performance using field based testing. A larger and funded RCT could expand a convenient sample to other stages of COPD severity, yet it is unknown if WBV will be of any benefit at all to people with COPD in a community setting. We agree that larger gains could be found in less active individuals, but we are focused on community dwelling individuals with mild COPD at this time. We have published an almost identical WBV intervention of healthy community dwelling older adults and reported significant improvement in functional performance of the lower limbs (Furenss & Maschette, 2009).

3) Please describe your “community setting“ in more detail.

The manuscript was modified so that ‘community setting’ was replaced with ‘home-based’

4) Authors plan to use a peak-to-peak displacement of 2 mm. To the experience of the reviewer this is a quite low amplitude. Greater gains of WBVT might be observed when using an amplitude of 4-6 mm. This also represents a more realistic “real-life” exercise program.

This is a very interesting point made by the reviewer. This research is unique because WBV has never been used for people with COPD in a community setting and because we are using lower intensity WBV than other WBV interventions. We do not want our participants to be exposed to unnecessary high WBV when we have shown the intensity we are using acceptable for improving functional performance of the lower limbs among healthy community dwelling older adults (Furness & Maschette, 2009). A lower BMD in COPD patients and previous history of some medications precluded a prescription of higher WBV loading. There are no guidelines for realistic or best practice WBV intensity among the literature. It is known that higher intensity WBV increase risk of fracture of fragile vertebrae (Kiiski et al., 2008) and that for adults the intensity should be lower at commencement of intervention (Crewther, Cronin & Keogh, 2004). The prescribed WBV intensity in this study has some rigour because: (1) the efficacy of the intensity has been established for healthy older adults (Furness
& Maschette, 2009), (2) we are not exposing participants to unnecessary high load, and (3) the risk of adverse bone events, while not quantified, is reduced.

The manuscript was modified:

**WBV intervention (paragraph 2)**

A side alternating vibration platform (Amazing Super Health, Melbourne, AUS) will be used. For each vibration bout, platform frequency will be 25 Hz, peak-to-peak displacement 2.0 mm, peak acceleration ~24.67 m.s⁻², and gravitational force ~2.52 g. The WBV intensity was chosen to reduce the risk of fracture to fragile bones [36] and potential for other injury [37]

5) **Outcome measures section: please provide more information on how you will perform the mentioned exercise tests especially the 5-chair stands test and timed up and go test.**

The manuscript was modified:

**Outcome measures**

Reliability of outcome measures will be established over a test-retest-retest protocol [Weir]. Exercise tolerance variables will be immediate responses to WBV; (1) perceived dyspnoea quantified with the Borg CR-10 visual analogue scale, (2) heart rate, and (3) saturation of haemoglobin. Functional performance variables will be simulated ADLs and kinematic markers of gait; (1) the 5-chair stands test, (2) the timed up and go test, (3) stride length, (4) stride time, and (5) stride velocity. Data will be collected at baseline and subsequent fortnight for 14 weeks. Data of all dependent variables will be collected to quantify at least one of three different data classifications: (1) immediate, (2) acute, and (3) long-term. Immediate perceived dyspnoea, heart rate, and saturation of haemoglobin will be collected during the final WBV or PLACEBO bout (after 30 seconds of the 60 second bout). Acute kinematic markers of gait will be collected within two minutes of a completed WBV or PLACEBO bout [38,39]. Long-term simulated ADLs and kinematic markers of gait will be collected at least 48 hours after a WBV or PLACEBO bout [40,41].
To complete the 5-chair stands test the participant is asked to sit in a standard height (46 cm, including back rest) chair with arms folded across the chest. The participant is then asked to stand and sit five times [42-44].

To complete the timed up and go test, the participant is asked to sit in a standard height (46 cm) arm (63 cm) chair. The participant is then asked to stand, walk three metres to a marker on the floor, turn, return, and sit on the chair [45-47].

Kinematic markers of gait will be quantified with the GAITRite® electronic walkway. Participants will be instructed to walk at a self-selected comfortable speed along a straight, flat, and even walkway area containing the mat. Body length is measured from the base of the foot (unshod) to the crown of the head while standing in the anatomical position. During data collection, participants will walk (shod) over the mat five times in a discontinuous process with an approach and departure distance equal to two body lengths. The procedure was reliable for step length, step time, and velocity among older woman (ICC range 0.860 to 0.940; mean age = 68 years) [48].

6) Outcome measures section: authors should think about including a 6-minute-walking test or an incremental shuttle walk test, as these two field exercise tests are of common practice in evaluation pulmonary rehabilitation programs (see ATS/ERS guidelines)

We agree with the reviewer that the 6MWT and an incremental shuttle walk test could be incorporated to the research design. We went with the TUG test and 5 chair stands test to best demonstrate improvement in field tests for functional performance (i.e., muscular strength and power). We have also incorporated kinematics of gait to support the field tests. Even in our large hospital we have trouble with the 6MWT due to logistics. Conducting the test in the home of each participant would be unrealistic because: (1) appropriate logistics will not exist, and (2) reliability could not realistically be established across each home of the participants.

We would like to stress that WBV is not a component of pulmonary rehabilitation, so we chose fields tests that best represent ADLs and can be easily completed in a timely
manner in the home of the participant. We first want to describe effects of WBV on people with COPD in a community setting rather than effects of WBV with pulmonary rehabilitation to people with COPD. Furthermore, we are interested in muscular strength and power rather than aerobic performance because evidence of WBV to improve AC is very limited and equivocal.