Author's response to reviews

Title: Benefits of Whole Body Vibration Training in Patients Hospitalised for COPD Exacerbations - a Randomized Clinical Trial

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Author's response to reviews: see over
Thank you very much for the constructive review of our manuscript “Benefits of Whole Body Vibration Training in Patients Hospitalised for COPD Exacerbations - a Randomized Clinical Trial”. Below we address a point to point reply to the reviewer comments.

**Reviewer 1**

1- **No power calculation is provided- why were 40 chosen?**

The reviewers are right. We did not perform a formal power calculation. Right from the beginning we regarded the study as a proof of concept study. At the point of time when we planned the study, no data about whole body vibration in exacerbated COPD patients had been published. We clearly addressed this lack in the manuscript.

2- **It is not stated whether this was an ITT analysis, although it would appear from the Consort diagram that this is a completers rather than an ITT analysis.**

*It is apparent in the discussion that there was incomplete data on 6MWT (we are told that ‘some patients were not able to perform the 6MWT due to severity of disease (we are not told how many) and that there was missing SGRQ data on at least one. We are not told how missing data was handled.*

In the completers analysis we only included patients where we had data on the day of admission and the day of discharge. This was due to the statistical analysis (Wilcoxon matched-pairs signed-ranks test) which is suggested for this situation. The information about missing data could be found in the legend for figure 2: In the WBC group complete data about 6-minute walking test and chair rising test was available in 19 patients (14 respectively). In the control group only 14 data sets were available for both outcome measures. As the imbalance of missing data may have biased the results in favour of the WBV group we repeated the 6-MWT analysis by setting the missing admission data to the lowest obtained value. Doing that the between group difference still remained significant (supplement figure 4).

3- **3 patients in the control group were not included as they had an ‘early discharge’. Since the analysis is from admission to discharge, why were they not included? Leaving out the patients in the control group who did best is bound to bias the results in favour of the intervention group.**

That is another important point that the reviewer addressed. We performed a Fisher’s exact test to determine whether the dropout rate (3/23 vs. 6/26) was significant. We did not see a statistical significant difference (p=0.49). This point was added to the results section.

4- **Lack of blinding: it must have been clear to the participants whether they were in the ‘active’ or ‘control’ groups, which may bias results, particularly in patient reported outcome measures such as QOL.**
That is an important point – the patients were not blinded for the procedure. We did not do a sham procedure. We inserted a sentence in the discussion section.

5- Method of randomization is not specified.

Thank you for pointing to that lack of reporting. The randomization was performed by a third party (a statistician from the sleep laboratory of the University of Marburg). A computer generated list was used to produce envelopes that were stored in a locked room. The investigator who wanted to include a patient called the statistician, reported the patient’s identification number and received the allocation to one of both treatment groups. We included that information in the Methods section.

6- Baseline characteristics- although it is stated that there was no difference between groups, 5 of the control group vs. 1 of the intervention group were in GOLD 1-2 stages, so the intervention group may have been more severe. This is also suggested by a lower % predicted FEV. In addition 14% of controls vs. 24% of active arms were on oral steroids, a potential confounder. Also, it is apparent for the results section that that there were marked differences in the 6MWT distances on admission between groups, although not presented in the table.

This is an important point the reviewers addressed. Thank you very much. We have performed statistics on that point and did not detect significant differences. As the reviewer pointed out and because of the small number of patients, the imbalance still might have influence on the result. On the other hand, to our knowledge, current literature has not defined predictors of rehabilitation success[1-4]. In detail, neither FEV₁ nor steroid use has been convincingly described as predictors of rehabilitation success.

7- Fig 2 shows that there was a further imbalance in that 19 of the intervention group were able to perform the 6MWT but only 14 of the control group were fit enough to do so.

This was due to the statistical analysis (Wilcoxon matched-pairs signed-ranks test) which is suggested for this situation. As this imbalance of missing data may have biased the results in favour of the WBV group we repeated the statistical analysis of the 6-MWT by setting the missing admission data to the lowest obtained value and including these pairs in the analysis. This procedure does maximize the putative effect in the control group. Doing that the between group difference still remained significant (supplement figure 4).

8- There is something very odd in the 6MWT results, in that the control group had a REDUCED distance at discharge compared to admission- how can this be? They received medical and physiotherapy for their exacerbation and were judged to have improved enough to go home. For me this is inexplicable and causes me concern about the whole study. A similar result is seen in the other
exercise capacity test, the CRT, where the control group are reported to be considerably more disabled on discharge than on admission.

9- This is also apparent in the QOL data, where the control group showed NO improvement in CAT or SGRQ from admission despite full standard treatment for a COPD exacerbation- how can this be?

Thank you very much for discussing these important points. We believe that both the intervention patients and the controls spend the majority of their time in bed while being hospitalized. This inevitably causes a loss of muscle strength[5,6]; furthermore, in COPD patients this phenomenon is not unusual and goes in line with published data[7]. We believe that the usual physiotherapy as it is done in our hospital which may reflect the situation in many hospitals does not cover that lack. Regarding QoL and discharge it has to be acknowledged (supplement figure 2) that also patients in the control group improved the symptom subdomain of the SGRQ but did not show improvement in the other domains. As the decision to discharge a patient is mainly depended on symptoms it seems understandable why patients have been discharged despite having a worse QoL score. We included a full paragraph in the manuscript.

1. There is no power calculation

The reviewers are right we did not perform a power calculation. We performed a hypothesis generating study. To our knowledge, before having started the study nobody ever evaluated whole body vibration in exacerbated COPD patients before. We clearly addressed this lack in the manuscript.

2. It does not appear that concealed allocation was used.

Thank you for that consideration. The randomization was performed by a third party (a statistician from the sleep laboratory of the University of Marburg). A computer generated list was used to produce envelopes that were stored in a locked room. The investigator who wanted to include a patient called the statistician, reported the patient’s identification number and received the allocation to one of both treatment groups. Therefore, concealed allocation was used. The screening investigator was unaware of the group the patient would be randomized to.

3. It is unusual that the control group had no improvement in functional walking capacity between admission and discharge. Individual data suggest that some patients in this group actually had a marked deterioration in 6MWD. Please provide more information. Given that criteria for safe discharge usually involves improvement in ambulation to the level required for self care in the community, it seems unusual that the control group patients did not achieve this.

Thank you very much for discussing that important point. We believe that both the intervention patients and the controls spent too much time in bed during the
hospitalization which usually causes a loss of muscle strength. That goes in line with
published data [7,8]. We believe that the usual physiotherapy as it is done in our
hospital which reflects most likely the situation in many hospitals does not cover that
lack. This is also stated in a very recent review article about physiotherapy during an
acute exacerbation [9]. Regarding discharge we believe that the decision to
discharge was more dependent on symptoms. Supplement figure 2 demonstrated
that also patients in the control group improved the symptom subdomain of the
SGRQ but did not show improvement in the other domains. We included a full new
paragraph in the discussion section of the manuscript.

4. **A goal of the study was to assess whether WBV was safe but there were no
outcome measures for this in the methods, and no outcome data were reported.**

Thank you for addressing that point. We apologize for being imprecise. Included
patients did not report adverse events, but the data were not assessed this data with
a specific questionnaire. We changed that in the manuscript.

5. **The standard physiotherapy regimen does not seem to include much in the
way of ambulation training or early rehab. Please comment as to whether this
control intervention should be considered the gold standard for physiotherapy
care during an acute exacerbation.**

We fully agree with that point. We would not describe the control standard
physiotherapy as a gold standard, rather more as an expression of a real life situation
in many hospitals.

6. **Please comment on the success of the blinding of assessors. Given all the
patients are on the ward together, unblinding could occur easily.**

6-MWT and CRT were assessed by nurses and staff of the lung function lab. These
assessments were not performed on the ward. Furthermore, patients were
transported via wheelchair to the WBV device from different wards. Blood samples
were taken by medical students. All assessors had not being told that patients
participated in a study. However, as patients were not blinded, we cannot exclude
that patients told the assessors that they were part of a study.

7. **Methods says that 40 patients were randomized, but actually in the
CONSORT diagram it becomes clear that 49 were randomized and no intention
to treat (ITT) analysis was conducted. Please report what happened to the
withdrawals and make it clear that no ITT was conducted.**

We apologize for that mistake- we corrected that in the manuscript. We also included
the information that we performed a completers analysis.
8. **The statistical analysis could be revisited - consider a technique that takes into consideration the repeated measures.**

Thank you for that suggestion. We analyzed the data in two ways. First we calculated the values (discharge – admission) on an individual basis. To assess whether the within-group difference was significant (the delta) we used the Wilcoxon matched-pairs signed-ranks test that takes into consideration repeated measurements. To assess whether the deltas were statistically significant between the two groups we used the Mann-Whitney U-test.

9. **In the discussion the reader discovers that some patients could not perform the 6MWT, the primary outcome, at admission. Whilst this is not surprising, it should be declared in the results so that the reader knows exactly how many patients were included in analysis of the primary outcome.**

That is a very important point the reviewer mentioned. We included the information about missing data in the legend for figure 2: In the WBC group complete data about 6-minute walking test and chair rising test was available in 19 patients (14 respectively). In the control group only 14 data sets were available for both outcome measures. As the imbalance of missing data may have biased the results in favour of the WBV group we repeated the 6-MWT analysis by setting the missing admission data to the lowest obtained value. Doing that the between group difference still remained significant (supplement figure 4).

**Minor comments**

1. **When were the bloods taken? The methods do not say.**

We apologize for being imprecise. The blood was taken after signing of the informed consent and on the day of discharge (between 7 am and 10 am) - we corrected that in the manuscript.

2. **Please describe the outcomes in more detail. For instance, presumably only one 6MWT was done at each time point due to the acute nature of the patients. Most readers will not know what a chair rising test is.**

Thank you for addressing that point, we gave more information in the manuscript.

3. **Please report length of stay early in the results section and put it in the table. If the reader does not know that the LOS was the same in both groups, the rest of the results cannot be interpreted.**

We apologize for that and corrected that in the manuscript.

4. Please check formatting of reference 27.
The wrongly formatted reference was corrected in the manuscript.
Reference List


