Reviewer’s report

Title: Size-adjusted muscle power and muscle metabolism in patients with cystic fibrosis are equal to healthy controls – a case control study

Version: 1 Date: 05 Nov 2019

Reviewer: Jana DeBrandt

Reviewer's report:

Dear authors,

I would like to thank you for your extensive responses to my queries. My main concerns were addressed. I however have some minor queries that need to be addressed before publication.

In general: Please be consistent in wording about the 'knee extension task'. Sometimes it is not really clear if you are talking about that task.

ABSTRACT

Abstract: line 35: please describe which 'task'

Abstract: line 33: just to make sure I understand correctly: The 15 extra participants for the high intensity task were included on top of the 20 CF / 23 CONT participants? Or you first had 15 CF and 13 CONT and decided to recruit more and add a test? You need to realize that as you didn't power your study and you decided to change your protocol, that your subgroup is in my opinion underpowered. As long as you clearly state this as a limitation in the discussion, I agree for publication. I know that access to MRI scanning is difficult, but at least you should have done a power calculation to know how many patients you exactly needed.

Abstract: line 47: please include p-value

Abstract: line 53: please add ';' instead of '),' before 'power drop' + add p-values
Abstract line 60: please describe 'the exercise task in the MRI' as 'the knee-extension task'. Now it is confusing.

Abstract: page 2 - line 7: please write again 'knee extension exercise or task'

BACKGROUND

Background: line 10 - page 5: 'constraints in anaerobic and aerobic capacities': please write first 'aerobic' and then 'anaerobic'

Background: line 15 - page 5: do you mean eligible for 'lung transplantation'?

Background: line 17 - page 5: I would place this sentence 'Interestingly, both, aerobic and anaerobic exercise capacity are related to quality of life [10]' before 'In addition to pulmonary function and physical activity, muscle function is an important predictor of aerobic capacity [9]' as your next sentence is about muscle function and I think the text flows better in that way.

Background: line 27 - page 5: What do you exactly want to say with this sentence?: 'Therefore, peripheral muscle function needs to be considered when analysing reduced exercise capacity as studies have proven that improving lung function by bronchodilators does not increase peak aerobic capacity [11] but patients with CF are able to fatigue peripheral muscles despite ventilatory limitations [12]. I guess that you want to say that reduced exercise capacity in CF is not only because of ventilatory problems but also because of muscle dysfunction? Correct? I struggle a bit with the second part of your sentence when you talk about 'but patients with CF are able to fatigue peripheral muscles despite ventilatory limitations [12]'. What does this mean in regards to exercise capacity if the CF patients are able to fatigue? Please provide clarity.

Background: line 47 - page 5: is this sentence 'In fact, in a mouse model, reduced contractile function of diaphragmatic muscle from CF-mice was observed in the presence of an inflammatory stimulus [17]' related to the CFTR gene? If not I would move this sentence one up.
Background: line 42 - page 5: the CFTR gene is also found in healthy skeletal muscle. Is this ever been measured in CF in the quadriceps muscle? I would guess so. If so could you elaborate a little bit?

Background: line 32: page 6: 'We think that controlling for muscle size by ANCOVA is the most accurate approach to assess muscle function during exercise.' I do not think it is necessary to say that you will control through ANOVA. If you just say that you will control for muscle size this is ok I think.

Background: line 7 page 7: Please switch the place of aerobic and anaerobic in the next sentence: 'Combining MRI muscle spectroscopy with anaerobic and aerobic exercise...'

METHODS

Methods: line 7 - page 8: please write 'oxygen saturation' instead of 'oxygen saturations'. Can you also add manufacturers of your equipment (ECG, oxygen saturation, wingate bike)?

Methods: line 7 - page 9: please write the following sentence also in grams per kg body weight like the sentence before: 'Maximal work load was assumed to be 0.12 kg/kg bodyweight in males and 0.09 kg/kg bodyweight in females.'

Methods: line 60 - page 10: you already say that you control for height, CF or not and qCSA in the previous sentence. So please remove this sentence: 'They were controlled for the CF status (CF or CON), qCSA, and height.'

Methods: line 3 - page 11: can you please explain again which tests you compare exactly. Meaning which data points were exactly taken for the analysis during the high intensity and incremental protocol? Now it is not clear enough.
RESULTS:

Results: line 35 - page 11: now you control exercise capacity by qCSA by dividing it. How did you exactly do this? Is this standardly used? Why don't you just do an ANCOVA? I think it is a bit weird to see the unit vo2peak/qCSA ml/min.

Results: line 45 - page 11: I requested a comparison of the subgroups to the whole cohorts. Now you include together the CF and Control for subgroup and total group (table 5). This data depicted like this is a bit strange I feel. The only reason why I suggested to compare the subgroup CF vs total cohort CF, and subgroup Cont vs total cohort Cont is just to know if they are not completely different from each other on baseline. There can for example be a bias on the subgroup because they were willing to do an extra test, so maybe they were more motivated or had a better exercise capacity or any other reason. So I don't think you need to make a table for this. I would suggest to compare per group (CF: subgroup vs total group) and (Contr: subgroup vs total group) the parameters and see if there is any differences. And just write one or two sentences on this when you talk about the subgroup analysis. For example: high intensity CF subgroup didn't differ from the total CF group on '.................'.

Results: in general: explorative: I would like to see the linear regression (ANCOVA) with gender (M/F) included. Or can you two separate ANCOVAs? One for all the women and one for all the men? I now this will lower the sample size. But just in an explorative way? As you can now see in your correlation plots, it is really the men in the top on the right and the women on the bottom on the left. And maybe this correlation on the total sample (women and men) together is mainly caused by that. Because you have two clouds and if you draw a regression equation through it, it is quite logically that it is a good fit. So can you just do a correlation for all the men together and one correlation for all the women together to explore if in both men and women the correlation holds?

Results: line 24 - page 12: you write 'reflecting moderate to high correlation coefficients for qCSA and peak power, mean power and Lastmax MRT'. I do not see any correlation coefficients reported in the manuscript. Please add.

Results: line 5 - page 13: can you please explain which data points you exactly compared during the high intensity and incremental protocol? Now it is not clear enough. You can also not write $P = 0.000$, it needs to be $P < 0.001$
DISCUSSION:

Discussion: line 40 - page 13: please rephrase to 'a localized muscle function test (i.e. incremental exercise test in the MRI) WAS PERFORMED IN COMBINATION with the investigation of muscle metabolism'

Discussion: line 53 - page 13: I think it is rather a score 'on' on the wingate test than 'in' the wingate test.

Discussion: line 12 - page 14: please replace 'was' by 'were'

Discussion: line 37 - page 16: you use the word 'sprint group'. This is the first time you use it. Please refer to a more used term. I guess the high intensity subgroup?

Discussion: line 42 - page 16: I think based on the 5 vs 10 subgroup analysis this conclusion 'Still, since data is controlled for muscle size we think that this influence is but marginal' is too free. I would like to see a conclusion more in the sense of: 'more research is necessary needs to confirm this data' and gender needs to be balanced to trust the results completely.

TABLES

Table 1: sometimes you put a range and sometimes not. Please be consistent. Please use () brackets for range and [] for %

Table 1: Please replace TLCOC% by TLCO%

Table 1: Peak heart rate: please round it up to the decimal. Example: 171.0 \( 171 \text{ bpm} \). Same for O2 saturation.
Table 3: sometimes you put a range and sometimes not. Please be consistent. Please use () brackets for range and [] for %

Table 3: Do not write $P = 0.001$ but $P < 0.001$ in the table

Table 4: sometimes you put a range and sometimes not. Please be consistent. Please use () brackets for range and [] for %

Table 5: I would delete it. See comment above.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

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