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: 0 Date: 15 May 2019

Reviewer: Jana DeBrandt

Reviewer's report:

Manuscript - General comment: please be consistent in wording: sometimes you use incremental cardiopulmonary cycling test, sometimes incremental cycling test. Please always use the same wording for the same thing. Also you use the wording 'muscle function', 'muscle power', 'muscle performance', 'muscular exercise capacity', 'muscle capacity'. Please be consistent and accurate to the definitions of each parameter. I agree that with a wingate test you measure power output. But with a knee-extension incremental protocol, I don't think this is power. If you need to maintain a specific load for 5 min (contract - release), I believe this is muscle endurance. Please adapt the whole manuscript based on what you feel are the most appropriate terms but be consistent.

Abstract - Methods - line 16-20: now you state twice that the incremental CPET is performed. I would limit this to one time. Also I don't know if I completely agree with the fact that the incremental CPET is a muscle function test. In part yes, but it is a general exercise test. Also in table 1 you don't put the CPET data under muscle function. You describe them in table 1 under exercise capacity.

Abstract - Methods: you don't mention that qCSA is measured. As this is the outcome you correct your data for, it is very important to incorporate this in your abstract and how you measured it.

Abstract - Results: you don't mention the results on the incremental CPET on the bicycle and muscle metabolism after adjustement

Abstract - Conclusion: you use the term power for all outcomes (see comment above about using the correct wording for you muscle outcomes).
Background - line 10  page 5: change 'poor muscle mass' into 'decreased muscle mass' if that is what you mean. Steroid use and inflammation they play a role in limiting exercise or in initiating muscle dysfunction?

Background - line 18 - page 5: what does the CFTR do in the muscle (also in the discussion you only cover this shortly)? I actually do struggle a bit with the first 2 paragraphs. You say already on line 8-10 that the disease plays a role. Why do you start line 16 with 'However.... the muscle is primarily affected by the disease as...... '. So disease has a major impact apparently. I just don't understand the use of the word 'However'.

Methods - Population - line 27 - 30: Please add a reference after the diagnosis sentence. Groups were not matched on gender. Do you think this can bias your results?

Methods - Population: how and from where were participants recruited?

Methods - Lung function: FEV1 always needs to have the 1 in subscript. How was diffusion capacity measured. Which technique? Add reference.

Methods - exercise testing: how did the familiarization go? Please provide details. How much time was there between Wingate and incremental CPET? I think reference 22 is not adequate enough to make sure that the incremental CPET that you are describing is reproducible. I would like to see information on the following: did you measure ECG, blood pressure, saturation? did you have a resting period, warm up, recovery? If yes, how long and at which workload? At how many RPM needed the patient to cycle? How was gas exchange measured? Was this Breath by Breath? Was there standardized encouragement during the exercise tests? Participants between the age of 12 to 42 were included. The protocol of Godfrey is based on childrens height. I guess you did not use this protocol for adolescents and adults? Which protocol did you use for them?

Methods - MRI spectroscopy: why do you need the steady state exercise over 5 min with a constant load? You don't report results about that part. I don't see the added value. Or do you measure something during those 5 min steady state that is needed for the incremental protocol? How long did the participants needed to let hold the contraction? 1 sec hold, 2 seconds relax? What was the frequency of extensions per minute?
Methods: MRI spectroscopy: how did you anticipate the patients maximal load?

Methods: MRI spectroscopy: how did you choose the subgroup for the high frequency steady state protocol?

Methods: statistical analysis: did you perform a power calculation for the trial? And also for the subgroup trial? Definitely for the subgroup trial 5 vs 10 might be underpowered. Was all data normally distributed? Why didn't you take 'weight' as a control variable as well? This parameter is also different between the 2 groups. Wouldn't it also be interesting to take gender as a control variable as percentages of women in each group are different. Did you test this significantly if this percentage is different?

Results: do you have data on the length of the testing protocol under MRI per participant? And how much was the increase of maximal load during the incremental knee extension protocol (maximal load minus start load)?

Results: Wouldn't it be interesting to compare the subgroups with the whole cohort also statistically? To see if they differ or not in characteristics? I would add table 4 to table 1 so that you can easily compare the subgroups with the 2 cohorts.

Results - line 34 page 9: please use VO2 peak with ‘2’ always in subscript instead of VO2 max

Results: please add peak workload data if available to incremental CPET data. Did you also control the incremental CPET data for qCSA and height. I would be interested to see what comes out of that analysis. In the discussion you state that the difference remains after controlling. If you state this, you need to write this in your results as well.

Results: I miss data on the steady state knee extension test. Why is this data not reported?
Results: According to the correlations. Now you perform the correlation for the whole group (CON and CF together). Is it not more appropriate to perform the correlations separately per group? Now you mix your population, which makes it difficult to interpret the data correctly.

Results: high intensity protocol. I think you need to be careful with this analysis. This is only a 5 vs 10 analysis and I guess the study is not powered for that sample size. If you look at table 4, you see that the MRI spectroscopy data actually is different between the groups. And this was not like this in the incremental knee extension protocol. Don't you think because of the small sample, you might not reach statistical significance while actually there seems to be a different response. Can you test more patients with this protocol to create more power for this analysis? And can you also balance the gender out better, now it is 1 vs 6 women.

Results: muscle metabolism: is the paired sample t-test performed in the whole cohort? CON and CF together? If so, please make this clear. Would it be interesting to perform a paired sample t-test per group?

Results: are the MRI spectroscopy data also controlled for qCSA and height?

Discussion - line 30 page 11: what do you mean with 'no qualitative functional differences to the leg muscles of healthy controls was observed'. Why qualitative? You have quantitative data.

Discussion - line 60 page 11: i think you need to write 'the aforementioned potential....'

Discussion: I believe that only the left leg was used in the testing protocol. Did you question the participants on sport activities? Maybe it was better to use the dominant or the non-dominant leg because sport activities can influence that.

Discussion: line 33 - 38 page 13: Physical activity is not the same als exercise training. I don't think by controlling for QCSA that you also control for training status. Please remove this from the discussion.
Tables - general comment: please be consistent in use of points, plus-minus, etc. Now there is sometimes no space, too much spaces, small letters, big letters, subscripts, etc....

Tables: table legend: just write ***p&lt;0.001, ** p&lt;0.01, * p&lt;0.05 instead of the way you have done it now (please adapt for every table).

Tables: Add % of women in row 1 of tables.

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

No

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

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Please indicate the quality of language in the manuscript:

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