Confidential comments to editors

Title: Pulmonary Function and Exercise Tolerance in Pre-dialytic Patients with Chronic Kidney Disease: A Cross Sectional Study.

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Comments: see over
Juiz de Fora, 18th April 2013

TO: Dr. Hayley Henderson

Ref: Pulmonary Function and Exercise Tolerance in Pre-dialytic Patients with Chronic Kidney Disease: A Cross Sectional Study (BMC Series 2101092966996335)

On behalf of all co-authors, I am resubmitting the enclosed material for possible publication in the *BMC Nephrology*. I hereby certify that all authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its resubmission to the *BMC Nephrology*. I also enclose a detailed point-by-point response to the reviewers’ concerns. I believe that the manuscript has strongly benefited from their expert analysis.

I hope that the reviewers and yourself find this revised version acceptable for publication in the Journal.

Sincerely yours,

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Ruiter de Souza Faria

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Response to Reviewer Neil Smart

First of all we would like to thank you for the helpful and cogent analysis of our study. Please see below the answers to your queries and suggestions.

Quality of written English: Needs some language corrections before being published.
ANSWER: Following your suggestions, we revised the language.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
ANSWER: The statistical professor of our group confirmed the analysis of this study.
Response to Reviewer Andrew Williams

First of all we would like to thank you for the helpful and cogent analysis of our study. Please see below the answers to your queries and suggestions.

Methods Page 6 final paragraph:
Please identify in the text that VO2 max is a predicted value. I suggest changing the word "determined" to "predicted" in the sentence beginning "Peak oxygen consumption maximum....."
ANSWER: The word “determined” was replaced by “predicted”.

Final paragraph of results:
Please replace “e” with “and” throughout this paragraph.
ANSWER: The word “e” was replaced by “and”.

Results Paragraph 2
Follow-up time suggests time since a treatment or intervention was initiated. This is not the case in this study. My personal preference is to use the phrase “time since diagnosis” to indicate disease duration.
ANSWER: The reviewer is right. In this revised version, the suggested sentence was rewritten.
Response to Reviewer Emma Watson

I have read through the paper and the authors’ response to the reviewers comments. From the comments made by referee 1, the main problem seems to be that of sample size and how representative it is to the wider renal population. Having conducted these types of studies ourselves, we are very familiar with the difficulty in recruiting patients into this type of study and the large number of patients that must be screened in order to recruit just a few. Its well-known exercise type studies are not easy to recruit for and I don’t believe this study is any better or worse than those previously conducted. The problem of a representative study population is also a common one. The types of patients that will consent to a study involving any kind of exercise test is probably naturally biased to the healthier ones, putting a question mark over how far the results are typical of the general renal population, but unfortunately there is no easy solution to this. However, I believe the study has been weakened by excluding those patients over the age of 65, this has vastly reduced their sample population and contributes to a lack of representation, as the over 65’s make up a large proportion of the patient numbers - the upper age limit needs some justification. I therefore don’t fully agree with referee 1, I don’t believe the study is fundamentally flawed, these types of problems are common in conducting studies of this nature.

ANSWER: We agree with the reviewer’s point. However, please note that we excluded the patients older than 65 years because the aging is associated with a progressive decrease in pulmonary function and exercise tolerance, which could be a confounding variable (see references below). We included the “aging” in the second paragraph of the discussion.


Referee 1 also states the study adds nothing new to the literature, but the pulmonary function question asked by these authors is novel, however I feel the authors need to justify the investigation of it more clearly in the introduction as to an unfamiliar reader the reason for this unclear and confusing.

**ANSWER:** We entirely agree with the reviewer. In this new version, we included this question in the last sentence of the second paragraph of the introduction.
Response to Reviewer #4

General Comments
The style in which the paper is written is inconsistent, it switches from the first to the third person throughout. For example see final paragraph on page 5. Please be consistent and always write in the third person.
ANSWER: The reviewer is right. In this revised version, we wrote in the third person.

Whilst I appreciate English is not the authors first language I really feel it would benefit from proof reading by a native English speaker to remove the errors relating to language.
ANSWER: Following your suggestions, we revised the language.

Please refer to renal function as eGFR (estimated GFR) not just GFR.
ANSWER: We included “eGFR” instead of “GFR” throughout the manuscript.

All p values need only to be presented to two decimal places not three.
ANSWER: This change was made.

Be consistent with how you present data, sometimes its presented as P = 0.03, others as P=0.03.
ANSWER: This change was made.

Major Comments
The introduction needs much more justification for the investigation of pulmonary function. This is discussed in terms of haemodialysis patients, but no information is provided for the justification that this is a problem worth investigating in pre-dialysis patients.
ANSWER: We entirely agree with the reviewer. In this new version, we included this question in the last sentence of the second paragraph of the introduction.
The hypothesis includes that changes in exercise tolerance are associated with eGFR – however, this is now well accepted and there is plenty of data to support this. This has therefore been proven and shouldn’t be included in the hypothesis.

**ANSWER:** Sorry for this rather basic mistake. The hypothesis was deleted.

**Minor Comments**

**Abstract**

In the results section of the abstract it is not clear how to interpret the VO2 peak values – what are they percentages of? Further down they are referred to as relative values, please state units as mL/kg/min – remove dots and negative marks. Remove percentages from abstract and present as relative to body weight – percentages are meaningless and do nothing to inform the reader about your patients.

**ANSWER:** This change was made.

The above also applies to 6MWT and spirometry data.

**ANSWER:** This change was made.

In the conclusion be slightly more conservative when presenting the correlation data – this is only a weak correlation and may overstate the importance of it. Also please refer to exercise as maximal and submaximal not maximum and submaximum, which is not grammatically correct.

**ANSWER:** The reviewer is right. In this revised version, the conclusion was rewritten. The words “maximum” and “submaximum” were replaced by “maximal” and “submaximal” throughout the study.

**Background**

As mentioned above, as the paper focuses on pre dialysis patients, the authors need to include some information in the introduction on pulmonary function in these patients to justify investigating its possible contribution to reduced exercise tolerance.

**ANSWER:** We entirely agree with the reviewer. In this new version, we included these questions in the last sentences of the second and third paragraphs of the introduction.

It is well documented that exercise tolerance reduces as patients progress towards end stage and VO2 peak is approx 60% lower than controls (eg Clyne et al. 1994). However,
none of this previous research is presented in the introduction or discussed in light of the results in the discussion section. This needs to be addressed.

**ANSWER:** This reference was added in the last sentence of the third paragraph. We included this study in the paragraph 4 of the discussion.


**Methods**

Pg 5 para 3: I understand that reviewer 2 asked for further details of measurements, which has been added in. However, it reads as a response to a reviewers comment and should be integrated into the paper a bit better.

**ANSWER:** This change was made. Measurement units were added.

Pg 5 para 3: Please define CPET as this is not the first use.

**ANSWER:** This change was made.

Pg 6: The CEPT paragraph is confusing. Authors have stated “Peak oxygen consumption maximum (VO2Max) – this sentence doesn’t make sense, furthermore VO2 Max is not referred to anywhere else in the paper. This reads rewriting. The section in bold doesn’t make sense either. If the values in the paper are the VO2Peak values that were achieved during the ramp test expressed as a percentage of what was predicted by computer software this needs to be explained. This is not really a satisfactory way of presenting VO2Peak data as percentages mean nothing to the reader, values relative to body weight would be much more meaningful. Presenting values as percentage of their predicted values leaves readers wondering why 100% of predicted wasn’t able to be achieved, especially in the controls. Was the calculation used over predicting VO2 Peak, was the analysis if the expired gas correct or were the patients not motivated or pushed enough to achieve their actual VO2Peak??

**ANSWER:** We agree with the reviewer and the CPET paragraph was rewritten. The VO2Max was deleted and we included the explanation of predicted VO2peak. In fact, the end of CPET as the time point in which the patients signaled to stop exercising or could not maintain the work rate required for 10s despite being encouraged by the investigators.
Pg 6: VO2 peak is described as the highest O2 reached during the test which is worrying. VO2Peak is defined as a plateau in O2 consumption, if no plateau occurs it indicates VO2 peak will increase should exercise continue. Please clarify if a plateau was achieved during ramp tests.

**ANSWER:** We partially agree with the reviewer’s point. The highest VO2 attained during the exercise test is defined as VO2peak. On the other hand, the VO2max is reached when the plateau of VO2 occurs despite the increases of work rate during exercise test. In this study, our patients did not reach the VO2 plateau (VO2max) because they signaled to stop exercising despite being encouraged by the investigators. Thus, we used VO2peak instead of VO2max.

**Results**

Pg 8: Paragraph 3 has obviously been added in at the request of the reviewers, but isn’t really integrated into the paper properly.

**ANSWER:** O que dizer

Pg 8: last paragraph, the authors state that “in the CPET VO2peak was lower in G4 and G5…. when presenting results in this way it really helps to interpret the data if p values are included in the text.

**ANSWER:** We included the p values in this sentence.

Authors need to be more conservative how they interpret the correlation data. If you take the VO2peak correlation with eGFR for example r = 0.430. The correlation coefficient squared is a useful way to estimate how much variability in one variable can be explained by another ( r²). So if r=0.430, r² = 0.184. This means that 18% of the variability in VO2Peak can be explained by eGFR and over 80% is accounted for by another variable that was not included in the analysis. The authors need to be aware that while these correlations may be significant they are not all that meaningful. This requires some discussion on page 10 para 2.

**ANSWER:** We agree with the reviewer. The correlations are described as weak.
Discussion

Pg 10 para 2: description of anaerobic threshold needs rewording. At the moment it reads that above AT only aerobic glycolysis occurs and not that this energy system accounts for the majority of the energy produced.

**ANSWER:** This change was made.

Pg 10 para 4 (last para): I don’t understand the point the authors are making here “in addition, pulmonary function as assessed by spirometry showed no differences between groups, supporting the findings obtained with the cardiopulmonary test” – what findings are these? This requires some clarification.

**ANSWER:** This sentence was rewritten for clarity.

The authors state that reduced exercise tolerance may be due to changes in CV or peripheral muscles, however this describes just one part of a complex physiology and doesn’t consider possible decrements in cardiovascular function and transport of oxygen, muscle perfusion, oxygen extraction by the peripheral muscles and activity of enzymes in energy pathways. If this discussion is to be instigated it needs to be more thorough. – this discussion seems to be continued on page 11 and should be included with the rest of this section on page 10.

**ANSWER:** Well taken point. In this revised version, we changed the order of this discussion.

Pg 11: when authors state “in our study CKD patients showed lower values of PImax than the control group” this needs to be more conservative and state that there is a trend because that statement is not supported by the stats p=0.06.

**ANSWER:** This sentence was rewritten.

Pg 12: the authors state that changes in pulmonary function may have been more pronounced if they had studies more recently diagnosed CKD – why should this be the case? It is my understanding that this is only a problem that really develops as CKD progresses.

**ANSWER:** This sentence was removed.
Conclusion
The authors need to be careful what they conclude about relationships with disease severity as I have concerns about the strength of these correlations.
ANSWER: The conclusion was rewritten.

I don’t believe this study presents enough evidence to suggest that pulmonary function should be regularly tested, for what clinical reason? Furthermore whilst I agree exercise testing is important initially for exercise prescription, I don’t believe there is sound rationale for regular exercise testing either. The conclusions should be moderated slightly.
ANSWER: The conclusion was rewritten.

Table 1
• Control group abbreviation appears to be incorrect
ANSWER: This change was made.

• Please correct incorrect spelling of hypertensive
ANSWER: This change was made.

• More justification is required for the control group who have been presented in the table as having an eGFR of 77, which by definition is CKD stage 2. Please include in the methods section something to confirm these are healthy controls such as absence of proteinuria etc.
ANSWER: This change was made.

Table 3
• Please present VO2peak and VO2AT units as mL/kg/min and be consistent with this throughout the paper.
ANSWER: This change was made.

• Is VE minute ventilation? The legend describes it as volume per minute – volume of what? • It needs to be made clearer what VO2 peak % is.
Table 4

- It is unnecessary to correlate VO2peak and 6MWT values with eGFR – this doesn’t add anything to the paper especially as these percentages are based on values not measured by the authors. Please remove them from the table.

  ANSWER: This change was made.

- What is VO2LA? Should this be VO2AT?

  ANSWER: This change was made.

- Please present VO2peak values as mL/kg/min.

  ANSWER: This change was made.

Figure 3

- Be consistent with how you describe 6MWT – sometimes its 6 minute walk test, sometimes its 6 minute walking test.

  ANSWER: This change was made.