Author’s response to reviews

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

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Author’s response to reviews: see over
Dear Editor Dr. Hayley Henderson and Reviewers of our original article entitled, Pulmonary Function and Exercise Tolerance in Pre-dialytic Patients with Chronic Kidney Disease: A Cross Sectional Study. BMCSeries 2101092966996335

Thank you for your email of June 20th with the evaluation of our manuscript. We are happy because our manuscript is potentially acceptable for publication in BMC Nephrology. Indeed, we carefully considered the comments made, revised the text and are now resubmitting it as encouraged by you. In the attached revised version, we hope we have answered the comments of all referees to their satisfaction. We take the opportunity to thank for all your comments and criticisms, which have certainly improved the quality of this paper.

Yours sincerely,

Ruiter de Souza Faria
Corresponding author on behalf of all authors.

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Reviewer Neil Smart
Comments to the Author:

This work is a cross-sectional analysis of lung function in exercise tolerance in pre-dialytic patients with stage III-V kidney disease. The work conducted is sound, but the overall design is limited in a number of ways.

First of all, we would like to thank you for the very important questions you have posed, which helped us improve the paper with interesting and important information for the readers.

Major Problems
The sample contains 29 CKD patients, but over 300 were screened so it is questionable whether CKD patient data presented are representative of this patient group. Moreover it seems those selected were known to or related to the researchers which suggests selection bias. There were only 9 controls, although sample size seems adequate.
If the methodological qualities of the problems in the paragraph above are considered acceptable, the question must be asked "what new does this data tell us?" The answer is nothing new, we know pre-dialytic patients are de-conditioned and the study adds relatively little. Also the conclusions regarding use of screening and exercise testing appear to be without foundation, why would we waste tax funds in a public healthcare system or, in an un-socialized medicine system, why would the individual (or their insurance company) waste funds to look for something we already know. Although I agree that exercise training at this stage would be beneficial and testing to assist with exercise programming maybe justified.

As described in the final of introduction:

Despite their potential relevance in CKD, exercise tolerance and pulmonary function have been little studied in patients not yet on dialysis.

We described below the literature review that shows the paucity of papers on the subject and the few results were published in heterogeneous populations (with other risk factors for decreased pulmonary function and exercise tolerance) and evaluating only respiratory function or exercise tolerance, never both in association.

Regarding CHRONIC KIDNEY DISEASE AND RESPIRATORY FUNCTION, on 11th November 2011, we conducted a literature review by using the keywords LUNG FUNCTION, RESPIRATORY FUNCTION, PULMONARY FUNCTION AND KIDNEY DISEASES, CHRONIC KIDNEY DISEASES, CHRONIC RENAL FAILURE, as well as their synonyms in the databases EMBASE, WEB OF SCIENCE, PUBMED, and COCHRANE. We found a total of 1,052 articles. We selected articles in English, Portuguese, and Spanish and excluded 981 articles because they did not present abstracts, dealt with issues that were not within the scope of the search, or were written in a different language from those listed above. In total, 70 articles were included (References listed below). We observed that 46% of the studies were performed in hemodialysis (HD) patients; 10%, in peritoneal dialysis (PD) patients; 10%, in patients who had undergone renal transplantation; 19%, involved several types of renal replacement therapy (RRT) and pre-dialysis; 1.5%, were experimental research on dogs; 8%, review articles; and only 5.5% evaluated patients undergoing pre-dialysis. With respect to study design, all the studies that evaluated patients in pre-dialysis with or without RRT were cross-sectional.
Regarding CHRONIC KIDNEY DISEASE AND PHYSICAL CAPACITY, on 11th November 2011, we conducted a literature review by using the keywords PHYSICAL CAPACITY, FUNCTIONAL CAPACITY, PHYSICAL FITNESS KIDNEY DISEASES, CHRONIC KIDNEY DISEASES, CHRONIC RENAL FAILURE, as well as their synonyms in the databases EMBASE, WEB OF SCIENCE, PUBMED, and COCHRANE. We found a total of 255 articles and selected articles in Portuguese, English, and Spanish. We excluded 171 articles that did not present abstracts or dealt with issues that were not within the scope of the search. A total of 83 articles were evaluated (References below). Among the articles, 40% were performed using patients with HD; 4.8%, using patients with PD; 7.2%, using patients who had undergone renal transplantation; 16.8%, involved various types of RRT and pre-dialysis patients; 1.2%, were experimental research on mice; 24%, were review articles; and only 5%, evaluated pre-dialysis patients.

This study was conducted in a single treatment centre for patients with chronic kidney disease, and the sample was as large as possible. For the selection, patient criteria were used in order to exclude bias that usually compromises both respiratory function (smoking, previous lung disease) and physical capacity (disabling musculoskeletal abnormalities, uncontrolled hypertension), thus lowering the sample size.

This issue is discussed in the last paragraph of the Discussion, where we report the study's limitations.

References:

**Pulmonary Function and Chronic Kidney Disease**


41. Pechter U, Maaroos J, Mesikepp S, Veraksits A, Ots M. Regular low-intensity aquatic exercise improves cardio-respiratory functional capacity and reduces


Physical Capacity and Chronic Kidney Disease


Minor comments
Clarify what is VO2 (%)? is this predicted % of max? If so state how predicted values were calculated.

Oxygen uptake percentage (VO2 (%)) is the percentage of VO2 max achieved for each patient in maximal cardiopulmonary exercise testing. All patients underwent a brief simulation of the test to become familiar with the procedures performed, were interviewed about physical activity, and were classified as sedentary (did not perform physical activity) or active (at least mild physical activity performed 3 times per week for 30 min). Then, the software calculated the predicted VO2 max for the patient, which was obtained from equations given by the American College of Sports Medicine that were elaborated for the Ramp Protocol (Maeder et al., 2005, cited below). The program would suggest an initial and final speed and also an initial and final inclination of the treadmill to achieve VO2 max between 8 and 12 min.

The cited reference has been inserted in the manuscript.

Would be helpful to state how long the CKD patients had disease, this would better justify the selection from the 300 screened. As many younger patients (over 65 years have been excluded) do not group thru the decades of chronic deterioration that is typical of CKD patients in class III-V.

Due to the fact that CKD is most often asymptomatic in its early stages, exact data about time of establishment of CKD for each patient is not available in this database, as in many others. Mean follow-up time was 4.47 ± 2.67 years, varying from 1 to 8 years, with a median of 4 years. (this information is available in the Results section). Of interest, we point out that complications of CKD are mostly linked to the stage of the disease, and not to time of its diagnosis, as time of progression to end-stage disease can vary widely among patients, not showing a correlation with the time elapsed from the diagnosis.

Based on Pereira et al., 2012 the average age of patients seen in our clinic was 65.4 ± 15.1 years, while 47.3% stage 4. The sociodemographic characteristics of these patients, (except for age: exclusion criterion in our study) is similar to our study showing that our sample is representative of the population. Regarding the causes of exclusion, that is in the algorithm mentioned in the study as Figure 1.


Reviewer Andrew Williams
Comments to the Author:

There is a wide range of evidence around the effect of end stage renal disease on exercise tolerance and the effect of various exercise training protocols on this. However to date there
is little published work on the effect of less advanced CKD on exercise tolerance and possible contributors to exercise tolerance in this population. This study provides interesting data related to exercise intensity and pulmonary function in CKD which may assist in the targeting of treatments designed to improve exercise tolerance and quality of life in this population. Nevertheless the sample size is small and there are a number of issues that should be described in more detail.

We would like to thank you for your constructive criticism, positive comments, and encouragement.

1. This is a small study with just 38 participants in total (29 with CKD) and there were a number of compared variables that approached significance between the groups in this study. It is possible this may be due to insufficient statistical power. However there is no information presented regarding any calculation of required sample size on the basis of what constitutes a meaningful difference in the measured variables prior to the study. Was any such calculation performed and if so what sample size was identified?

We agree with your observation that it is extremely important. However, as also discussed with Reviewer 1, this study was conducted in a single treatment centre for patients with chronic kidney disease, and the sample was as large as possible. For the selection, patient criteria were used in order to exclude bias that usually compromises both respiratory function (smoking, previous lung disease) and physical capacity (disabling musculoskeletal abnormalities, uncontrolled hypertension).

In our study, the population size was fixed, and restrictive criteria were used to draw the sample from this population; furthermore, there is no previous published data that would enable us to estimate the sample size effect or standard deviation. To answer your question, we used a pilot study published by the group that detected abnormalities in respiratory function in 30% of the same population. We estimated that the study had a power of 60% by using the pilot study to evaluate the magnitude of the effect. At any rate, it was not possible to increase the sample size because of the issues stated above, and its size, in our opinion, does not affect our results.
2. Page 5, line 21: please identify whether the two sessions used for measurement of respiratory variables took place on the same day or separate days.

The pulmonary function tests and functional capacity tests are exercise-dependent tests, and were therefore performed in different days so that the results would not be compromised because of fatigue in these tests. Evaluations were performed at 3 different visits. At first, we performed blood tests and 6MWT. In the second visit, we performed spirometry and manovacuometry with an interval of 1 hour between these tests; CPET was performed only on the third visit. The visits took place in a 15- to 30-day interval.

This information was added in Methods section.

3. Page 6, line 10: Please list the criteria used to stop the CPET.

The criteria for discontinuation of CPET are the same as those recommended by the American Thoracic Society (2003) and are listed below. However, in all tests there were no complications; in addition, all tests were stopped when the patients reached physical exhaustion. This information was added in the Results section:

- Significant chest pain
- Pallor and cold sweats
- Disorientation and loss of coordination
- Dizziness and pre-syncope
- Intolerable Dyspnea
- Cyanosis
- Significant ST-segment depression
- Inversion of T waves and the appearance of Q wave
- Progressive and multiform ventricular ectopy
- Appearance of the R wave on the T wave
- Three or more ventricular premature beats
- Paroxysmal ventricular tachycardia
- 2nd or 3rd degree atrioventricular block
- Decrease in systolic blood pressure > 20 mmHg
- Pattern of left bundle branch block
- Intense chronotropic insufficiency
Sustained supraventricular tachycardia
Exercise SaO₂ < 80%
Symptomatic claudication
Patient requests interruption

4. Page 7, line 8: More detail is required on which between group comparisons were assessed with ANOVA, or chi-squared, or Kruskal-Wallis or students t-tests. It is not necessary to list the variable but to identify the type of data I.e: normally distributed data was analysed using ANOVA….

5. Page 7, line 9: It needs to be clarified how the students t-tests were used given participants were divided into four separate groups. Were t-tests used as post-hoc tests or in another way?

To answer points 5 and 6, we have described the analysis in greater detail; the article has been modified accordingly.

The descriptive analysis and the normality test (Shapiro Wilk) were performed. We used descriptive statistics to explore patterns in the demographic, clinical, and laboratory variables, and in the variables that assess exercise tolerance and respiratory function. The data were expressed as means and standard deviations or percentages, depending on the distribution. Initially the group was divided in patients and controls and Student’s T test and Chi Squared were utilized for comparison. Subsequently, patients were divided into groups corresponding to CKD stages 3, 4, and 5 and compared with the control group. Among group comparisons were carried out with normally distributed data using ANOVA. For non-normally distributed data we used chi-squared test. We tested for correlations between variables with Pearson or Spearman’s correlation tests, based on the distribution of the variables. We used a significance level of p < 0.05 and a confidence interval of 95%. Analysis was carried out using SPSS 13.0 software.

Results
6. The methods state that data were calculated in a range of ways depending on the distribution. However in the tables all data seems to be presented as mean ±SD? Please clarify how data was presented in tables and where appropriate in the text.

The variables were normally distributed (described as mean and standard deviation) or were categorical (as described as percentage) and therefore no need to use the Kruskal-Wallis Test, only ANOVA and the chi-square test. This subject has been modified in methods.

7. A range of medications commonly taken by individuals with CKD and other chronic diseases have the potential to effect results of outcome measures in this study. Inclusion of a list of relevant medications taken by participants would provide valuable information. In addition discussion of the potential effects of these medications (eg. EPO) on outcome measures (if and where applicable) would be valuable.

In our study, only 2 (6.8%) patients were anaemic, and these were incidents in the clinic and they had not yet reversed this condition, and used erythropoietin. About 37.9% of the patients used beta-blockers, and all hypertensive patients were using ACE inhibitors and/or angiotensin receptor blockers; sodium bicarbonate, calcium chelating and vitamin D agents were used where necessary, in accordance with the guidelines of the Brazilian Society of Nephrology. We added this information in Results section.

Accessed in:

Doença Renal Crônica (Pré-terapia Renal Substitutiva): Tratamento

Doença Renal Crônica (Pré-terapia Renal Substitutiva): Diagnóstico

8. FEV1 and FVC correlate with GFR in the current study. However the FVC and FEV1 were well above expected population values raising the question of whether they were an appropriate control group. What effect did their results have on the relationship between pulmonary function and GFR?
Our results allowed us to conclude that the patients in earlier stages of CKD had a normal ventilatory capacity, whereas those who in the final stages of CKD showed a reduction in ventilatory capacity. This situation does not compromise lung function as severely as in patients with lung diseases, but it may be related to the reduction in physical capacity. Since this is a cross-sectional study, we cannot conclude about the causes of these changes.

This limitation is mentioned in the Discussion section.

9. Peak HR during the CPET was lower in the CKD patients than the healthy controls which raises the issue of whether reduced exercise tolerance is due to pathophysiology or reduced motivation. Was any record kept of reasons for stopping the exercise test?

Many patients use beta-blocking drugs that are known to interfere directly with the heart rate. During maximal exercise (Table below) as a percentage of predicted heart rate (HR) was reduced in those who used such drugs. All tests were stopped when the patients reached physical exhaustion, and decreased HR was observed in patients who used beta blockers.

<table>
<thead>
<tr>
<th>Beta-blockers</th>
<th>No (N = 18)</th>
<th>Yes (N = 11)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRrest</td>
<td>78.61 ±15.40</td>
<td>74.82 ±10.72</td>
<td>0.481</td>
</tr>
<tr>
<td>HRprev</td>
<td>163.33 ± 8.28</td>
<td>167.00 ± 7.16</td>
<td>0.235</td>
</tr>
<tr>
<td>HRmax</td>
<td>146.56 ± 19.17</td>
<td>126.09 ± 16.18</td>
<td>0.006</td>
</tr>
<tr>
<td>HRmax (%)</td>
<td>89.63 ± 9.85</td>
<td>75.39 ± 8.07</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

10. Table 1: please include details of significant results between groups for individual biochemical measures (as performed for other outcome measures in table 3).

In Table 1 were included the biochemical units.
Discussion

11. Page 10, lines 16-25: the relevance of this paragraph to the findings of the current study is unclear. The reason for including it needs to be better explained or the paragraph should be removed.

We agree with the comment of the reviewer; this paragraph has been deleted from the article.

12. Reasons for poor exercise tolerance in CKD patients have been discussed including ventilatory changes as well as changes in cardiovascular or peripheral muscles. Other possible contributory factors that should be discussed are oxygen transport and altered buffering capacity given the significant results for haemoglobin and HCO3.

In the fifth and sixth paragraphs of the discussion session, we discuss the main factors responsible for limiting exercise tolerance in these patients and in the sixth paragraph was included anemia as a factor in reducing this tolerance, as well as a reference in the literature.
The reduced exercise capacity in patients on HD may be due to changes in transport mechanisms and oxygen extraction. The transport of oxygen in these patients may be altered by reduced cardiac output, changes in maximum heart rate and decreased arterial oxygen by anemia, while the impairment of oxygen extraction may be due to uremic myopathy and disuse atrophy (Moore et al., 1993; PAINTER et al., 1987). In pre-dialysis patients, we not found studies assessing these important variables. The mean hemoglobin was also appropriate in our sample and not correlated with lung function and CPET related variables.
We added this information in Discussion section.


Minor Essential revisions:
1. Page 5, Line 8: parathormone intact molecule – I assume you mean Parathyroid Hormone Intact molecule?
   This word has been corrected.

2. Page 8, line 1: PRmax, VO2AT and HRmax need to be defined as they have not been previously defined in the text.
   PRmax has been replaced by RPmax, and all the abbreviations have been defined in the text.

3. Page 8, line 10: Correct grammar in sentence beginning “Most studies of respiratory function…”
The text was submitted to a new revision of the English.

4. Page 8, line 16: Change coufounders to confounders
   This word has been corrected.

5. Page 10, line 14: members. Do you mean limbs?
   This word has been corrected.

6. Page 10, lines 16-25: remove quotation marks from around this paragraph.
   As described above in point 11, this paragraph has been deleted from the article.

7. Table 1: units for biochemical measures need to be included in the table.
   The units have been included in the table.

8. Figure 2: please include units for GFR on x-axis.
   The unit has been included in the figure.

Discretionary Comments:

1. Page 1, Title: It might be useful to include some detail of outcomes in the title. A suggested title is: Pulmonary function and Exercise Tolerance are related to disease severity in Pre-Dialytic Patients with Chronic Kidney Disease: A Cross-Sectional Study.
   We have accepted the suggestion of the reviewer and modified the title of the article.

Discussion

2. It was not addressed as a hypothesis but it would be interesting to see the relationship between pulmonary function and exercise tolerance presented and discussed.

   We performed the correlation between pulmonary function and exercise tolerance and we observed a weak correlation between FVC (%) and VO₂peak: r = 0.0337 and p = 0.048; FVC (%) and VO₂peak (%): r = 0.374 and p = 0.027; and FEV₁ (%) and VO₂peak (%): r = 0.365 p = 0.031.

   These data were added in the Results section.
As described on page 9 Discussion session:

Our study also recorded shorter distances walked in the 6MWT by CKD patients, and this result was more evident in those with lowest GFR. Reduced exercise tolerance in these patients may be related to changes in cardiovascular or peripheral muscles, because ventilatory changes were not observed during the cardiopulmonary test. In addition, pulmonary function as assessed by spirometry showed no differences between groups, supporting the findings obtained with the cardiopulmonary test. Moreover, there was only a weak correlation between pulmonary function and exercise tolerance (FVC (%) e VO2peak: r = 0.337 e p = 0.048; FVC (%) e VO2peak (%): r = 0.374 e p = 0.027; e FEV1 (%) e VO2peak (%): r = 0.365 e p = 0.031).