Reviewer's report

Title: Oxygen kinetics during 6-minute walk tests in patients with cardiovascular and pulmonary disease.

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Reviewer: Norman R Morris

Reviewer's report:

This study examined oxygen uptake kinetics during a six minute walk test in a group of cardiovascular and pulmonary patients. Whilst we still consider cardiopulmonary exercise testing (CPET) as the gold standard for gas exchange measurement in clinical populations, it unfortunately remains a little used clinical tool due to the cost, required expertise and the fact that the tests typically need medical supervision. The authors defined a new mean response time measure (wMRT) which is the mean response time normalised for the work rate. This is an interesting measure and it may prove useful in future clinical studies, however I believe the authors need to address a few issues.

Major Revisions and Considerations (General Comments)

• A major limitation of this study is the fact that the authors only used a single transition (single 6MWT) to measure determine tau and the oxygen uptake kinetics. Given this there will be significant noise in the data. The authors should provide details on the fitted model including details of the goodness of fit.

• This manuscript would be better served if the normal group of subjects was a similar age as the clinical groups. The fact that normal group is so much younger than the clinical groups makes this data difficult to compare. Typically there is a slowing of oxygen uptake kinetics as we age and as such you cannot make any real decision on how the, older, clinical groups compare.

• The authors did not measure peak exercise capacity independently, which is another limitation; rather they used selected criteria for achieving maximum. Why did they authors not also look at RER? In healthy subjects, the criteria used for the maximum in an incremental test is RER in excess of 1.1, HR within 90% of age predicted maximum and plateau in the VO2, despite an increase in the external work. Clearly the final criteria cannot be used, however it would be useful for the authors to note how many had an RER in excess of 1.1. I would argue the authors need to temper the argument somewhat on how many subjects actually met maximum.

• The prognosis data is interesting, however it seems strange that the author’s data suggest that PAH patients have the poorest wMRT, yet this was not associated with a poorer prognosis in this group.

• The authors need some further rationale on the mMRT figure. It would be good to know how reproducible this figure is and how it compares to normal age-matched controls.
Major Revisions and Considerations (Specific Comments)

Abstract
• Results: what is meant by ‘bad outcome’ - suggest use term like poorer

Methods
Did the authors perform a second 6MWT as per the guidelines? If so which test was reported.
• The authors only did one transition and then fitted the data. This leads tends to impact on the fit of the data and typically we see either 2 or 3 transitions required in order to reduce the signal to noise. Can the authors provide the details on the goodness of fit of the parameters.
• How were the control subjects selected? Not sure the control group is that useful given they are so much younger than the clinical groups and hit the upper limit of the 6MWT.

Results
• Please include the end exercise VO2 data, VO2 as a percent predicted of maximum and heart rate in Table 1. If the clinical populations were working at a similar percentage of maximum then would you need to normalise for workrate (i.e. use the wMRT)?
• The authors should include the correlation data for the MRT as well
• Have the authors examined the relationship between the wMRT and the steady state VO2 expressed in ml/kg/min? Would not you expect a better fit when controlling for body weight?
• What was the cutoff for a high vs low wMRT?

Discussion
• Suggest the authors do not use the term ‘peak’ rather the authors should use end-exercise oxygen uptake. Peak value is associated with an incremental exercise test and while the VO2 achieved by these patients may be close to this value, it should not be interpreted as the peak value. Indeed it is more likely that only in more severe patients that the VO2 achieved during the 6MWT is similar to that achieved during an incremental CPET.
• Discussion, 4th paragraph. The physiology here should be examined. Firstly I do not agree that the increase in kinetics mostly depends on the increase in rate of increase of pulmonary blood flow. In this study the authors are mainly looking at phase II kinetics and this is due to both the increase in cardiac output AND the widening of the arterio-venous difference i.e. a peripheral component. It does appear from the authors data that PAH patients may have slower kinetics – which indeed could be due to the an impaired increase in the pulmonary blood flow, however one could not rule out the peripheral impact either. Secondly the increase in cardiac output at the onset of exercise is due to an augmented stroke volume AND it is also due to a rapid increase in heart rate – this neutrally mediated response is rapid.
• Discussion 8th paragraph: Those individuals that did not reach a plateau in their VO2 may have been exercising above their anaerobic threshold – and hence would have had a VO2 slow component that caused the VO2 to drift. I would not agree that these patients necessarily increased their walking speed.

• The manuscript should note the limitations of these results, in particular the limited value of the kinetics given that only a single transition was undertaken.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare I have no competing interest