Author's response to reviews

Title: Does Pulmonary Rehabilitation address Cardiovascular Risk Factors in Patients with COPD?

Authors:

Nichola S Gale (galens@cf.ac.uk)
James M Duckers (jamie.duckers@wales.nhs.uk)
Stephanie Enright (enrights@cf.ac.uk)
John R Cockcroft (cockcroftjr@cf.ac.uk)
Dennis J Shale (shaledj@cf.ac.uk)
Charlotte E Bolton (charlotte.bolton@nottingham.ac.uk)

Version: 3 Date: 3 March 2011

Author's response to reviews: see over
Dear Dr Shipley

Please find revised manuscript. We thank the reviewers for their helpful comments. We have addressed these and agree this has enhanced the paper and hope you and the reviewers find acceptable. Our response is as follows:

Reviewer 1: Peter Calverley

Minor

1. You should be explicit about whether cardiac therapies other than anti-hypertensives and statins were being used. It is no mean achievement to recruit a population like this where there is so little co-medication and this may have weighted things against you having an even larger effect. A comment about this would be reasonable.

There were no other cardiac drugs other than those given for hypertension or a statin. In addition, there was no change to antihypertensives or other therapy during the course of the rehabilitation. At the end of the study, clinically relevant results (BP, lipids etc) were fed back to the GP for their action as required. We have added a sentence, page 8, paragraph 3.

2. Conversely participation in the rehabilitation course may improve adherence to therapy – could this explain any of the benefit seen?

We agree that addressing lifestyle could improve adherence with other medication that had been previously prescribed. This is just as important but parallel to the direct rehab programme. We have added a comment, page 13, paragraph 2.

3. Some more information about the patients who did not complete the programme is needed. Where they different with respect to disease severity PWV from other participants?

We had previously included the statement ‘There was no difference in age, gender, baseline lung function, haemodynamic variables or body composition between patients who completed study assessments and those who did not’ on page 9, paragraph 3 of the manuscript. We felt further numbers was confusing but would be happy to add if you felt needed. Of note, all the p values were > 0.2 and majority above 0.58.

Discretionary

1. Although the power was low, was there any relationship between the magnitude of improvement in exercise performance and the change in PWV?

We have added ‘ISWT and SGRQ improved, although these did not relate to change in aortic PWV’, page 10, paragraph 1
2. In an ideal world the smoking controls should have undergone a similar fitness increasing regime or better a programme of mild fitness improvement which would have produced comparable absolute increases in performance. I suspect the effect on PWV would have been similar to the COPD patients but this remains a speculation. A statement about the lack of a complete control arm is worth including in the discussion.

We have added a comment to limitations, page 13, paragraph 2. Although do comment that a comparable course for this group would be difficult. In deed, we did consider several options for a comparator group in the design of the study but felt neither this or sham rehab were options.

3. Another reason why the brachial PWV did not change is that it was not different from the ‘normal’ group to begin with. It would be helpful as to whether you considered the control values of the PWV to be high at study onset. Six patients (but no controls) had an aortic PWV > 12m/s -this has been considered to be a cut-off. However, PWV varies with age and a further paper “Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: ‘estimating normal and reference values”. Eur Heart J. 2010 Oct;31(19):2338-50; considers this. At this time, we have opted to present the results as they are rather than dichotomising.

Reviewer 2: Martijn A Spruit

1. Please explain the poor ICC for the augmentation index is rather low. Can you still use this outcome to assess the effects of pulmonary rehabilitation? Please note, that aortic PWV was our main outcome variable for this paper not AI which had a very good ICC. The poor ICC reflects the variability of AIX in this population and highlights the limitations of this AIX in older patients (>50 years), as stated in the discussion. AIX is derived using a transfer function from the radial pulse pressure waveform, which has been validated but can be open to some variability (Chen CH, et al. Circulation 1997).

2. Please provide p-value for proportion of hypertensive patients (41%) vs. hypertensive healthy subjects (25%). At baseline 41% of patients and 25% of controls met the criteria for hypertension (p=0.19). We have not added this as we would not attempt to hide the fact there are a different proportion hypertensive in the 2 groups, even if it does not reach significance.

3. Do the correlations between aortic PWV and IL-6 remain in only the group of COPD patients? If not, I suggest to remove this from the manuscript. The relationship of aortic PWV and IL-6 removed as it did not reach significance in this group of patients alone.

4. Where were healthy subjects recruited? This has been added, page 5, paragraph 2.
5. The authors provide nicely a power calculation in the statistics paragraph based on the 2007 Sabit paper. Nevertheless, it remains unclear why the aortic PWV of the COPD patients in the Sabit paper had a aortic PWV of 11.4 m/s while this was clearly lower in the current manuscript (9.8 m/s). The 'suitability for pulmonary rehabilitation' is too vague. Could there be a selection bias? Other outcome assessors/technicians? Etc.

The aortic PWV was lower than reported by Sabit, which may be explained by the differences in the populations studied. The present population had a large proportion of females, who had lower aortic PWV. Additionally, patients suitable for pulmonary rehabilitation may be fitter. Importantly we also excluded patients with cardiac disease from our previous study and the FEV1 of the subjects for rehabilitation was worse than those in Sabit et al.. Patients for this study were consecutively approached from those accepted for rehabilitation but are pre-selected in terms that they have been deemed appropriate to refer to rehabilitation in the first place and have been accepted by the team. Whereas, Sabit et al took patients with COPD who met the criteria irrespective of other considerations. Importantly, relating to the second point, the aortic PWV in controls was comparable with that of Sabits’ paper which suggests no systematic or technical error. The personnel involved in both studies had substantial experience measuring PWV in preparation and in a number of prior research projects. Further, an experienced independent operator reviewed the traces to ensure good quality readings were achieved.

6. Please explain the low proportion of male patients.
There was a lower proportion of males than females, however recruitment was undertaken on an incidental basis. Eligible individuals were recruited consecutively without bias. Slightly more females attended rehabilitation in general over the study period; but the more marked difference is likely to be accounted for less male patients meeting the criteria for entry.

7. Please provide more details on the pulmonary rehabilitation program.
As the focus of this paper was arterial stiffness, only a brief overview of the pulmonary rehabilitation programme was included. The programme and efficacy of the pulmonary rehabilitation programme at Cardiff has been established and therefore was referred to in the reference where it was documented in full with a brief summary added to this paper (Griffith et al 2000 Lancet; 355:362-368)

8. Please provide mean (SD) improvement in ISWT and SGRQ.
The overall change with rehabilitation was ISWT +83.2 (42.1) m and total SGRQ of -11.5 (13.7) units. We report on page 10 the number exceeding the MCID and present pre and post ISWT and SGRQ in the Table 3 with the p value for the paired t test performed (both p<0.001). These improvements are in agreement with the improvement seen with rehabilitation of patients with COPD during this time. We have not added in these extra figures as we felt it was adequately addressed for the purposes of this paper, focusing on the haemodynamic measures.

9. The authors expected a 15% drop in aortic PWV, while the actual decline is
about 5%. Please explain this discrepancy.

*We have added a comment, page 13, paragraph 2.*

10. Please add page numbers.

*Page Numbers added*

11. Please provide a graph with the individual data points before and after pulmonary rehabilitation for aortic PWV and systolic BP for the patients with COPD who competed the pulmonary rehabilitation.

*We presented data in this format for the BTS Winter Meeting but the feedback from members of the audience was it did not contribute to the paper as the scale for BP and PWV (and the differing starting points) did not allow presentation of the (smaller) change seen with rehabilitation well. An alternative is to present the change as a % of baseline; however, we have considered this approach and do not think it would add to the paper and in deed may detract. We would be happy to revise this if the editor felt it was needed.*

Thank you again for your consideration of this paper.

Yours sincerely,

Nichola Gale and Charlotte Bolton