Author’s response to reviews

Title: The impact of high-flow nasal cannula oxygen therapy on exercise capacity in fibrotic interstitial lung disease: a proof-of-concept randomized controlled crossover trial

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Author’s response to reviews:

Dear Dr. Robin L. Cassady-Cain

Associate Editor, BMC Pulmonary Medicine

Point-by-point response to comments on our manuscript (PULM-D-19-00193)

We greatly appreciate being given the opportunity to revise our manuscript (Manuscript number: PULM-D-19-00193, Title: The impact of high-flow nasal cannula oxygen therapy on exercise capacity in fibrotic interstitial lung disease: a proof-of-concept randomized controlled crossover trial). Below, you will find point-by-point responses to each comment. We believe the manuscript is now much improved, and we hope you find our changes acceptable.

To Reviewer 1 (Dr. Kazuma Nagata)

C1: This is quite an interesting study, but I have some major concerns as can be summarized as follows:
- small sample size and the real inclusion size is far away from the estimated sample size which was 20 in each arm
- heterogeneity of FILD; IPF, NSIP, CTD-ILD, and unclassifiable IIP

R1: Thank you for your comments.

Our sample size calculation determined that we needed eight patients per group, for a total of 16 patients. Considering an expected dropout rate of 10%, we recruited a total of 20 patients as planned. We have added a description of this.

We also appreciate your important comment on the heterogeneity of FILD. Recent clinical studies have demonstrated the similarities in genetics, pathophysiology, and clinical course between IPF and non-
IPF-FILD. Additionally, previous reports showed the reduced exercise capacity in patients with non-IPF-FILD, similar to that in patients with IPF. Considering these findings, we recruited patients with all forms of FILD. Moreover, in the present study, there were no significant differences in the baseline data between IPF and non-IPF-FILD. Based on your comments, we have added a comparison of baseline data between IPF and non-IPF-FILD in supplementary Table S1, and the following text in the Results and Discussion.

P8, L8-11: Based on previous studies, a sample size of 16 patients with randomization was required to detect a mean difference in the endurance time of 2 minutes between VM and HFNC (8 patients in each group), with a power of 80% at a two-sided alpha level of 0.05.16, 17

P12, L3-5: Between April 2016 and June 2017, 711 patients with FILD were screened for eligibility. After screening, 20 patients were enrolled and randomized for the prospective crossover trial as planned (Figure 1).

P12, L7-9: There were also no significant differences in any of the data between IPF and non-IPF-FILD cases (Supplementary Table S1).

P18, L17-18, P19, L1-5: Second, the heterogeneity of FILD needs to be considered. Recent clinical studies have demonstrated similarities in genetics, pathophysiology, and clinical course between IPF and non-IPF-FILD.35-37 Additionally, previous reports showed a reduced exercise capacity in patients with non-IPF-FILD, similar to that in patients with IPF.38-39 Considering these findings, we recruited patients with all forms of FILD.

C2: There is no comment about the duration between the baseline CWRET and the high-intensity CWRET or randomization. The duration should be addressed.

R2: Thank you for your comment. The median duration between the baseline CWRET and randomization was 2 days (interquartile range 2-7 days). We have added the following text in the Results.

P12, L12-13: The median duration between the baseline CWRET and randomization was 2 days (interquartile range 2-7 days).

C3: The authors state: "Carryover effects were considered negligible, because the washout period was sufficient." I suppose that 1-day is not sufficient to neglect carryover effect. Please clarify this point.

R3: Thank you for your comment. To minimize the potential bias and carryover effects, we used a generalized linear mixed-effects model adjusted for device, sequence, and period as fixed effects, and subject within sequence as a random effect. However, the carryover effects may still need to be considered. According to your suggestion, we have changed the description.

P19, L5-9: Third, the carryover effects may need to be considered. To minimize the potential bias and carryover effects, we used a generalized linear mixed-effects model adjusted for device, sequence, and period as fixed effects, and subject within sequence as a random effect.

C4: The authors state: "Although we compared the baseline characteristics between HFNC good responder and non-responder, no significant differences were found." It is so important to identify the differences between good responder and non-responder. Was there any differences of the response to oxygen therapy between those groups? If no, can you discuss the possible factors which make the differences?

R4: Thank you for your comment. We assume that the most appropriate settings for HFNC may be different for each patient. HFNC clearly improved endurance time and exertional dyspnea in some patients (Case 1, 11, 12, 16, 19). Subgroup analysis of endpoints in HFNC good responders also revealed that HFNC significantly extended the endurance time compared with VM (VM 6.4 [95%CI
4.5-8.3] min vs HFNC 7.8 [95%CI 5.8-9.7] min, p=0.046), while no similar effect was observed in VM good responders. There are several potential mechanisms for these beneficial effects – washout of the physiological dead space, improvement in mucosal dryness with heated and humidified oxygen, and positive airway pressure. On the other hand, HFNC was inferior to VM in a few patients (Case 6, 7, 9). Two of them complained about nasal pain, although it improved immediately. We suppose that the flow rate of 50L/min might have been too strong for them. Although the flow rate was determined with reference to previous studies, further validation studies will be required. Based on your comment, we have added the following text.

P11, L9-10: Subgroup analyses of endpoints in VM/HFNC good responders were conducted.

P13, L15-18, P14, L1-8: Among HFNC good responders (n=13), the majority were also VM good responders (n=11, 85%). In this subgroup, HFNC was superior in 6 patients, VM was superior in 1 patient, and the two were equivalent in 6 patients (superior: &gt; 100 seconds or 33 % improvement in endurance time). HFNC clearly reduced exertional dyspnea compared to VM in some patients (Case 1, 11, 12, 16, 19) (Supplementary Figure S3). Subgroup analysis of HFNC responders revealed that HFNC significantly extended the endurance time compared with VM (VM 6.4 [95%CI 4.5-8.3] min vs HFNC 7.8 [95%CI 5.8-9.7] min, p=0.046), while no similar effect was observed in the analysis of VM responders (Table 4, Supplementary Table S2). No significant differences were found in baseline characteristics between HFNC good responders and non-responders (Supplementary Table S3).

P15, L12-19, P16, L1-18, P17, L1-8: HFNC clearly improved endurance time and exertional dyspnea in a limited number of patients (Case 1, 11, 12, 16, 19). We may conjecture several potential mechanisms for these beneficial effects. First, washout of the physiological dead space may have improved patients’ work of breathing. Bräunlich et al.22 reported that HFNC decreases respiratory rate and carbon dioxide (CO2) levels in patients with IPF and COPD. A recent randomized controlled crossover trial also showed that HFNC decreases respiratory rate and CO2 levels in stable COPD patients.23 These beneficial effects may have contributed to improving exercise capacity and exertional dyspnea. Second, improvement in mucosal dryness with heated and humidified oxygen may have improved patient comfort during exercise. Chanques et al.24 reported that under-humidified high-flow oxygen therapy was associated with patients’ discomfort and mouth-throat dryness. HFNC can deliver heated and humidified oxygen, which may have led to greater comfort during exercise. Finally, positive airway pressure may have improved dynamic hyperinflation and alveolar collapse. A previous report showed that HFNC increases airway pressure as flow increases.25 In a recent clinical study, HFNC improved the tidal volume and end-expiratory lung volume compared with conventional oxygen therapy in COPD patients.13 Even though we excluded patients with concurrent airflow limitations (FEV1/FVC&lt;0.7), these effects might be associated with the improvement of oxygenation and exercise capacity. Unfortunately, we could not assess physiological variables including end-expiratory pressure and end tidal CO2. Future researches may reveal the exact mechanisms.

Conversely, we found that HFNC was inferior to VM in a few patients (Case 6, 7, 9). A recent experimental study using an airway model made with a 3D printer demonstrated that increasing the flow rate of HFNC generates higher positive end-expiratory pressure (PEEP) but does not necessarily increase the washout effects.26 In our study, two patients complained about nasal pain, although it improved immediately. We suppose that the flow rate might have been too strong for them. Although the flow rate was determined with reference to previous studies, further validation studies will be required.10-12
C5: The authors concluded that HFNC was not superior to VM for FILD, but they do not explain the possible reason of this result. HFNC has some additional effects such as positive airway pressure or wash-out effects compared to VM, which is thought to be beneficial for exercise, but the result of this study did not reflect these effects. These effects do not have the positive effects for FILD patients? Or this is just due to the limitation of this study design including sample size? Please address this point.

R5: Thank you for your comment. As mentioned above, HFNC was superior to VM in some FILD patients and it significantly extended the endurance time in the subgroup analysis. Therefore, we believe that HFNC has potential benefits for improving exercise capacity in FILD patients. Our results may be due to the small sample size and unchanged flow rate. Further appropriate settings and larger studies may reveal the benefits of HFNC. Based on your comment, we have added the following text.

P4, L1-2: HFNC did not exceed the efficacy of VM on exercise capacity in FILD, but it may be beneficial if the settings match.

P15, L3-10: Contrary to our expectations, this study did not meet the prespecified endpoints. However, the majority of patients responded well to HFNC, and the effect was superior to VM in some patients. Moreover, HFNC significantly extended the endurance time compared with VM in the subgroup analysis. Although we could not prove its efficacy due to the small sample size and unchanged settings, HFNC oxygen therapy may improve exercise capacity in FILD patients.

To Reviewer 2 (Dr. Nicole Goh)

C1: The authors state that the evidence for the use of supplemental oxygen in ILD is scarce. The authors are correct in their statement in that there is no direct evidence for the use of LTOT in ILD - evidence is gathered from COAD - and there is very little evidence for the use of ambulatory oxygen in ILD. However, there are now a number of studies supporting the use of supplemental oxygen in short bursts for field test and the authors should be stating these, as they are relevant in this context.

R1: Thank you for your comment. We fully agree with the reviewer’s comments that there are increasingly studies supporting the use of supplemental oxygen in short bursts for field test. According to your comment, we have changed the following text.

P5, L9-18, P6, L1-2: Recently, there is a growing body of evidence that the supplemental oxygen is effective in improving the exercise capacity of FILD patients. A previous double-blind, placebo-controlled, randomized crossover trial demonstrated that ambulatory oxygen did not improve exercise capacity and exertion dyspnea compared with placebo-air.6 On the other hand, a recent prospective, open-label, crossover randomized controlled trial (AmbOx) showed that supplemental oxygen improves exercise capacity and exertional dyspnea compared with placebo-air in FILD patients.7 Another randomized crossover trial also showed that supplemental oxygen provided through an oxygen conserving device improved endurance time and desaturation in FILD patients.8 Based on these findings, short-burst supplemental oxygen during exercise is becoming common practice for FILD patients.9

C2: Supplemental oxygen delivered in short bursts are generally delivered by nasal prongs and not generally via Venturi mask - could they authors please comment on this?

R2: Thank you for your comment. The VM generally has few air leaks and allows delivery of a more stable FiO2 than nasal prong. Previous researches have compared VM and HFNC to verify the effectiveness of HFNC. Considering these findings, we selected VM as a control group.

C3: Was pulmonary hypertension (PHT) accounted for?

R3: Thank you for your comment. All patients underwent echocardiography or right heart catheterization, and 12 patients were diagnosed with PH (right ventricular systolic pressure \( \geq \) 35mmHg and/or mean pulmonary artery pressure \( \geq \) 25mmHg). We have added the data in Table 1 and the following text in the Methods and Results.
We also investigated the relationship between VM/HFNC non-responders and pulmonary hypertension (PH) assessed by either echocardiography (right ventricular systolic pressure \( \geq 35\text{mmHg} \)) or right heart catheterization (mean pulmonary artery pressure \( \geq 25\text{mmHg} \)).

Echocardiography or right heart catheterization was performed in all patients, and 12 patients were diagnosed with PH (Table 1).

**C4:** Could the non-responders be patients with PHT?

**R4:** Thank you for your comment. There was no significant difference in the proportion of HFNC non-responders between patients with and without PH (PH 33% vs non-PH 38%; chi-squared test, \( p \)-value 0.848). Additionally, there was no significant difference in the proportion of VM non-responders between patients with and without PH (PH 33% vs non-PH 12%; chi-squared test, \( p \)-value 0.292). Although further studies are needed, the effects of these devices may not be necessarily affected by PH.

We have added the following text in the Results and Discussion.

There was no significant difference in the proportion of HFNC non-responders between patients with and without PH (PH 33% vs non-PH 38%; chi-squared test, \( p \)-value 0.848). Additionally, there was no significant difference in the proportion of VM non-responders between patients with and without PH (PH 33% vs non-PH 12%; chi-squared test, \( p \)-value 0.292).

**C5:** The exclusion criteria should be made clear in the text.

**R5:** Thank you for your comment. We have described the exclusion criteria in the Methods section (P7, L12-18).

**C6:** You are assuming that the difference between the 2 delivery systems is PEEP - how could you discount that there is no PEEP with your Venturi system?

**R6:** Thank you for your comment. Unfortunately, we could not assess the PEEP in the 2 delivery systems in this study. We have added the following text as a limitation.

Unfortunately, we could not assess physiological variables including end-expiratory pressure and end tidal CO2. Future researches may reveal the exact mechanisms.

**C7:** How did you choose the flow rates? The maximum flow rate for HFNC is 60L/min

**R7:** Thank you for your comment. Many previous studies have assessed the utility of HFNC at 50L/min or less. We determined the flow rate with reference to previous studies, but further validation studies may be needed. We have added the following text in the Discussion.

Although the flow rate was determined with reference to previous studies, further validation studies will be required.

**C8:** You postulated that the PEEP with HFNC might decrease physiologic dead space and flush out CO2 - did you measure end tidal C02 (capnography)? The authors have made assumptions about a few things but have not gone to any lengths to prove or disprove a theory

**R8:** Thank you for your comment. We could not measure the end tidal CO2 in this study. We have added the following text as a limitation.

Unfortunately, we could not assess physiological variables including end-expiratory pressure and end tidal CO2. Future researches may reveal the exact mechanisms.

**C9:** The discussion is merely a summary of the literature and the findings again. A more in-depth
discussion about why you think differences were not seen should be attempted. Could this be related to device or different disease (COAD vs ILD)?

R9: Thank you for your comment. We assume that the appropriate settings of HFNC may be different for each patient. HFNC clearly improved endurance time and exertional dyspnea in some patients (Case 1, 11, 12, 16, 19). We suppose there may be several potential mechanisms for these beneficial effects – washout of the physiological dead space, improvement in mucosal dryness with heated and humidified oxygen, and positive airway pressure. On the other hand, HFNC was inferior to VM in a few patients (Case 6, 7, 9). Two of them complained about nasal pain, although it improved immediately. The flow rate of 50L/min might have been too strong for them. Although the flow rate was determined with reference to previous studies, further validation studies will be required. Additionally, differences in pathophysiology between FILD and COPD might be associated with the results. Although the pathophysiology of both diseases is complex, FILD is mainly affected by restrictive impairment, while COPD is mainly affected by airflow limitation. Previous studies have demonstrated that non-invasive ventilatory support by continuous positive airway pressure (CPAP) and pressure support ventilation (PSV) improves exercise performance and exertional dyspnea in COPD patients. On the other hand, Moderno et al. showed that CPAP did not improve exercise performance compared with proportional assist ventilation (PAV) in IPF patients. Considering these findings, decrease in the work of breathing may be more important than increase in PEEP for improving exercise capacity in FILD patients. More appropriate settings to decrease the work of breathing may improve the exercise performance of HFNC non-responders. Based on your comment, we have added the following text.

P11, L9-10: Subgroup analyses of endpoints in VM/HFNC good responders were conducted.

P15, L12-18, P16, L1-18, P17, L1-18, P18, L1-5: HFNC clearly improved endurance time and exertional dyspnea in a limited number of patients (Case 1, 11, 12, 16, 19). We may conjecture several potential mechanisms for these beneficial effects. First, washout of the physiological dead space may have improved patients’ work of breathing. Bräunlich et al.22 reported that HFNC decreases respiratory rate and carbon dioxide (CO2) levels in patients with IPF and COPD. A recent randomized controlled crossover trial also showed that HFNC decreases respiratory rate and CO2 levels in stable COPD patients.23 These beneficial effects may have contributed to improving exercise capacity and exertional dyspnea. Second, improvement in mucosal dryness with heated and humidified oxygen may have improved patient comfort during exercise. Chanques et al.24 reported that under-humidified high-flow oxygen therapy was associated with patients’ discomfort and mouth-throat dryness. HFNC can deliver heated and humidified oxygen, which may have led to greater comfort during exercise. Finally, positive airway pressure may have improved dynamic hyperinflation and alveolar collapse. A previous report showed that HFNC increases airway pressure as flow increases.25 In a recent clinical study, HFNC improved the tidal volume and end-expiratory lung volume compared with conventional oxygen therapy in COPD patients.13 Even though we excluded patients with concurrent airflow limitations (FEV1/FVC<0.7), these effects might be associated with the improvement of oxygenation and exercise capacity. Unfortunately, we could not assess physiological variables including end-expiratory pressure and end tidal CO2. Future researches may reveal the exact mechanisms.

Conversely, we found that HFNC was inferior to VM in a few patients (Case 6, 7, 9). A recent experimental study using an airway model made with a 3D printer demonstrated that increasing the flow rate of HFNC generates higher positive end-expiratory pressure (PEEP) but does not necessarily increase the washout effects.26 In our study, two patients complained about nasal pain, although it improved immediately. We suppose that the flow rate of 50L/min might have been too strong for them.
Although the flow rate was determined with reference to previous studies, further validation studies will be required.10-12

Differences in pathophysiology between FILD and COPD should be considered. Although the pathophysiology of both diseases is complex, FILD is mainly affected by restrictive impairment, while COPD is mainly affected by airflow limitation. Previous studies have demonstrated that non-invasive ventilatory support by continuous positive airway pressure (CPAP) and pressure support ventilation (PSV) improves exercise performance and exertional dyspnea in COPD patients.27, 28 On the other hand, Moderno et al.29 showed that CPAP did not improve exercise performance compared with proportional assist ventilation (PAV) in IPF patients. Considering these findings, a decrease in the work of breathing may be more important than an increase in PEEP in improving the exercise capacity in FILD patients. Our study included 35% of HFNC non-responders. The most appropriate individual settings to decrease work of breathing may improve their exercise performance.

C10: You mentioned that one test for done on the first day and the second one on the second day - were these consecutive days? This should be made clearer

R10: Thank you for your comment. These tests were performed on two consecutive days. We have added the following text.

P9, L12-16: In group A, a high-intensity CWRET using VM was performed on the first day, and a test using HFNC was performed on the following day. In group B, a high-intensity CWRET using HFNC was performed on the first day, and a test using VM was performed on the following day.

C11: You stated that HFNC did not exceed the efficacy of VM in endurance time (HFNC: 6.8 ± 4.7min vs VM: 7.6 ± 6.3min). What was the p value?

R11: Thank you for your comment. As shown in Table 2, the p-value was 0.669. We have added the p-value in the Abstract and Results.

P3, L18-20: There was no significant difference in endurance time between HFNC and VM (HFNC 6.8 [95% CI 4.3-9.3] min vs VM 7.6 [95% CI 5.0-10.1] min, p=0.669).

P12, L16-18: HFNC did not exceed the efficacy of VM in endurance time (HFNC 6.8 [95% confidence interval (CI) 4.3-9.3] min vs VM 7.6 [95% CI 5.0-10.1] min, p=0.669).

C12: I acknowledge that your numbers are small, but did you analyze the results of just the responders only?

R12: Thank you for your valuable comment. We performed subgroup analyses in HFNC good responders. Among HFNC good responders (n=13), the majority of them (n=11, 85%) were also VM good responders. When we compared HFNC and VM directly in this group, we found that HFNC was superior in 6 patients, VM was superior in 1 patient, and the two were equivalent in 6 patients (superior: ≥ 100 seconds or 33% improvement in endurance time). Subgroup analysis of endpoints in HFNC good responders revealed that HFNC significantly extended the endurance time compared with VM (VM 6.4 [95%CI 4.5-8.3] min vs HFNC 7.8 [95%CI 5.8-9.7] min, p=0.046), while no similar effect was observed in VM good responders. These results may indicate that HFNC oxygen therapy can improve exercise capacity when the settings are appropriate. According to your suggestion, we have added the Table 4, Supplementary Table S2, and the following text in the Methods, Results, and Discussion.
Subgroup analyses of endpoints in VM/HFNC responders were conducted. Among HFNC good responders (n=13), the majority were also VM good responders (n=11, 85%). In this subgroup, HFNC was superior in 6 patients, VM was superior in 1 patient, and the two were equivalent in 6 patients (superior: &gt; 100 seconds or 33 % improvement in endurance time). HFNC clearly reduced exertional dyspnea compared to VM in some patients (Case1, 11, 12, 16, 19) (Supplementary Figure S3). Subgroup analysis of HFNC responders revealed that HFNC significantly extended the endurance time compared with VM (VM 6.4 [95%CI 4.5-8.3] min vs HFNC 7.8 [95%CI 5.8-9.7] min, p=0.046), while no similar effect was observed in the analysis of VM responders (Table 4, Supplementary Table S2). No significant differences were found in baseline characteristics between HFNC good responders and non-responders (Supplementary Table S3).

Moreover, HFNC significantly extended the endurance time compared with VM in the subgroup analysis.

I don't think the findings that both HFNC and VM are better than baseline are surprising given what we know already about the benefits of short bursts oxygen in field tests.

Thank you for your comment. We fully agree with the reviewer’s comment. We have added the following text in the Discussion.

In the present study, both VM and HFNC significantly improved oxygenation and exertion dyspnea compared with the baseline test. There was no significant difference in the proportion of responders between patients with and without PH. Our findings emphasize the importance of supplemental oxygen for improving exercise capacity in FILD patients.

Thank you again for your comments on our paper. If any parts are still insufficiently clear, please let us know. We will revise the manuscript further.

Sincerely yours,
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