Novel drinkable oxygen nanobubbles: A pilot randomised, double-blind, cross-over trial on Pulmonary Fibrosis patients

Mihir Sheth,
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford;
mihir.sheth@ndorms.ox.ac.uk
Peter Saunders,
Respiratory Medicine, Oxford University Hospital;
peter.saunders@ouh.nhs.uk
Nikolaos I. Kanellakis,
Chinese Academy of Medical Sciences Oxford Institute, University of Oxford;
nikolaos.kanellakis@ndm.ox.ac.uk
Christopher Turnbull,
Respiratory Medicine, Oxford University Hospital;
Nuffield Department of Medicine, University of Oxford;
christopher.turnbull@ouh.nhs.uk
Nick P Talbot,
Department of Physiology, Anatomy and Genetics, University of Oxford;
Respiratory Medicine, Oxford University Hospital;
nick.talbot@dpag.ox.ac.uk
Ashok Handa,
Nuffield Department of Surgical Sciences, University of Oxford;
ashok.handa@nds.ox.ac.uk
Eleanor Stride,
Department of Engineering Science, University of Oxford;
eleanor.stride@eng.ox.ac.uk
Najib M Rahman,
(Corresponding Author)
Respiratory Medicine, Oxford University Hospital;
Nuffield Department of Medicine, University of Oxford;
najib.rahman@ndm.ox.ac.uk

Conflict of Interest:
Eleanor Stride is a co-inventor on a patent (Stride, E., Averre, R., Owen, J. (2015) Nanoencapsulated Oxygen. UK Patent Application No. 1512728.5), which has been filed in relation to one of the formulations described in the paper and licensed to Avrox Technologies Ltd. Avrox Technologies Ltd., however, did not fund this work or play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. All other authors have no completing interest to declare.

Funding:
The authors also gratefully acknowledge the support of Gilberto Sayao da Silva whose donation to the University funded Mihir Sheth's salary. This work was also supported by the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Science (CIFMS), China (grant number: 2024-I2M-2- 001-1)

Contributor Statement:
Mihir Sheth: Conception, Data curation, Investigation, Project Administration, Original Draft Preparation.
Peter Saunders: Investigation, Methodology
Nikolaos Kanellakis: Conception, Investigation, Review and Editing
Christopher Turnbull: Formal Analysis, Review and editing
Nicholas Talbot: Methodology, Review and Editing
Ashok Handa: Conception, Methodology, Review and Editing
Eleanor Stride: Funding Acquisition, Conception, Methodology, Review and Editing
Najib Rahman: Conception, Methodology, Review and Editing
NR acted as guarantor

Abstract:
20% of UK adults suffer from chronic respiratory diseases, resulting in reduced oxygen absorption from the air, and subsequently in reduced oxygen delivery to tissues. Orally delivered oxygen nanobubbles (ONB) are a novel therapy of lipid-coated nanobubbles filled with oxygen that can deliver oxygen to the blood via the gastrointestinal tract, improving oxygen delivery to tissues.

A pilot randomised, cross-over, double-blind, placebo-controlled clinical study was conducted with pulmonary fibrosis patients completing 6 Minute Walk Tests (6MWTs) to investigate whether orally delivered ONB could improve exercise performance.

Twenty-eight patients were enrolled and 27 completed the study. The drink was safe and well tolerated, with no adverse events reported by any patient. Drinking ONB resulted in participants walking 9.3m (0.8-17.8m; $p<0.05$) less compared to placebo. No differences in change in heart rate, oxygen saturations, or breathlessness were seen after the 6MWT between the 2 drinks. A subgroup analysis showed that drinking ONB first resulted in an increase in the second 6MWT (2 hours later), which was not seen with participants that drank the placebo first. Further studies are needed to investigate the clinical usefulness of ONB.

Summary:

- An oral formulation of oxygen nanobubbles has been developed with the aim of enhancing oxygen delivery in patients with chronic respiratory disease.
- Previous studies in healthy volunteers indicate that the nanobubbles may have a beneficial effect upon exercise capacity.
- A pilot randomised crossover, double-blind, study was conducted on 27 patients with Pulmonary Fibrosis (PF) to determine if there was any impact on the outcome of a 6 Minute Walk Test – a sub-maximal clinical test used as an indicator of day-to-day exercise ability.
- The results suggest that the nanobubbles are safe, well tolerated and but there was no clinically significant impact on exercise capacity in PF patients, which differs from results in healthy volunteers and further investigation is required to fully elucidate the mechanism(s) of action.
- There is a need to understand the mechanism of action in both healthy volunteers to determine how the nanobubbles can improve the lives of patients, as this could potentially improve patient's lives during and after pulmonary rehabilitation.

Introduction

Approximately 1 in 5 adults (12.7 million) in the UK have chronic respiratory illnesses[1], including interstitial lung diseases such as pulmonary fibrosis (PF)[2]. PF impairs gas exchange in the lung by reducing the rate of diffusion of gas across the blood-gas barrier resulting in ventilation-perfusion mismatch[3,4]. This causes exertional desaturation thus limiting daily activities, increased breathlessness, and impaired quality of life[5,6].

It has been shown that exercise training improves exercise tolerance and health-related quality of life[7], however, there is a 70-150 day wait time for pulmonary rehabilitation in the UK and not all patients are considered suitable. Supplemental oxygen for PF patients[8] has been shown to increase arterial oxygen saturation[9], decrease pulmonary ventilation[10], lower submaximal heart rate and blood lactate concentration[11], and increase maximal oxygen uptake[12]. Visca *et. al* showed that supplemental oxygen provides significant improvement in quality of life, particularly in breathlessness and chest symptoms, but not in psychological scores[13] and this is likely due to the feeling of being "tethered" to the heavy, unwieldy oxygen cylinders limiting patients' ability and willingness to leave home[14,15]. There is thus a need to provide oxygen to these patients in a way that improves their exercise performance and the ability to move freely.

Orally administered oxygen nanobubbles (ONB) made from lecithin have been shown to improve oxygen levels in hypoxic tumours in mice[16,17] and to improve exercise performance in healthy humans within 10 minutes[18]. The mechanism of action is not fully understood, but it is thought that ONB diffuse through the stomach tissue and accelerate oxygen uptake to tissues either through increasing oxygen carrying capacity of blood and/or fusing with the cells[16,19], therefore potentially delivering oxygen in a manner that is not impacted by V/Q mismatching found in PF.

The aim of this study was to investigate whether ONB could be used similarly to improve exercise capacity in PF patients using the 6 Minute Walk Test (6MWT), a clinically validated measure of exercise ability. The study was designed as a pilot cross-over trial to investigate the effect of orally administered ONB on the 6MWT within 10 minutes of consumption.

Methods

Design

The trial was an *in vivo* double-blind, randomised, placebo-controlled, 2 period cross-over study. Patients were randomly assigned to consume either ONB or a placebo drink (PLA) in period one, followed by the other drink in period two. Tests for each participant were completed over a single day. The timeline of the trial was as follows (Figure 1), randomisation (30 mins), consume drink one (10 mins), first 6MWT (10 mins), rest (2 hours), consume drink two (10 mins), second 6MWT (10 mins).

Ethics

The study protocol was approved by the Berkshire Research Ethics Committee (Ref: 22/SC/0360), conducted in accordance with the Declaration of Helsinki and was prospectively registered (NCT05711290). All participating subjects provided written informed consent.

Patient and Public Involvement
All participants took part in a qualitative interview to understand the impact of Pulmonary Fibrosis and what interventions would be valuable to them to inform future study development.

Patient Group
Participants were included if they were older than 18 years, had Progressive Pulmonary Fibrosis (per ATS/ERS guidelines[20,21]), and were able to walk independently without a walking aid. Exclusions were a transfer capacity of the lung (TLCO) <30%, unstable ischaemic heart disease or pulmonary hypertension, or allergy to any of the ONB drink ingredients.

Intervention
The ONB drink was formulated as detailed in Owen *et. al*[16] from glycyrrhizin, lecithin, citric acid, and glycerol. The PLA drink contained the same ingredients in the same ratio, except for the lecithin which is required to create nanobubbles. Each formulation was packed into identical sachets labelled B101 or B102. Prior to the 6MWT, each sachet was mixed with 200ml of bottled water, shaken vigorously for 30s, and then oxygenated by sparging with oxygen gas at 1L/min for 3 minutes. Participants waited for 10 minutes after consuming the drink, and then completed a 6MWT. These nanobubbles have a size of 260 ± 70 nm and a concentration of $1.90 \pm 0.22 \times 10^{12}$ bubbles/ml[19]. This size distribution and the concentration can be used to calculate the volume of gas enclosed which show that bubbles encapsulate 3-6ml of Oxygen in a 200ml drink.

Randomisation and Blinding
The drinks were prepared and assigned an identification designation by a team member not involved in the study visits or outcome assessments. Each drink was served in a 330ml water bottle in a black sleeve to maintain blinding. The researchers, clinicians, statistician, and patients were all blinded to the drink allocation until the full final analysis was complete.

Outcomes
The primary outcome was the 6 Minute Walk Distance (6MWD). The 6MWT was carried out as per ATS/ERS guidelines[22]. The secondary outcomes were change in Heart Rate (ΔHR), change in Oxygen Saturations (ΔSpO_2), and change in breathlessness measured by the mBORG scale calculated as the difference between post-6MWT measurement and pre-6MWT (or resting) measurement. A follow up call the next day kept a track of any adverse events the patients may experience.

Statistical Analysis Plan
The sample size was determined by using a minimum clinically important difference of 30m[23], a within-subject SD of 34m on the 6MWT[24], 5% significance and power of 0.9. Using these assumptions, a total of 26 participants were required in a cross-over randomised trial.

Data were analysed on a per protocol basis, only including subjects who completed both 6MWT with both drinks (ONB and placebo). Mixed effect models were used to assess the effect of ONB compared to placebo on each outcome. These models included the outcome

as the dependent variable, and the participant as a random effect, and were adjusted for age, sex, FVC, TLCO, baseline saturations, and coexistent heart disease diagnosis. A post-hoc adjustment for measurement order was also included in the model.

Results

Patient recruitment and timelines

306 patients were screened from the start of the trial in March 2023 to the completion in August 2023, from which 28 patients met the inclusion criteria for the study and gave consent. 14 participants were each randomised into ONB-PLA and PLA-ONB arms. 27 participants completed the study. One participant from the PLA-ONB arm withdrew from the study due to an inability to complete two 6MWT in a day. All follow up was completed by August 2023. Figure 1A provides the CONSORT diagram that shows participant recruitment.

Baseline characteristics

The median (first quartile, third quartile) age was 78 years (72, 80), the mean ± standard deviation Body Mass Index was 28.0±4.0 kg/m^2, and 21 (75%) were male. 17 (61%) were ex-smokers with median smoking history of 22.5 pack-years (5.3, 34.3). The patients' last available pulmonary function test showed a mean FEV1 of 91.3±17.3%, FVC of 86.6±18.0%, and TLCO 57.4±16.0% predicted. Twenty-seven participants completed both walks and were included in the analysis. Participant characteristics can be found in Supplementary Table 1.

Primary Outcome

Participants had a mean 6MWD of 392 ± 91m after ingesting ONB, and a mean 6MWD of 401 ± 94m after ingesting PLA (Figure 2A). For all participants, the mean 6MWD after ingesting the first drink was 390 ± 87m, and after consuming the second drink was 404 ± 99m (Figure 2B). For the ONB-PLA arm (n=14), the 6MWD after ingesting ONB and PLA was 392 ± 88m, and 415 ± 102m respectively. For the PLA-ONB arm (n=13), the 6MWD after ingesting ONB and PLA was 392 ± 99m, and 388 ± 89m respectively.

The mean intra-patient difference in the 6MWD (6MWD (ONB) – 6MWD(PLA)) for the ONB-PLA and PLA-ONB arms were -22.5 ± 23m and 4.62 ± 18m, respectively suggesting an order effect (Figure 2C).Welch's unpaired t-test of the change in 6MWD between the ONB-PLA arm and the PLA-ONB arm, showed a difference between the means of -27 ± 8m (p=0.0028). The measurement order was considered in the mixed effect model analysis.

In the mixed effect model, the effect of ONB was a 9.3m (0.8-17.8m; p=0.03) reduction in 6MWD compared to PLA and the effect of 6MWT measurement order was a 13.6m (5.2-22m; p=0.003) improvement in the second 6MWT compared to the first. All results and outcomes can be seen in Supplementary Table 2.

Secondary Outcome

After completing the 6MWT, compared to resting values, the median SpO_2 decreased with both drinks (5.6 ± 7.3% for ONB and 6.9 ± 5.6% for PLA) the mean heart rate increased with both drinks (20.7 ± 17.2bpm for ONB and 24.9 ± 14.9bpm for PLA) and the median breathlessness increased on the mBORG scale (1.8 ± 1.3 points for ONB and 1.7 ± 1.4 points for PLA). There were no statistically significant differences in the change in SpO_2, HR, or breathlessness after the 6MWT between the two arms(Supplementary Table 2).

In the mixed effect model, the effect of ONB compared to PLA was a reduction of 1.3% (-1.8 – 4.4%; p=0.39) in ΔSpO_2, a reduction of 4.2bpm (-11.7 to 3.3bpm; p=0.26) in ΔHR, and an increase of 0.1 points (-0.4 to 0.7 points; p=0.63) in breathlessness on the mBORG scale.

On follow-up calls, none of the participants reported any adverse effects from the drinks.

Discussion (Reflections and Limitations)

In contrast to previous findings in healthy volunteers, the primary hypothesis, that orally administered ONB can improve exercise performance within 10 minutes of drinking in patients with PF, was not supported. It was shown to be safe, and well tolerated within this patient population. This study was completed in less than 6 months, showcasing the desire of patients to participate in studies testing a novel, easy-to-use intervention and the feasibility of larger studies.

A possible explanation is that the ONB had a slight detrimental effect to the participant's exercise ability. Due to the limitations of the cross-over study with no baseline measurement there is possible confoundment of the learning effect, a delayed effect, or even a positive impact of the PLA to the participant's exercise ability. Future studies should consider a conventional comparative randomised controlled trial, using placebo and portable oxygen as comparators with more physiological measurements and a baseline assessment to assess the impact.

It is possible that the time-to-effect and the washout period were underestimated for PF patients. Based on prior studies in athletes and considering patient comfort, it was estimated that the time-to-effect would be ~10 minutes, and a washout period of 2 hours sufficient. Further analysis, however, suggests these may have been a substantial underestimate. Athletes can have a higher basal metabolism rate (BMR) than untrained individuals for their body size and body[25], and whilst patients with PF will have a slightly higher BMR, it is still likely to be less than that of a young athlete of the same height and weight[26]. The medications taken by IPF patients also affect the GI tract (most notably causing nausea/vomiting or diarrhoea) and the lack of warm-up exercises could also affect the rate of absorption from the GI system. Furthermore, we did not conduct an Arterial Blood Gas on the patients, as we felt it would be too burdensome and invasive for the patients, which would have limited the feasibility of this pilot study.

Sub-group analysis showed that participants in the ONB-PLA arm walked 22.5m further in the second 6MWT, while the PLA-ONB participants walked 4.6m further in the second 6MWT. This could be explained by either a learning effect (a previous study reported mean learning effect to be 21m[27]), or a delayed effect of the ONB due to slower absorption and action of ONB from the GI tract in PF patients Further studies should be designed to account for the delay and differentiate between learning effect and the impact of the ONB.

A further possibility is that the nanobubbles remain in the blood, improving oxygen delivery to tissue over time. A study by Zierenberg and Grundy showed the half-life of elimination of lecithin in humans to be 31-65 hours. The absorption reached its peak in <12 hours[28]. Initially the mechanism of action was hypothesized to be that the ONB would increase the

oxygen carrying capacity of blood through continuous oxygenation and reoxygenation of the nanobubbles. Earlier experiments in a flow loop [16] have shown that ONB have a pO2 of 72kPa while oxygenated water has a pO2 of 58kPa. From the oxygen saturation curve[29], in the 80-90% SpO2 range that was seen in participants here, a change of 1 kPa of partial pressure of O2 in blood, results in a 1-2% change in SpO2. Thus, even if 10% of oxygen nanobubbles moved from the GI tract to the blood, they could produce a measurable change in oxygen carrying capacity in the blood. This could explain why in prior studies a significant impact was seen in power, while the amount of oxygen delivered was miniscule. This study's findings give rise to an alternate hypothesis that the nanobubbles may instead be quickening the transfer of oxygen between the tissue and the red blood cells as the solubility of oxygen in the gas pocket of nanobubbles and in the hydrophobic core of lecithin is much better than in water. [30] Further studies in lab and in clinic should try to ascertain the mechanisms of action to better understand the impact on humans.

A crossover design was chosen to minimize the risk of inter-patient variation, provide greater statistical strength and reduce the number of participants required. In addition, some of the known disadvantages of the crossover design (e.g. larger dropout rate, and instability of the patient's condition) were mitigated in this study as both tests occurred on the same day. This also provided the additional benefit of controlling for other factors such as diet, liquid consumption, day-to-day variability and co-morbidities.

Most of the recruited participants had mild-moderate PF (with mean FVC of 86%, and TLCO of 57%), for whom adequate oxygen is being perfused for sub-maximal exertion, and thus may not see a noticeable immediate benefit from the ONB. If so, a greater impact of ONB on exercise capacity may be seen in patients with more severe exercise-related hypoxaemia than those in the current cohort. Many of the participants had mobility restrictions due to pain in legs or osteoarthritis. This potentially impacted changes in 6MWD, limiting their ability to walk further regardless of the effect of ONB. Care must be taken in future studies and additional methods of measuring oxygen consumption such as arterial blood gas and/or lactate should be evaluated alongside the 6MWD.

Conclusions

The results of this pilot study did not support the hypothesis that ONB improves 6MWD in PF patients 10 minutes after consumption. This study showed that ONB are safe and well tolerated in the target population and demonstrates the feasibility of larger studies. Analysis of the data suggests this may have been due to insufficient time being allowed between consumption and the test and/or for clearance. Further studies are recommended to test the effect of the drink across a few days with more baseline physiological measurements, and further investigation should be conducted to better understand the uptake kinetics and dose-response relationship of ONB in PF patients.

References

1. Strachan D. Lung disease in the UK – big picture statistics | British Lung Foundation [Internet]. 2016. Available from: https://statistics.blf.org.uk/lung-disease-uk-big-picture

2. Rajan SK, Cottin V, Dhar R, Danoff S, Flaherty KR, Brown KK, et al. Progressive pulmonary fibrosis: an expert group consensus statement. Eur Respir J [Internet]. 2023 Mar;61(3). Available from: https://erj.ersjournals.com/content/61/3/2103187 https://erj.ersjournals.com/content/61/3/2103187.abstract

3. Strickland NH, Hughes JMB, Hart DA, Myers MJ, Lavendar JP. Cause of regional ventilation-perfusion mismatching in patients with idiopathic pulmonary fibrosis: a combined CT and scintigraphic study. Am J Roentgenol. 1993 May 27;161(4):719–25.

4. Plantier L, Cazes A, Dinh-Xuan AT, Bancal C, Marchand-Adam S, Crestani B. Physiology of the lung in idiopathic pulmonary fibrosis. Eur Respir Rev [Internet]. 2018 Jan 24 [cited 2025 July 1];27(147). Available from: https://publications.ersnet.org/content/errev/27/147/170062

5. Walterspacher S, Schlager D, Walker DJ, Müller-Quernheim J, Windisch W, Kabitz HJ. Respiratory muscle function in interstitial lung disease. Eur Respir J. 2013 July;42(1):211–9.

6. Marciniuk DD, Watts RE, Gallagher CG. Dead Space Loading and Exercise Limitation in Patients With Interstitial Lung Disease. Chest. 1994 Jan;105(1):183–9.

7. Dowman LM, Mcdonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Available from: http://thorax.bmj.com/

8. O'Driscoll RB, Howard L, Earis J, Mak V, Bajwah S, Beasley R, et al. BTS Guideline for oxygen use in adults in healthcare and emergency settings. Thorax. 2017;72(Supplement 1):i1–90.

9. Bannister RG, Cunningham DJC. THE EFFECTS ON THE RESPIRATION AND PERFORMANCE DURING EXERCISE OF ADDING OXYGEN TO THE INSPIRED AIR. Vol. 25, J. Physiol. (I954). 1954. p. 8–37.

10. ASMUSSEN E, NIELSEN M. Studies on the Regulation of Respiration in Heavy Work. Acta Physiol Scand. 1946;12(2–3):171–88.

11. Ekblom B, Huot R, Stein EM, Thorstensson AT. Effect of changes in arterial oxygen content on circulation and physical performance. https://doi.org/101152/jappl197539171. 1975;39(1):71–5.

12. Welch H. Hyperoxia and human performance: a brief review. Med Sci Sports Exerc. 1982;14(4):253–62.

13. Visca D, Mori L, Tsipouri V, Fleming S, Firouzi A, Bonini M, et al. Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx): a prospective, open-label, mixed-method, crossover randomised controlled trial. Lancet Respir Med. 2018 Oct;6(10):759–70.

14. Wacker ME, Jörres RA, Karch A, Wilke S, Heinrich J, Karrasch S, et al. Assessing health-related quality of life in COPD: Comparing generic and disease-specific instruments with focus on comorbidities. BMC Pulm Med. 2016 May;16(1):1–11.

15. Graney BA, Wamboldt FS, Baird S, Churney T, Fier K, Korn M, et al. Informal caregivers experience of supplemental oxygen in pulmonary fibrosis. Health Qual Life Outcomes. 2017 July;15(1):1–6.

16. Owen J, McEwan C, Nesbitt H, Bovornchutichai P, Averre R, Borden M, et al. Reducing Tumour Hypoxia via Oral Administration of Oxygen Nanobubbles. PLOS ONE. 2016 Dec;11(12):e0168088.

17. Owen J, Logan K, Nesbitt H, Able S, Vasilyeva A, Bluemke E, et al. Orally administered oxygen nanobubbles enhance tumor response to sonodynamic therapy. Nano Sel. 2022 Feb;3(2):394–401.

18. King DG, Stride E, Mendis J, Gurton WH, Macrae H, Jones L, et al. A Double-Blind, Randomized, Placebo-Controlled Pilot Study examining an Oxygen Nanobubble Beverage for 16.1-km Time Trial and Repeated Sprint Cycling Performance. J Diet Suppl. 2024;21(2):167–81.

19. Knowles HJ, Vasilyeva A, Sheth M, Pattinson O, May J, Rumney R, et al. Use of oxygen-loaded nanobubbles to improve tissue oxygenation: Bone-relevant mechanisms of action and effects on osteoclast differentiation. Biomaterials. 2023 Dec;122448.

20. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Antoniou KM, Bissell BD, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Httpsdoiorg101164rccm202202-0399ST. 2022 Apr;205(9):E18–47.

21. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. AMERICAN THORACIC SOCIETY DOCUMENTS Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Jpn Respir Soc [Internet]. 2018; Available from: http://www.atsjournals.org/doi/suppl/10.1164/rccm.201807-1255ST.

22. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS Statement: Guidelines for the Six-Minute Walk Test. https://doi.org/101164/ajrccm1661.at1102. 2012 Dec;166(1):111–7.

23. Nathan SD, Bois RMD, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Validation of test performance characteristics and minimal

clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med. 2015 July;109(7):914–22.

24. Ross RM, Murthy JN, Wollak ID, Jackson AS. The six minute walk test accurately estimates mean peak oxygen uptake. BMC Pulm Med. 2010;10:31.

25. Sjödin AM, Forslund AH, Westerterp KR, Andersson AB, Forslund JM, Hambræus LM. The influence of physical activity on BMR. Med Sci Sports Exerc. 1996;28(1):85–91.

26. Fitting JW, Frascarolo P, Jequier E, Leuenberger P. Resting energy expenditure in interstitial lung disease. Am Rev Respir Dis. 1990;142(3):631–5.

27. Holland AE, Hill CJ, Dowman L, Glaspole I, Goh N, Lee AL, et al. Short- and Long-Term Reliability of the 6-Minute Walk Test in People With Idiopathic Pulmonary Fibrosis. Respir Care. 2018 Aug;63(8):994–1001.

28. Zierenberg O, Grundy SM. Intestinal absorption of polyenephosphatidylcholine in man. J Lipid Res. 1982;23:1136–42.

29. Siggaard-Andersen O, Wimberley PD, Göthgen I, Siggaard-Andersen M. A mathematical model of the hemoglobin-oxygen dissociation curve of human blood and of the oxygen partial pressure as a function of temperature. Clin Chem. 1984 Oct;30(10):1646–51.

30. Kimmich R, Peters A, Spohn KH. Solubility of oxygen in lecithin bilayers and other hydrocarbon lamellae as a probe for free volume and transport properties. J Membr Sci. 1981 Jan;9(3):313–36.

Figure Legends:

Figure 1: (A) CONSORT diagram for recruitment and completion of participants in the study. (B) Flow of the study for participants screened and consented.

*Figure 2: (A) Comparison of 6-Minute Walk Distance(6MWD) after consumption of either placebo (PLA) (*401 ± 94m*) or oxygen nanobubbles (ONB) (*392 ± 91m*). (B) The 6MWD after the first walk (*390 ± 87m*), and the second walk (*404 ± 99m*), irrespective of the drink. (C) Post-hoc analysis showing the change in in the 6MWD for participants in each arm, showing a significant potential delayed effect for ONB.*