Short Communication

Exercise tolerance in patients with idiopathic pulmonary fibrosis, effect of supplemental oxygen.

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Summary

Exercise tolerance in patients with idiopathic pulmonary fibrosis IPF is mainly limited by mechanical constrain of ventilation and high physiologic dead space. Oxygen enriched gas inhalation seems to increase ventilatory efficiency by reduction of dead space to tidal volume ratio (V_D/V_T) which probably mirrors improved pulmonary capillary flow and leads to longer physical tolerance at lower level of minute ventilation. The effect is noticeable at F_IO_2 that can be delivered in rehabilitation purposes or daily living activities.

Exertional dyspnea with limitations of ordinary tasks are among the early symptoms of patients with idiopathic pulmonary fibrosis (IPF)[1]. The majority of works published on this topic explains the patients' shortness of breath as a result of the decrease of lung compliance, leading to mechanical limitation of ventilation and increased energy expenditure of respiratory muscles[2,3]. With the exemption of early stages of IPF, physical activity is also accompanied by blood oxygen desaturation that is attributed to a shorter contact time between erythrocytes and alveoli wall during the increased cardiac output and the decrease of mixed venous oxygen content (C_vO_2). It has been assumed that an increase of venous admixture in systemic circulation further impedes the perception of dyspnea via hypoxic stimulation of the respiratory center[4]. Tissue hypoxia also adds to the decrease of anaerobic threshold and leads to further increase in ventilatory demand of physical activity. From a clinical perspective, blood oxygen saturation levels are considered an important parameter because its decrease during resistance testing serves as a predictive parameter of survival in patients with IPF[5]. Outpatient oxygen therapy has, therefore, been suggested as a means of improving physical activity tolerance and quality of life in patients with significant resistance desaturation[6,7]. However, the results of past studies have not been uniformly conclusive as oxygen inhalation neither improves physical strain tolerance in most cases, nor does it alleviate the sensation of dyspnea[8,9].

Only in recent years has the etiology of dyspnea granted attention to the effectiveness of ventilation, most commonly assessed by the slope of minute ventilation to CO_2 output ratio (V_E/VCO_2 slope), parameter originally derived from gas exchange measurement during cardiopulmonary exercise test (CPET). First mentions of an increase in physiological dead space (V_D) in IPF patients were published in the context of secondary pulmonary arterial hypertension (PAH)[10]. With the increase of the V_E/VCO_2 slope, the decrease of partial CO_2 pressure at the end of exhalation ($p_{ET}CO_2$), and pulmonary transfer factor for CO (TL_{CO}) a higher probability of secondary PAH occurrence was described. The main aim of this study was to determine the key mechanisms responsible for limitations to physical activity of patients with IPF and whether oxygen inhalation during physical strain leads to improved performance or a decrease in ventilatory demand of motion. The secondary aim was to assess a possible role of secondary pulmonary hypertension on ventilatory efficiency.

Ten patients with IPF diagnosed based on ATS/ERS criteria, who had shown a decrease in blood-oxygen saturation during a recent cardiopulmonary exercise test (CPET) were chosen to participate in this study. All study procedures were performed according to the Declaration of Helsinki, revised form of 2013. This research project has been approved by the hospital Ethics Committee and all patients signed informed consent in order to participate.

Patients (3 women, 7 men, aged 57-71 years, BMI 28.9 ± 5.3) with advanced disease (slow vital capacity (SVC) 65.9 ± 13.6% predicted, TL_{CO} 43.5 ± 13.2% predicted) underwent a

CPET with continuous assessments of oxygen (O_2), and carbon dioxide (CO_2), and airflow (Ergostik, Geratherm, Bad Kissingen, Germany), with and without oxygen application, during various days and in random order. All patients underwent a ramp protocol 10-15W/min to reach their peak performance within 8-12 minutes[11]. In the duration of both tests, arterial blood was drawn in two-minute intervals by means of indwelling catheter in the left radial artery. Gas mixture was delivered from a central oxygen unit using a Bird gas blender set on 0.35 F_IO_2 or compressed air outlet, via plastic pouch with two one-way valves, one for inhalation and the second for overflow. The gas mixture was brought to the inhalation port of a Y piece connected to a face mask. Accuracy of F_IO_2 was continuously controlled using a parallel sensor of the ergometric system. Right heart catheterization was done three hours following a second resistance test in the supine position according to Seldinger method via vena jugularis interna. Resting heart and pulmonary arterial pressures were measured using calibrated pressure sensors. All data, expressed as mean ± standard deviation (SD), were tested for normality of distribution by the Kolmogorov-Smirnov test, possible relations were tested using Pearson correlation coefficient, comparisons were made by paired t-test using GraphPad Prism 4.0 (San Diego, CA, USA), $p < 0,05$ were considered significant.

Exercise tolerance during air inhalation ($F_IO_2 = 0.21$) was moderately decreased (the peak oxygen consumption (pVO_2) 62.0 ± 18.3% predicted, Watt 61.8 ± 26.1% predicted) with significantly decreased ventilation effectiveness (V_E/VCO_2 slope 44.4 ± 14.2) and depended namely on mechanical limitation of ventilation (V_T/SVC, $r = 0.6771$, $p < 0.05$) and ventilation effectiveness (V_E/VCO_2, $r = -0.7195$, $p < 0.01$). Desaturation severity did not correlate with strain tolerance. Resting mean pulmonary artery pressure (mPAP) showed mild precapillary pulmonary hypertension (20.3 ± 4.7 mmHg) in half of the patients (pulmonary capillary wedge pressure, PCWP, 7.0 ± 3.7 mmHg). mPAP did not show any relation to ventilatory efficiency and correlated only to the transfer coefficient for carbon monoxide (K_{CO}, $r = -0.6829$, $p < 0.05$) and the difference between arterial and end-tidal pCO_2 (peak $p_{(a-ET)}CO_2$, $r = 0.8246$, $p < 0.005$) at peak performance.

During oxygen inhalation (table 1) exercise tolerance increased slightly (load, 78.5 ± 27.7 versus 91.3 ± 23.6 Watt, $p < 0.05$) while V_E (52.9 ± 17.6 versus 49.1 ± 15.0, $p < 0.01$) and V_E/VCO_2 slope (44.4 ± 14.2 versus 33.6 ± 7.6, $p < 0.05$) decreased (picture 1). With higher F_IO_2 V_D/V_T ratio tended to be lower at rest and significantly decreased at the end of exercise test (44.7±10.2 versus 32.2±13.7, $p < 0.05$, table 1). During oxygen inhalation, peak p_aO_2 correlated slightly with dead space size at the end of strain (peak V_D/V_T, $r = -0.763$, $p < 0.05$), but had no relation to V_E or ventilatory efficiency.

The findings show a few interesting results. Ventilatory efficiency belongs among frequent causes of limitation of physical activity in patients with IPF due to abnormally increased demand on ventilation[12,13]. The secondary PAH is often blamed for causing ventilatory inefficiency but remains untreated unless moderate to severe. The occurrence of PAH within our sample was consistent with previous works[14], its severity, however, was low and did not explain the magnitude of ventilatory inefficiency, despite the fact we measured pulmonary hemodynamics only at rest and so we could not predict the changes that occur during physical strain. We could suppose increased V_E/VCO_2 slope reflected worsening of pulmonary hemodynamics during exercise. Assessment of changes of V_E/VCO_2 slope requires some attention, however, since they may reflect variations in ventilatory control (p_aCO_2) or shifts in gas exchange efficiency (V_D/V_T)[15]. During oxygen inhalation (F_IO_2 0.35) ventilatory efficiency improved in parallel

with the reduction of V_D/V_T, while p_aCO_2 stayed unchanged, and so it can be assumed that decreased V_E/VCO_2 slope is at least partly caused by functional changes on pulmonary capillary level improving matching of ventilation and perfusion. In IPF patients, where there is a little space to improve V_D/V_T ratio by increasing V_T due to a significant mechanical constrain of ventilation, the decline in the physiologic dead space remains the main reason for gas exchange improvement. Oxygen inhalation then supposedly alleviates hypoxic vasoconstriction of pulmonary capillaries, and decreases V_D. Although not specifically assessed in this study, dyspnea seemed to decrease during oxygen inhalation because subjects handled higher physical load at lower level of minute ventilation through improved gas exchange efficiency. Minimizing hypoxic stimulation of ventilation by preventing arterial hypoxemia did not seem to contribute significantly because of lack of correlation of V_E with SpO_2 or p_aO_2, regardless of whether patients inhaled air or oxygen. Results of this study could assist to the introduction of a new criterion for the prescription of ambulatory oxygen therapy in patients with IPF and possibly other interstitial lung diseases. F_IO_2 of 0.35 can be achieved by using medium flow oxygen and face mask thus becoming available in clinical practice.

This study has many limitations, its validity is restricted mostly by its sample size, which could affect the significance of individual measurements. Additionally, information about oxygen inhalation could not be withheld from medical staff due to technical limitations. Despite these, we believe that this could not have had a significant impact on the results because exercise tolerance showed an improvement similar to previous studies [8]. Another limitation was the assessment of only one level of inspiratory oxygen fraction caused by the will of the participants. We chose a lower fraction (F_IO_2 0.35), compared to other studies, because we aimed to find out whether it is possible to affect physical strain tolerance using oxygen inhalation and, moreover, affect the ventilatory demand in the case of using a mobile source of liquid oxygen or physical training in rehabilitation facilities.

It can be concluded, that in our sample of IPF patients, physical strain tolerance is limited mainly by high ventilatory demand caused by decreased pulmonary compliance and an increase of physiologic dead space. Oxygen inhalation during inspiratory fraction F_IO_2 0.35 leads to improved ventilatory efficiency with decreased minute ventilation, which is accompanied by higher physical strain tolerance. To the authors' knowledge, this is the first study demonstrating that in patients in IPF, inhalation of oxygen enriched air reduces physiologic dead space and ventilatory demand by improving pulmonary capillary blood flow.

References:

1. Agusti C, Xaubet A, Agusti AGN, Roca J, Ramirez J, Rodriguez-Roisin R. Clinical and functional assessment of patients with idiopathic pulmonary fibrosis: Results of a 3 year follow-up. *Eur Respir J* 1994;7(4):643–650. doi: 10.1183/09031936.94.07040643.
2. DiMarco AF, Kelsen SG, Cherniack NS, Gothe B. Occlusion Pressure and Breathing Pattern in Patients with Interstitial Lung Disease. *Am Rev Respir Dis* 1983;127(4):425–430. doi: 10.1164/arrd.1983.127.4.425.
3. Schaeffer MR, Ryerson CJ, Ramsook AH, et al. Neurophysiological mechanisms of exertional dyspnoea in fibrotic interstitial lung disease. *Eur Respir J* 2018;51:1701726. doi: 10.1183/13993003.01726-2017.
4. Agustí AGN, Roca J, Gea J, Wagner PD, Xaubet A, Rodriguez-Roisin R. Mechanisms of Gas-exchange Impairment in Idiopathic Pulmonary Fibrosis. *Am Rev Respir Dis*

1991;143(2):219–225. doi: 10.1164/ajrccm/143.2.219.
5. Hallstrand TS, Boitano LJ, Johnson WC, Spada C a, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. *Eur Respir J* 2005;25(1):96–103. doi: 10.1183/09031936.04.00137203.
6. Arizono S, Furukawa T, Taniguchi H, et al. Supplemental oxygen improves exercise capacity in IPF patients with exertional desaturation. *Respirology* 2020;25(11):1152–1159. doi: 10.1111/resp.13829.
7. Miki K, Maekura R, Hiraga T, et al. Impairments and prognostic factors for survival in patients with idiopathic pulmonary fibrosis. *Respir Med* 2003;97(5):482–490. doi: 10.1053/rmed.2002.1469.
8. Bell EC, Cox NS, Goh N, et al. Oxygen therapy for interstitial lung disease: a systematic review. *Eur Respir Rev* 2017;26(143):160080. doi: 10.1183/16000617.0080-2016.
9. Schaeffer, Michele R, Molgat-Seon Y, Ryerson, Christopher J, Guenette JA. Suplemental oxygen and dyspnoea in interstitial lung disease: absence of evidence is not evidence of absence. *Eur Respir J* 2017;26:170033. doi: 10.1183/16000617.0033-2017
10. Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. *Chest* 1996;109(6):1566–1576. doi: 10.1378/chest.109.6.1566.
11. Radtke T, Crook S, Kaltsakas G, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *Eur Respir Rev* 2019;28(154):180101. doi: 10.1183/16000617.0101-2018.
12. 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. 2018;27(147):170062. doi: 10.1183/16000617.0062-2017.
13. Troy LK, Young IH, Lau EMT, Corte TJ. Exercise pathophysiology and the role of oxygen therapy in idiopathic interstitial pneumonia. *Respirology* 2016;21(6):1005_14. doi: 10.1111/resp.12650
14. Nathan SD, Noble PW, Tuder RM. Idiopathic pulmonary fibrosis and pulmonary hypertension: Connecting the dots. *Am J Respir Crit Care Med* 2007;175(9):875–880. doi: 10.1164/rccm.200608-1153CC
15. Ward SA. Ventilation/carbon dioxide output relationships during exercise in health. *Eur Respir Rev* 2021; 30: 200160. doi: 10.1183/16000617.0160-2020

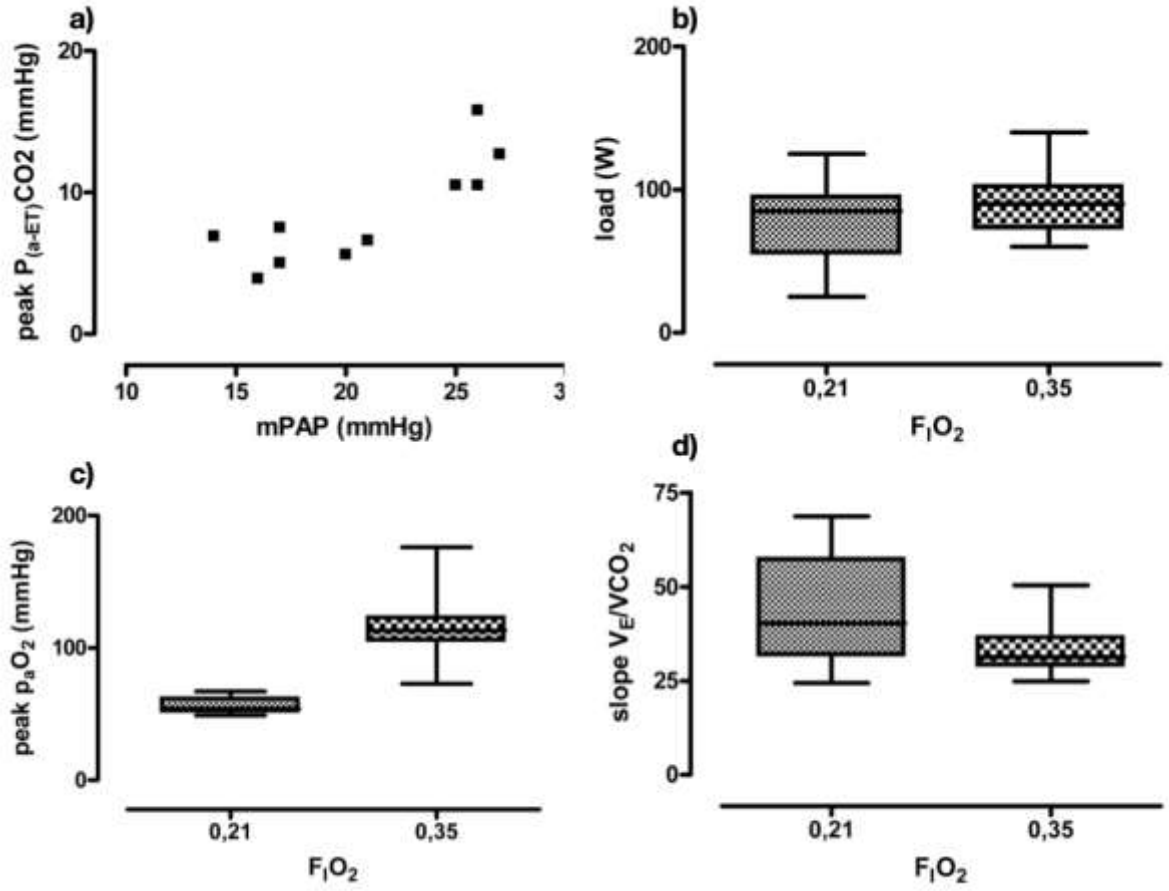

Figure 1.

a) Relationship between mPAP at rest and p(a-ET)CO2 at peak performance, Pearson r= 0.8246, $p < 0.01$

b) Improvement in strain tolerance during oxygen inhalation, Watt, paired t-test, $p < 0.05$

c) Improvement in paO2 at the end of strain during oxygen inhalation, paired t-test, $p < 0.05$

d) Drop of slope of VE dependency on VCO2 during oxygen inhalation, paired t-test, $p < 0.05$

	F_IO_2 0.21	F_IO_2 0.35	difference
p_aO_2 rest (mmHg)	76.8±7.3	145.6±11.2	p<0.05
p_aO_2 peak exercise (mmHg)	55.8±6.1	116.6±30.8	p<0.05
p_aCO_2 rest (mmHg)	37.9±4.0	39.0±6.8	p=0.8438
p_aCO_2 peak exercise (mmHg)	39.4±5.5	44.1±5.1	p=0.2188
$p_{(a-ET)}CO_2$ rest (mmHg)	7.96±4.9	7.2±6.2	p=0.1563
$p_{(a-ET)}CO_2$ peak exercise (mmHg)	8.5±3.8	6.9±7.9	p=0.8125
V_D/V_T rest	38.1±12.9	27.0±12.6	p=0.0781
V_D/V_T peak exercise	44.7±10.2	32.2±13.7	p<0.05
Peak load (W)	78.5±27.8	91.3±25.2	p<0.05
Peak HR (min^{-1})	116.2±23.8	121.5±20.0	p=0.9375
Peak V_E (l/min)	53.9±17.6	49.1±16.1	p<0.01
V_E/VCO_2 slope	44.4±14.2	33.6±8.1	p<0.05

Table 1. Changes of ventilatory and respiratory parameters with increasing inspiratory fraction of oxygen. Values are expressed as mean±SD, differences are calculated using paired t-test. p_aO_2 – arterial partial pressure of oxygen, p_aCO_2 – arterial partial pressure of carbon dioxide, $p_{(a-ET)}CO_2$ - the difference between arterial and end-tidal partial pressure of carbon dioxide, V_D/V_T – dead space to tidal volume ratio, HR – heart rate, V_E – minute ventilation, V_E/VCO_2 slope – slope of the ration of minute ventilation to carbon dioxide production.