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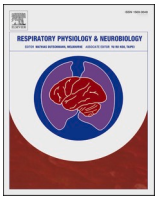

Short communication

Difference in expiratory flow limitations development in normoxia and hypoxia in healthy individuals

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ABSTRACT

The present study investigated the maintenance/repeatability of expiratory flow limitation (EFL) between normoxia and hypoxia.

Fifty-one healthy active individuals (27 men and 24 women) performed a lung function test and a maximal incremental cycling test in both normoxia and hypoxia (inspired oxygen fraction = 0.14) on two separate visits.

During exercise in normoxia, 28 participants exhibited EFL (55 %). In hypoxia, another cohort of 28 participants exhibited EFL. The two groups only partly overlapped.

Individuals with EFL only in normoxia reported lower maximal ventilation values in hypoxia than in normoxia (n=5; −13.5 ± 7.8 %) compared to their counterparts with EFL only in hypoxia (n=5; +6.7 ± 6.3 %) or without EFL (n=18; +5.1 ± 10.3 %) ($p=0.004$ and $p<0.001$, respectively).

EFL development may be induced by different mechanisms in hypoxia vs. normoxia since the individuals who exhibited flow limitation were not the same between the two environmental conditions. This change seems influenced by the magnitude of the maximal ventilation change.

1. Introduction

Expiratory flow limitation (EFL) refers to the inability to generate higher airflow despite greater respiratory effort and is common in both men and women (Molgat-Seon et al., 2022; Raberin et al., 2024). EFL can results in dynamic hyperinflation leading to decreased lung compliance and consequently increased work of breathing (Dempsey et al., 2020). Excessive work of breathing may trigger the respiratory muscle metaboreflex and limit limb blood flow (Dempsey et al., 2020). EFL could also be the cause of relative hypoventilation during exercise and be at the onset of exercise induced hypoxemia (Dominelli et al., 2013). While EFL was for long suspected to be more prevalent in women than men (Guenette et al., 2007), recent studies showed that female individuals do not report a greater prevalence of EFL in normoxia (Molgat-Seon et al., 2022; Raberin et al., 2024). Rather than sex, EFL in normoxia appears contingent upon an imbalance between ventilatory demands and ventilatory capacities (Molgat-Seon et al., 2022; Raberin et al., 2024).

Hypoxia, which is known to alter ventilatory drive in order to mitigate the decrease in alveolar and therefore arterial oxygen content, may influence the development of EFL. Indeed, during hypoxic exposure, an increased ventilation (primarily through increased tidal volume (Tipton et al., 2017)), named hypoxic ventilatory response (HVR), occurs to defend oxygen arterial content. However, to date, only few studies have investigated EFL in hypoxia (Cao et al., 2019; Chapman et al., 1998; Foster et al., 2014; Raberin et al., 2024; Weavil et al., 2015), and none of them have explored the maintenance of this phenomenon between normoxia and hypoxia. Previous studies reported that EFL developed in normoxia influences the ventilatory response during exercise in hypoxia, leading to an inability to increase ventilation during maximal exercise test (Chapman et al., 1998; Raberin et al., 2024), and to a greater demand on ventilatory reserve during time trial in hypoxia (Weavil et al., 2015).

Two studies have assessed EFL under hypobaric hypoxic conditions: an EFL prevalence of 50 % was reported in fourteen Kenyan endurance athletes born at altitude (2000 – 2400 m) and tested at an altitude of 1545 m (Foster et al., 2014), and of 35 % among seventeen athletes evaluated at 2500 m (Cao et al., 2019).

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However, data on the maintenance of EFL between normoxic and hypoxic condition are scarce. To the best of our knowledge, only one study (Cao et al., 2019) has reported, albeit not study, that male athletes developing EFL in normoxia were not exactly the same as those developing EFL in hypobaric hypoxia conditions. In hypobaric hypoxia, EFL may be slightly alleviated due to the lower air density, which induces reduced turbulent airflow. However, as shown by the prevalence of EFL at altitude in both lowlanders (Cao et al., 2019) and highlanders (Foster et al., 2014), the reduction in air density seems too small to alleviate EFL. Heliox, which is used in many studies to reduce the work of breathing, has an approximately six times lower density than air. A reduction in air density around 20 % (i.e., at 2500 m) is probably not enough to have a significant impact.

Therefore, the aim of this study was to investigate the maintenance of EFL, during maximal incremental exercise, between normoxia and hypoxia. Additionally, this study aimed to explore the origin of any switch in the development of EFL between the two conditions. We hypothesized that hypoxia may alter the development of EFL since it influences ventilation and solicits ventilatory reserve.

2. Methods

2.1. Participants

Participants enrolled in the present study took part in a larger protocol (Raberin et al., 2024). Fifty-one volunteers (24 women and 27 men) participated in this study. They were aged 18–35 years old, non-smokers, physically active ($\geq$ 2 hours of training/week at moderate to vigorous intensity) and did not suffer from any known cardiovascular, metabolic, or pulmonary disease. All participants resided at low altitude (i.e., $<$ 500 m), and none had been acclimatized to altitude. Participants were classified into four groups according to the occurrence of EFL in both normoxia and hypoxia: non-EFL in both conditions (non-$EFL_{N/H}$), EFL in both conditions ($EFL_{N/H}$), EFL developed only in normoxia ($EFL_{N+/H-}$), EFL developed only in hypoxia ($EFL_{N-/H+}$) (Fig. 1).

Approval for this study was obtained from the institutional ethical committee (CER-VD 2023–01638) and was conformed with the Declaration of Helsinki. All participants gave their written informed consent prior to participation.

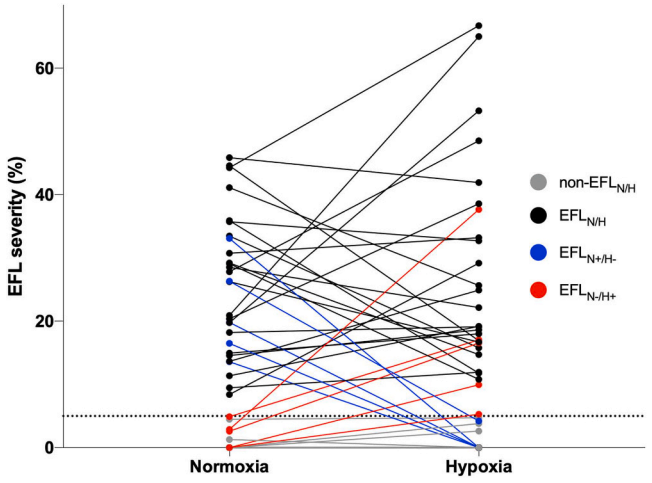

Fig. 1. Normoxia to hypoxia individual changes in expiratory flow limitation (EFL) severity. Grey color are participants without EFL (non-$EFL_{N/H}$), n=18 (6 males and 12 females, 14 of the participants reported a EFL severity of 0 %, that is not displayed in this figure). Black color are participants who develop EFL in both normoxia and hypoxia ($EFL_{N/H}$), n=23 (17 males and 6 females). Blue color are participants who develop EFL only in normoxia ($EFL_{N+/H-}$), n=5 (2 males and 3 females). Red color are participants who develop EFL only in hypoxia ($EFL_{N-/H+}$), n=5 (2 males and 3 females). Dashed line is the 5 % threshold of EFL severity.

2.2. Protocol

Participants visited the laboratory on three separate occasions. During the first session in normoxia and the third one in normobaric hypoxia, participants performed a lung function test, after a 10-minute resting period, followed by a maximal incremental test on a cycle-ergometer (Excalibur, Lode, Groningen, Netherlands). In the hypoxic condition, the inspired oxygen fraction (F_IO_2) was set at 0.140 ($\approx$ 3400 m). The participants were blinded to the condition. On the second visit, participants underwent two hypoxic chemosensitivity tests. Female participants scheduled their visits during the early follicular phase of their menstrual cycle based on self-reported history and were required to have a regular menstrual cycle for at least 6 months before the test. Over the 3 months' period of data collection, the environmental conditions during normobaric visit were 22.5 $\pm$ 1.1°C and 33.6 $\pm$ 6.7 % of relative humidity. During hypoxic visit, it was 24.6 $\pm$ 0.6°C, 45.4 $\pm$ 6.3 % of relative humidity and FiO_2 was quite stable at 0.143 $\pm$ 0.003. Temperature and relative humidity were not different between the four groups in normoxia and in hypoxia.

Pulmonary function, maximal incremental test, hypoxia sensitivity test and EFL determination were performed, as previously described (Raberin et al., 2024). Briefly, pulmonary function was assessed using a portable spirometer (Pony FX, Cosmed, Rome, Italy), according to standardized procedures with graded expirations to minimize the effect of thoracic gas compression that occurs during forced expiration. The first effort was always maximal, and the following four to six expirations were performed at decreasing efforts with continuous visual feedback (e.g., 80 % effort of the previous expiration). This procedure was repeated as soon as possible after maximal exercise ($<$ 2 min) to consider post-exercise bronchodilation.

The slope ratio (SR) was calculated to quantify the curvature of the maximal expiratory flow-volume (MEFV) curve, as previously described (Molgat-Seon et al., 2022; Raberin et al., 2024).

The maximal incremental test started with participants cycling at 20 W for 2 minutes followed by 1-min increments of 20–30 W, according to fitness level, until volitional exhaustion. Before each increment, participants performed an inspiratory capacity (IC) maneuver. Gas exchange, minute ventilation (V_E) (Quark CPET, Cosmed, Rome, Italy), HR (Physioflow enduro, Manatec Biomedical, Poissy, France), vastus lateralis tissue saturation index (Portamon, Artinis Medical Systems, Elst, The Netherlands), and earlobe pulse oxygen saturation (SpO_2) (Wristox, Nonin Medical Inc, Plymouth, MN, USA) were continuously recorded.

The Richalet test was performed to evaluated hypoxic ventilatory response at rest and during exercise, as previously described (Richalet et al., 2012). Briefly, participants were exposed to the following sequence: 4-min rest in normoxia, 4-min rest in hypoxia ($F_IO_2 = 0.115$), 4-min exercise (at 30 % of normoxic VO_{2max}) in hypoxia, 4-min exercise at the same intensity in normoxia. Participant inhaled hypoxic gas mixture generated with a gas-mixing device (Altitrainer, SMTEC SA, Nyon, Switzerland). HVR was calculated as the ratio between normoxia-to-hypoxia changes in ventilation over saturation normalized by body weight.

EFL was determined by maximal expiratory flow volume (MEFV) curve analysis measured on the ergometer in a sitting position. Expiratory efforts were aligned to the largest forced vital capacity (FVC) and superimposed on each other. The highest flow at any given lung volume was used to represent the boundary of the MEFV curve (Molgat-Seon et al., 2022; Raberin et al., 2024).

To determine operational lung volumes, subjects performed IC maneuvers before the end of each stage. Only data at maximal/near maximal exercise intensities were used for analyses. Approximately 5 tidal breaths before the IC maneuver were averaged and placed within the MEFV curve after correction for any device drift. The magnitude of EFL was calculated by dividing the volume of the tidal breath that

reached the border of the MEFV curve by the tidal volume (Molgat-Seon et al., 2022; Raberin et al., 2024). Subjects with a magnitude value, i.e., an EFL severity, over 5 % were considered flow limited (Molgat-Seon et al., 2022; Raberin et al., 2024).

2.3. Statistical analysis

A one-way ANOVA on rank (Kruskal-Wallis test) was used to compare the four groups. Bonferroni's post-hoc test was used to locate the difference when significant group effect was found. All statistical analyses were performed using SPSS-version 29.0 (SPSS Inc., Chicago, IL, USA).

3. Results

During exercise in normoxia, 28 participants (19 males and 9 females) exhibited EFL (55 %). A different set of 28 participants (19 males and 9 females) exhibited EFL in hypoxia (Fig. 1). Most of the participants did not switch from EFL to non-EFL and vice versa (80.4 %), but 19.6 % exhibited a change. Eighteen participants (35.3 %) did not develop EFL either in normoxia or in hypoxia (non-$EFL_{N/H}$; 6 males and 12 females; age 25 ± 4 yr, height 170 ± 8 cm, weight 59 ± 9 kg and body mass index BMI 20.4 ± 2.3 $kg.m^{-2}$). Twenty-three individuals (45.1 %) developed EFL in both conditions ($EFL_{N/H}$; 17 males and 6 females; age 26 ± 3 yr, height 176 ± 10 cm, weight 72 ± 12 kg and body mass index BMI 22.9 ± 2.0 $kg.m^{-2}$). 5 participants (9.8 %) developed EFL only in normoxia ($EFL_{N+/H-}$; 2 males and 3 females; age 24 ± 2 yr, height 172 ± 13 cm, weight 66 ± 11 kg and body mass index BMI 22.3 ± 1.3 $kg.m^{-2}$), and finally 5 individuals (9.8 %) reported EFL only in hypoxia ($EFL_{N-/H+}$; 2 males and 3 females; age 24 ± 2 yr, height 176 ± 9 cm, weight 66 ± 13 kg and body mass index BMI 21.0 ± 1.8 $kg.m^{-2}$).

Predicted spirometry indexes were not different among the four groups, and none of them could be classified as abnormal. However absolute forced expiratory volume in one second over FVC ratio was lower in the $EFL_{N/H}$ group compared to the non-$EFL_{N/H}$ one (Table 1). No difference in operating lung volume was reported between the $EFL_{N+/H-}$ and the $EFL_{N-/H+}$ group, while end-expiratory lung volume was lower in the non-$EFL_{N/H}$ compared to the $EFL_{N+/H-}$ group. The $EFL_{N+/H-}$ group showed different maximal VE (VE_{max}) changes between normoxia and hypoxia (-13.5 ± 7.8 %) compared to the $EFL_{N-/H+}$ (+6.7 ± 6.3 %) and the non-$EFL_{N/H}$ groups (+5.1 ± 10.3 %) ($p = 0.004$ and $p < 0.001$, respectively) (Fig. 2). Apart from VE_{max} changes between normoxia and hypoxia, no other variables, differed between the $EFL_{N+/H-}$ group and the $EFL_{N-/H+}$ group (Fig. 2A–D, and F and Table 1).

During the Richalet test, there were no between groups significant differences in resting hypoxic ventilatory response nor hypoxic ventilatory response during exercise (Fig. 2G & H).

Table 1
Pulmonary function and responses to maximal incremental exercise in non-$EFL_{N/H}$, $EFL_{N/H}$, $EFL_{N+/H-}$, and $EFL_{N-/H+}$ groups.

	Condition	non-$EFL_{N/H}$ (n=18)	$EFL_{N/H}$ (n=23)	$EFL_{N+/H-}$ (n=5)	$EFL_{N-/H+}$ (n=5)	ANOVA p value
FVC (L)	Normoxia	4.5 ± 0.8	5.4 ± 1.0	5.4 ± 0.9	5.4 ± 1.4	0.062
	Hypoxia	4.6 ± 0.9	5.4 ± 1.0	5.3 ± 0.8	5.4 ± 1.4	0.071
FVC predicted (%)	Normoxia	102 ± 10	103 ± 8	116 ± 11	108 ± 8	0.058
	Hypoxia	102 ± 10	103 ± 10	115 ± 11	108 ± 9	0.142
$FEV_{1.0}$ (L)	Normoxia	4.0 ± 0.7	4.4 ± 0.8	4.4 ± 0.8	4.4 ± 1.1	0.295
	Hypoxia	4.0 ± 0.7	4.4 ± 0.8	4.4 ± 0.9	5.1 ± 1.3	0.174
$FEV_{1.0}$ predicted (%)	Normoxia	105 ± 11	101 ± 7	110 ± 11	104 ± 7	0.280
	Hypoxia	106 ± 10	102 ± 9	110 ± 13	106 ± 10	0.204
FEV_1/FVC	Normoxia	89 ± 6	83 ± 5*	81 ± 8	82 ± 7	0.010
	Hypoxia	88 ± 2	82 ± 5*	82 ± 10	84 ± 10	0.010
FEV_1/FVC predicted (%)	Normoxia	102 ± 6	98 ± 6	95 ± 9	93 ± 5.4	0.059
	Hypoxia	103 ± 4	98 ± 6	96 ± 11	98 ± 12	0.067
FEF25 %−75 % ($L.sec^{-1}$)	Normoxia	4.8 ± 1.0	4.6 ± 1.2	4.0 ± 1.2	4.3 ± 1.5	0.651
	Hypoxia	4.7 ± 0.9	4.5 ± 1.2	4.3 ± 1.2	4.8 ± 1.6	0.918
FEF25 %−75 % predicted (%)	Normoxia	112 ± 20	99 ± 17	90 ± 21	90 ± 19	0.090
	Hypoxia	112 ± 12	98 ± 19	95 ± 25	105 ± 33	0.071
Peak expiratory flow ($L.sec^{-1}$)	Normoxia	8.5 ± 2.1	9.5 ± 2.4	9.6 ± 2.6	8.8 ± 2.6	0.606
	Hypoxia	8.9 ± 1.9	9.9 ± 2.2	9.5 ± 2.3	9.2 ± 2.6	0.430
VO_{2max} ($mL.min^{-1}.kg^{-1}$)	Normoxia	53.2 ± 96	58.2 ± 10.8	58.1 ± 3.3	52.5 ± 2.8	0.294
	Hypoxia	46.9 ± 7.2	48.9 ± 7.7	47.4 ± 1.9	47.1 ± 4.3	0.924
Breathing frequency ($1.min^{-1}$)	Normoxia	52 ± 8	59 ± 8	60 ± 11	55 ± 11	0.070
	Hypoxia	54 ± 8	58 ± 9	53 ± 15	56 ± 9	0.377
Tidal volume (L)	Normoxia	2.2 ± 0.5	2.7 ± 0.4*	2.5 ± 0.6	2.4 ± 0.6	0.040
	Hypoxia	2.2 ± 0.5	2.7 ± 0.4*	2.5 ± 0.7	2.4 ± 0.5	0.037
End-expiratory lung volume (%FVC)	Normoxia	31 ± 14	42 ± 8	55 ± 9*	43 ± 16	0.017
	Hypoxia	32 ± 11	43 ± 10	53 ± 5*	38 ± 9	0.009
End-inspiratory lung volume (%FVC)	Normoxia	81 ± 14	88 ± 18	96 ± 11	90 ± 18	0.207
	Hypoxia	82 ± 7	90 ± 15	95 ± 10	85 ± 6	0.109
Peak power ($Watt.kg^{-1}$)	Normoxia	4.6 ± 0.7	4.7 ± 0.8	5.1 ± 0.1	4.7 ± 0.7	0.329
	Hypoxia	4.2 ± 0.6	4.1 ± 0.6	4.3 ± 0.2	4.3 ± 0.2	0.607
RER	Normoxia	1.11 ± 0.10	1.07 ± 0.09	1.15 ± 0.12	1.08 ± 0.08	0.284
	Hypoxia	1.12 ± 0.06	1.11 ± 0.07	1.15 ± 0.09	1.13 ± 0.10	0.636
SpO_2 (%)	Normoxia	93.1 ± 4.1	93.9 ± 3.8	91.4 ± 5.8	94.4 ± 4.1	0.674
	Hypoxia	81.3 ± 4.7	80.7 ± 5.1	81.8 ± 5.2	82.6 ± 3.8	0.791
HR_{max} (bpm)	Normoxia	184 ± 8	182 ± 7	191 ± 9	185 ± 6	0.400
	Hypoxia	180 ± 8	175 ± 7	183 ± 10	180 ± 8	0.175
TSI (%)	Normoxia	57.1 ± 8.1	51.1 ± 9.2	58.6 ± 8.9	58.2 ± 8.2	0.150
	Hypoxia	57.5 ± 10.9	50.2 ± 9.9	52.5 ± 9.1	55.1 ± 6.3	0.082

non-$EFL_{N/H}$: participants without EFL, $EFL_{N/H}$: participants who develop EFL in normoxia and hypoxia, $EFL_{N+/H-}$: participants who develop EFL only in normoxia, $EFL_{N-/H+}$: participants who develop EFL only in hypoxia, FVC: forced vital capacity, $FEV_{1.0}$: forced expiratory volume in one second, $FEF_{25\ \%-75\ \%}$: forced expiratory flow from 25 % to 75 % FVC, VO_{2max}: maximal oxygen uptake, RER: respiratory exchange ratio, SpO_2: pulse oxygen saturation at maximal exercise, HR_{max}: heart rate at maximal exercise, TSI: vastus lateralis tissue saturation index at maximal exercise.

* significant difference compare to the non-$EFL_{N/H}$ group.

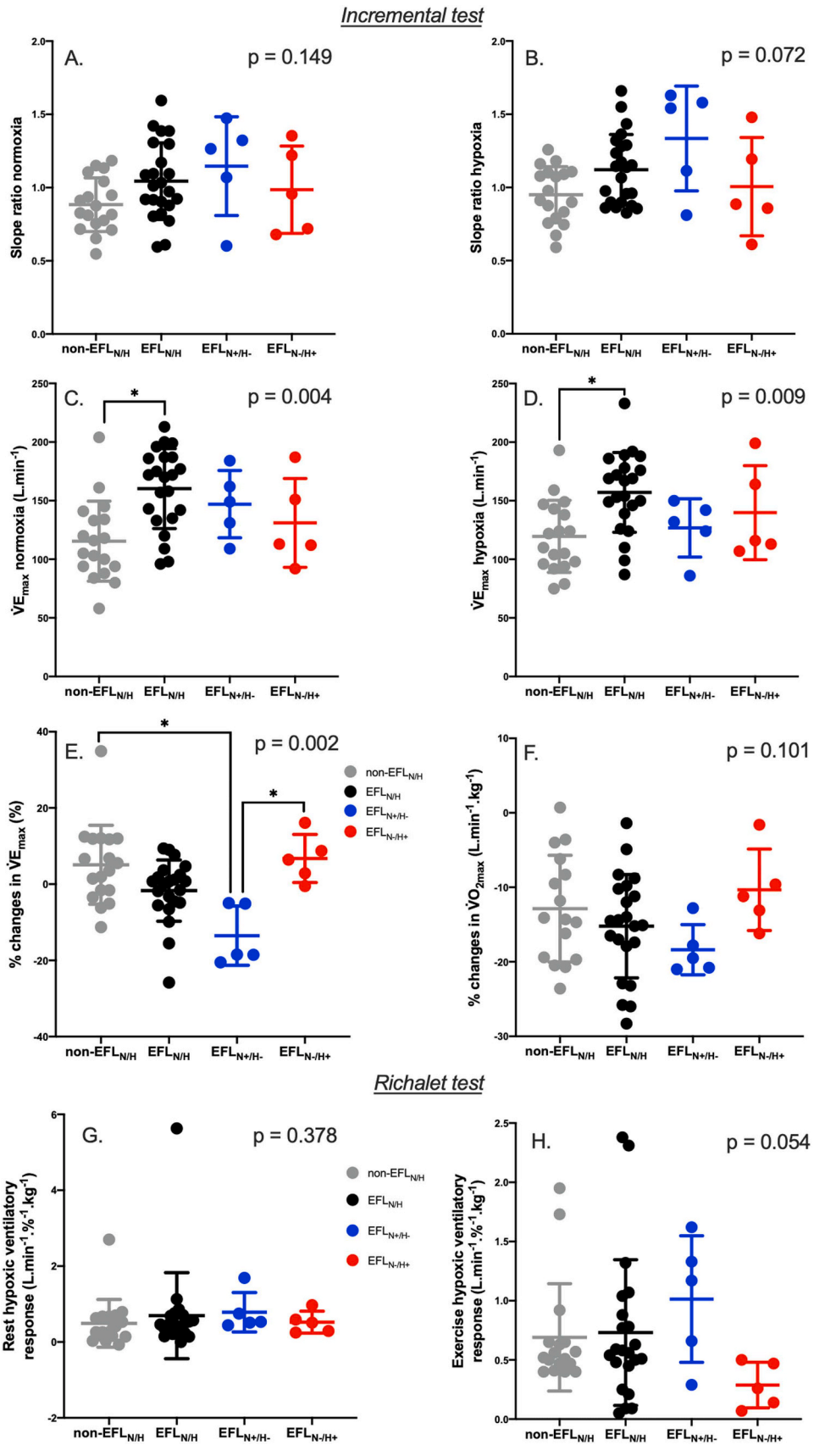

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Fig. 2. *Ventilatory capacities and ventilatory response to exercise and hypoxia in participants without EFL (non-EFL), participants who develop EFL in normoxia and hypoxia ($EFL_{N/H}$), participants who develop EFL only in normoxia ($EFL_{N+/H-}$), and participants who develop EFL only in hypoxia ($EFL_{N-/H+}$).* Panel A: slope ratio in normoxia. Panel B: slope ratio in hypoxia. Panel C: Maximal ventilation in normoxia. Panel D: Maximal ventilation in hypoxia. Panel E: Maximal ventilation percent changes between normoxia and hypoxia. Panel F: maximal oxygen uptake percent changes between normoxia and hypoxia. Panel G: Hypoxic ventilatory response at rest. Panel H: Hypoxic ventilatory response at exercise. VE_{max}: maximal ventilation. VO_{2max}: maximal oxygen uptake. * Post hoc difference ($p < 0.05$).

4. Discussion

The main finding of this study is that individuals can report EFL in normoxia only, in hypoxia only or in both conditions, suggesting that the mechanisms underlying EFL development may differ between environmental conditions.

In normoxia, EFL may be attributed to a mismatch between ventilatory capacities and ventilatory demands (Molgat-Seon et al., 2022; Raberin et al., 2024). In the present study, individual in the $EFL_{N+/H-}$ and the $EFL_{N-/H+}$ groups exhibited similar ventilatory capacities, as evaluated by the SR, and similar ventilatory demands, evaluated by VE_{max}. However, the switch from EFL to non-EFL or vice-versa can be linked to the ventilatory reserve (i.e., the difference between the maximal ventilation rate reachable and the maximal ventilation reached during a specific activity) utilization in hypoxia. Specifically, the individuals who developed EFL exclusively in hypoxia exhibited a significant increase in VE_{max}, they used a greater part of their ventilatory reserve, whereas their counterparts with EFL only in normoxia experienced a significant decrease in VE_{max} (Fig. 2E). It means that the ventilatory demand was increased in hypoxia in the $EFL_{N-/H+}$ group. This suggested that in hypoxia the development of EFL relied more on ventilatory demands than on ventilatory capacity. The difference in ventilatory response to incremental exercise in hypoxia was not associated with the hypoxic ventilatory response measured by the Richalet test (Fig. 2G & H). While the Richalet test involves an exercise phase at 30 % VO_{2max}, the intricate interplay between autonomic reflexes regulating ventilation during exercise (e.g., chemo- and metabo-reflexes interaction) makes definitive conclusions on the influence of chemosensitivity on the switch from EFL to non-EFL or vice-versa challenging to date.

Although the $EFL_{N+/H-}$ group did not solicit a large portion of its ventilatory reserve during exercise in hypoxia, since it reached a lower VE_{max} than in normoxia, it did not exhibit greater arterial oxygen desaturation or greater drop in VO_{2max} compared to the $EFL_{N-/H+}$ group (Fig. 2 and Table 1), suggesting that this change in VE_{max} did not significantly alter oxygen arterial content and performance during an incremental test. However, measurement of maximal voluntary ventilation was not performed and cannot confirm the difference in ventilatory reserve solicitation.

Even with our data on the cardiorespiratory and muscular system (Table 1), an explanation for the origin of the switch in the individuals exhibiting flow limitation between normoxia and hypoxia remains elusive. Sex-based differences in pulmonary system did not seem involved since the same percent of men and women composed the $EFL_{N-/H+}$ and $EFL_{N+/H-}$ groups (Guenette et al., 2007; Molgat-Seon et al., 2022; Raberin et al., 2024). Therefore, further studies are warranted to understand the causes and consequences of this phenomenon, particularly given the limited sample size of the $EFL_{N-/H+}$ and $EFL_{N+/H-}$ groups (n=5 for both groups), despite the inclusion of 51 healthy young individuals.

In conclusion, our observations indicate that in about 20 % of healthy individuals, EFL during maximal incremental exercise is not reproductible between normoxia and hypoxia. Furthermore, it suggests that in hypoxia, the development of EFL relies on ventilatory demands rather than on ventilatory capacities suggesting that the mechanisms underlying EFL development may differ between normoxia and hypoxia. Further studies on larger cohort are needed to confirm these observations.

CRediT authorship contribution statement

Nicolas Bourdillon: Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis. **Grégoire P Millet:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Antoine Raberin:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Forrest Schorderet:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Giorgio Manferdelli:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ruben Tato Perez:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Yannick Monnier:** Writing – review & editing, Methodology, Investigation, Formal analysis.

Data Availability

Data will be made available on request.

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