Upper-limb interval *versus* constant-load exercise in patients with COPD: a physiological crossover study

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Shareable abstract (@ERSpublications)
Interval exercise of the upper limb is more sustainable than continuous upper-limb exercise for the majority of COPD patients with moderate obstruction, leading to lower dynamic hyperinflation and symptoms at isotime. https://bit.ly/3tGA4l1

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Abstract

Objective Upper-limb exercise is recommended for patients with COPD, albeit there are limited data concerning the optimal modality to implement. We compared interval (INT-EX) to continuous (CONT-EX) upper-limb exercise in terms of exercise tolerance, ventilatory and metabolic responses when both conditions were sustained at an equivalent work rate.

Methods 26 stable COPD patients undertook three upper-limb exercise sessions to initially establish peak work rate (PWR) *via* an incremental exercise test and subsequently two equivalent work rate tests to the limit tolerance in balanced order: 1) INT-EX consisting of 30-s work at 100% PWR interspersed with 30-s work at 40% of PWR; and 2) CONT-EX at 70% PWR.

Results 20 patients (76.9%) had longer tolerance during INT-EX, while six out of 26 (23.1%) exhibited longer tolerance during CONT-EX. The average endurance time was 434.1±184.7 and 315.7±128.7 s for INT-EX and CONT-EX, respectively. During INT-EX at isotime (*i.e.* when work completed was the same between INT-EX and CONT-EX), the majority of patients manifested lower oxygen uptake, minute ventilation, pulmonary hyperinflation, heart rate, symptoms and higher CO_2 blood concentration. Patients with longer INT-EX had a lower comorbidity score (Cumulative Illness Rating Scale: 1.58±0.30 *versus* 1.88±0.29, p=0.0395) and better-preserved lung function (forced vital capacity 84.7±15.31% *versus* 67.67±20.56%, p=0.0367; forced expiratory volume in 1 s 57.15±14.59 *versus* 44.67±12.99% predicted, p=0.0725) compared to patients with longer CONT-EX.

Conclusion INT-EX is more sustainable than CONT-EX for the majority of COPD patients with moderate obstruction, leading to lower dynamic hyperinflation and symptoms at isotime. Further studies need to define the benefits of its application during pulmonary rehabilitation.

Introduction

Exercise intolerance is common in patients with COPD and is often attributed by clinicians to the intense sensations of breathlessness secondary to reduced ventilatory capacity and increased ventilatory demand [1]. In addition, in this population, there is evidence of intrinsic locomotor muscle alterations [2] causing peripheral muscle discomfort during exercise. Exercise training, as part of pulmonary rehabilitation (PR) for patients with COPD, reduces the intensity of these symptoms at a given level of exercise and improves both exercise tolerance and health-related quality of life (HRQoL) [3].

The optimal way to improve exercise tolerance in patients with COPD remains under evaluation [4]; albeit from a physiological point of view, interval compared to constant-load lower limb exercise may be more effective in improving exercise tolerance in patients with advanced COPD who typically cannot sustain intense loads for sufficiently long periods to acquire true physiological training effects [4]. This notion is based on experimental studies showing that interval compared to constant-load cycling is associated with greater exercise tolerance and reduced loads on respiration and circulation and symptoms of breathlessness and leg discomfort [5, 6]. In fact, at equivalent workloads, interval compared to constant-load cycling is associated with lower dynamic lung hyperinflation, blood lactate concentration, and greater respiratory and locomotor local muscle oxygen availability, allowing for a two-fold increase in total work output in patients with advanced COPD [7].

Upper-limb endurance exercise constitutes also a modality of exercise recommended for patients with COPD [3]. Evidence indicates that endurance upper-limb exercise training compared to no upper-limb training or a sham intervention improves dyspnoea and upper-limb fatigue and exercise tolerance, but not HRQoL in people with COPD [8–10]. However, the limited number of studies, the different modalities (supported, unsupported) and the exercise prescription (intensity and exercise protocol) tested until now precludes its wider application and clear suggestions regarding prescription in the PR setting.

Only a few physiological studies have compared different upper-limb exercise modalities, mainly evaluating differences between supported and unsupported exercise modalities showing that both induce dynamic hyperinflation in COPD [11–13]. To the best of our knowledge, derived from literature research on major scientific databases (PubMed, Cochrane Library, Scopus), no studies are comparing upper-limb interval exercise (INT-EX) to constant-load exercise (CONT-EX) in terms of exercise tolerance, and ventilatory and metabolic demands in patients with COPD.

In addition, given the leg cycle ergometer's higher tidal volume, minute ventilation and oxygen consumption compared to the arm cycle ergometer, caution is warranted in directly applying findings from lower limb exercise to upper-limb exercise, and dedicated studies are necessary for a comprehensive understanding [13].

Accordingly, this crossover study aimed to compare INT-EX to CONT-EX to evaluate exercise tolerance and physiological responses when both conditions were sustained at an equivalent work rate. Based on evidence from studies comparing lower limb interval to constant-load cycling, it was reasoned that INT-EX would be associated with longer exercise tolerance compared to CONT-EX due to lower ventilatory and metabolic requirements.

Methods

The study was conducted at Istituti Clinici Scientifici Maugeri IRCCS (Lumezzane (Brescia), Italy) in patients enrolled in a PR programme. The experiment was conducted within the first week of admission to inpatient hospital care. The following inclusion criteria were applied: 1) COPD diagnosis according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 criteria [14] with a post-bronchodilator forced expiratory volume in 1 s/forced vital capacity volume ratio (FEV_1/FVC) <0.7; and 2) clinical stability and optimal medical therapy according to GOLD guidelines [14].

Patients were excluded if they had: 1) each pathological condition that could act as a contraindication to exercise, potentially resulting in cardio-circulatory instability or worsening of the clinical presentation; 2) respiratory diseases other than COPD; 3) clinical signs of acute heart failure or heart disease (*i.e.* arrhythmia, ischaemic heart disease or cardiomyopathy); 4) prescription of long-term oxygen therapy or requirement for oxygen support during exercise; 5) engagement in an exercise training programme in the last 3 months; and 6) acute hospital admissions or COPD exacerbations within the past 6 weeks requiring therapy change. Before patient enrolment in the study, the associated risks and potential benefits of participation were explained, and patients provided their written informed consent. The study was approved by the Ethics Committee (CE2372, 14 January 2020) of Istituti Clinici Scientifici Maugeri IRCCS. The study conforms to the standards set by the Declaration of Helsinki.

Protocol

The following baseline evaluations were performed before engaging with the exercise protocols: 1) anthropometrics (weight, height, body mass index); 2) clinical characteristics (comorbidities by Cumulative Illness Rating Scale (CIRS)) [15]; 3) dyspnoea classification by the Medical Research Council (MRC) scale [16], the Barthel Dyspnoea Index [17] and the COPD Assessment Test [18]; 4) spirometry and post-bronchodilator static lung volumes according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) standards [19]; 5) 6-min walking test according to the ERS/ATS guidelines [20]; and 6) quadriceps muscle strength using the maximal isometric voluntary contraction technique of the right knee extensor using a dedicated dynamometer (Chatillon X-3328 Series; AMETEK, Inc, Berwyn, PA, USA) [21].

The main exercise study was conducted in three sessions. During the first session, patients underwent an upper-limb incremental cardiopulmonary exercise test (CPET) on an arm ergometer (Monark 881E Rehab Trainer) from 0 watts to the limit of tolerance (Tlim) to establish peak work rate (PWR). The work rate was increased by 5 W every minute, whereas Tlim was defined as the time point at which the work rate could not be increased further due to severe sensations of dyspnoea and/or arm discomfort (>8 on the Borg scale [22]) with the patients maintaining the arm cranking frequency of 60 rpm. The test was stopped when: 1) arterial oxygen saturation (S_{pO_2}) dropped below 80%; 2) heart rate was above the maximal predicted; 3) there was evidence of ST-segment depression on the electrocardiogram or 4) signs or symptoms of angina pectoris or malignant arrhythmias.

On two subsequent sessions (separated by at least 48 h), patients performed, in a balanced order sequence, two endurance arm cranking protocols to Tlim on the same arm ergometer (Monark 881E Rehab Trainer). Specifically, patients performed an INT-EX followed by a CONST-EX or a CONST-EX followed by an INT-EX with a 1:1 assignment. The INT-EX test consisted of 30-s work at 100% of PWR interspersed with 30-s work at 40% of PWR, and the CONT-EX test was sustained at 70% of PWR so that the average work rate every minute was equivalent between INT-EX and CONT-EX (figure 1). The 30-s INT-EX protocol was decided according to previous studies on COPD patients [23–25] describing feasibility and positive outcomes. All tests were performed with the arms elevated at 90° relative to the glenohumeral joint. The primary outcome of this study was to evaluate the time taken to reach Tlim (seconds) between the two different exercise conditions.

Across all three arm cranking tests, pulmonary gas exchange and ventilatory variables were recorded breath-by-breath by a portable metabolic cart (K5; Cosmed) and S_{pO_2} was determined using a pulse oximeter (Nonin 8500; Nonin Medical, North Plymouth, MN, USA). Heart rate was analysed by the R-R interval from a Bluetooth electrocardiogram trace (Checkme Pro Health Monit, Shenzhen Viatom Technology Co., Ltd). Blood pressure was measured by a sphygmomanometer every minute. The intensity of dyspnoea and leg discomfort during the tests were assessed using the modified Borg scale every minute [22].

In addition, a transcutaneous sensor (Sentec OxiVenTTM, Sentec, Therwil, Switzerland) being connected to the Sentec Digital Monitoring System (software version MPB-SW: V06.01.00; SMB-SW: V08.01.1) was placed with an attachment ring on the forehead of patients to continuously evaluate transcutaneous CO_2. The sensor was attached for at least 15 min (stability criterion) prior to exercise testing.

During INT-EX and CONT-EX protocols, patients performed inspiratory capacity manoeuvres at baseline and every 2 min, and at Tlim to identify the degree of dynamic lung hyperinflation assuming constant total lung capacity [1]. A reduction of 150 mL or more from baseline values was considered significant dynamic hyperinflation [26].

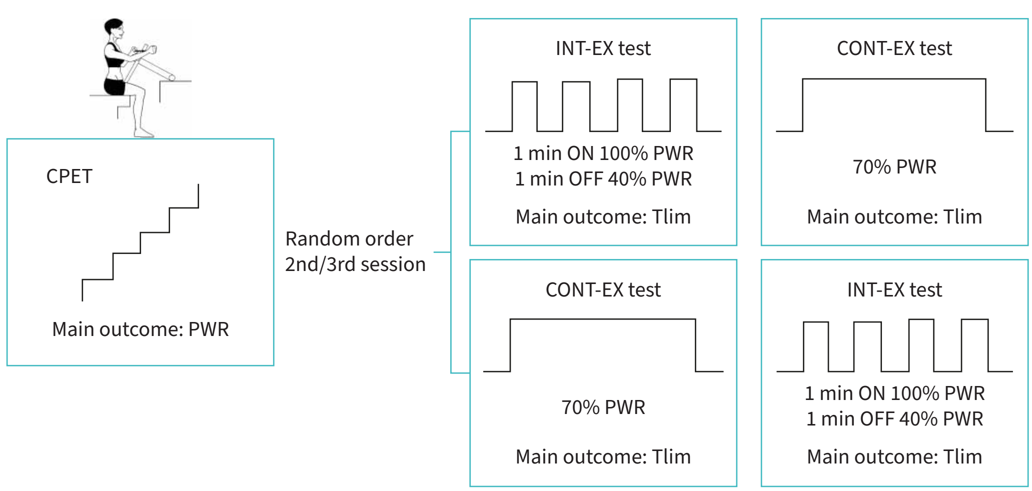

FIGURE 1 Study protocol. CPET: cardiopulmonary exercise test; INT-EX: interval exercise; CONT-EX: continuous exercise; PWR: peak work rate; Tlim: time to exhaustion.

Data analysis

Respiratory, cardiovascular, haemodynamic and transcutaneous data responses during all tests were averaged on blocks of 30 s. During both INT-EX and CONT-EX, key evaluation was performed at isotime: *i.e.* when work completed was the same between INT-EX or CONT-EX. Comparing variables at isotime was shown to be critical to the analysis of our data because it reflected physiological responses at an equivalent amount of arm work. For comparisons of physiological data between isotime and Tlim when the subject terminated the exercise before 30 s had elapsed, the values were averaged over the entire period.

Gross muscle efficiency (GE, %) was calculated by dividing the work by the total energy expended GE= (work output)/(energy expended) × 100 [27].

Net muscle efficiency (%) was also calculated by subtracting the corresponding resting energy expenditure from the total energy expended. Total energy expenditure was calculated using the last minute of the shortest test and compared with the isotime of the longest test [27].

Statistical analysis

Statistical analysis was performed using STATA 11 (StataCorp, LLC). Continuous variables were expressed as mean±SD, while binary and categorical outcomes were described as percentages. The primary outcome of this study was to evaluate the time taken to reach Tlim between the two different exercise conditions.

Based on literature data on COPD that employed a similar exercise protocol in lower limbs [28], we considered a Tlim for CONT-EX of 10.3 (1.6) min. Our hypothesis was that the Tlim during INT-EX would be higher by 10% compared to CONT-EX. In light of the absence of data on arm exercise, this hypothesis was delineated according to a researcher's theory based on previous pilot tests.

Based on the sample size calculation for the crossover study design, a total of 26 patients was deemed sufficient (α=0.05, β=0.80).

Differences at isotime and Tlim of time, work output, metabolic and respiratory parameters, and subjects' rating of breathlessness and muscle discomfort between the two exercise modalities were compared using dependent samples t-tests. When we analysed the variables across time, a repeated measure mixed model two-way analysis of variance was performed to detect changes between the two exercise modalities. *Post hoc* pairwise tests with Sidak adjustment were used when a significant interaction or main effect was identified. A p-value <0.05 was considered statistically significant.

Results

26 clinically stable patients with COPD were recruited for the study from January 2020 to January 2023. All participants successfully completed all three tests. Table 1 shows the participants' anthropometric and clinical characteristics and exercise performance characteristics.

Exercise tolerance between INT-EX and CONT-EX

Figure 2a shows individual values of the time taken to reach Tlim during the two different exercise modalities. The average time for INT-EX (434.1±184.7 s) was longer (p=0.0014) compared to CONT-EX (315.7±128.7 s). In the face of this significant result, a wide range of time to exhaustion was found during both tests, which was more evident during INT-EX. The data confirm our original hypothesis showing that 20 out of 26 (76.9%) of patients experienced longer tolerance during INT-EX, while only six out of 26 patients (23.1%) exhibited longer tolerance during CONT-EX (figure 2b).

Patients with longer INT-EX had a lower comorbidity score compared to CONT-EX (CIRS: 1.58±0.30 *versus* 1.88±0.29, p=0.0395) and better-preserved lung function (FVC 84.70±15.31% *versus* 67.67±20.56%, p=0.0367; FEV_1 57.15±14.59% *versus* 44.67±12.99%, p=0.0725). No other significant differences were found in baseline or CPET parameters between patients with longer INT-EX in comparison to patients with longer CONT-EX.

Comparisons between INT-EX and CONT-EX

Table 2 shows data gathered during the INT-EX and CONT-EX tests in all 26 patients at Tlim and at isotime that corresponds to the time of the shortest in-duration test. Metabolic and ventilatory responses and symptoms were similar at Tlim in the two conditions, suggesting equivalent cardiorespiratory involvement and similar physiological stress at the point of exercise cessation. Nevertheless, it is important to note that

TABLE 1 Demographic, anthropometric, clinical and exercise performance characteristics in the overall group (n=26)

Male, n (%)	18 (69.2)
Age years	69±7
BMI kg·m^{-2}	27.05±6.48
CIRS score	1.65±0.32
P_{aO_2} mmHg	72.2±8.7
P_{aCO_2} mmHg	39.7±5.3
pH	7.43±0.035
FEV_1 % pred	54.3±15.0
FEV_1 L	1.47±0.43
FVC % pred	80.8±17. 8
FVC L	2.81±0.71
FEV_1/FVC	52.8±10.3
RV % pred (n=22)	157.4±52.5
MRC score	2.38±0.94
Barthel dyspnoea score (n=24)	15.67±9.18
CAT score	19.19±6.71
6MWT m	395±102
6MWT % pred	81±20
Incremental cardiopulmonary exercise test (peak condition)	
WR W	27.3±11.6
V'_{O_2} mL·kg^{-1}·min^{-1}	12.17±3.36
V'_{CO_2} L·min^{-1}	0.87±0.31
RER	1.00±0.17
V'_{O_2}@AT mL·min^{-1}	750.79±230.68
V'_E L·min^{-1}	39.04±12.18
V_T L	1.26±0.34
BF breaths·min^{-1}	32.86±6.85
S_{pO_2} %	94.80±2.60
HR beats·min^{-1}	117±16
Borg dyspnoea score	6.46±2.27
Borg muscle discomfort score	7.54±1.61

Data are presented as mean±SD unless indicated otherwise. BMI: body mass index; CIRS: cumulative illness rating scale: P_{aO_2}: partial pressure of oxygen; P_{aCO_2}: partial pressure of carbon dioxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; RV: residual volume; MRC: Medical Research Council; CAT: COPD assessment test, 6MWT: 6-min walking test; WR: work rate; V'_{O_2}: oxygen uptake; V'_{CO_2}: CO_2 output; RER: respiratory exchange ratio; V'_{O_2}@AT: oxygen uptake at anaerobic threshold; V'_E: minute ventilation; V_T: tidal volume; BF: breathing frequency; S_{pO_2}: arterial oxygen saturation; HR: heart rate

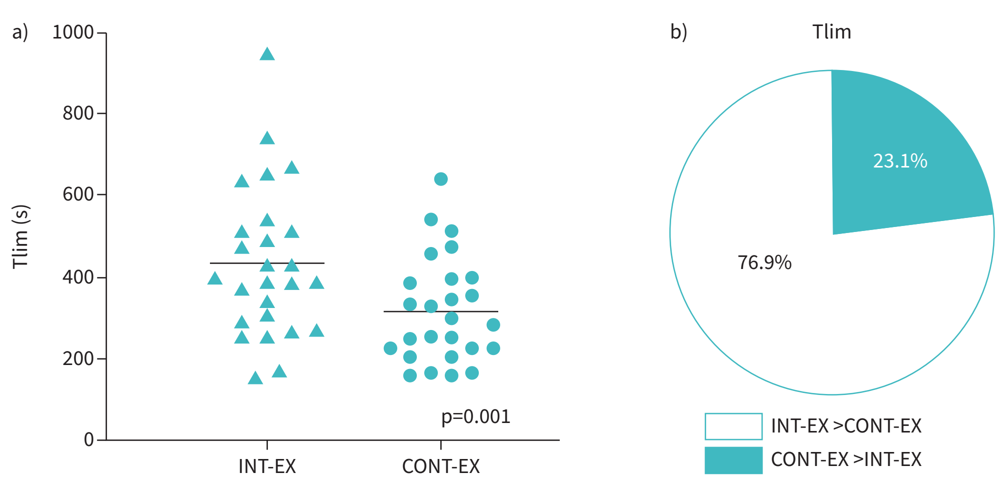

FIGURE 2 a) Individual and median values of Tlim for INT-EX and CONT-EX tests and b) rate of patients experiencing greater Tlim during INT-EX or CONT-EX. The black line corresponds to median value. Tlim: time to exhaustion; INT-EX: upper-limb interval-load exercise; CONT-EX: upper-limb constant-load exercise.

TABLE 2 Tlim and isotime conditions in the two tests for the overall group

	Tlim INT-EX	Isotime	Tlim CONT-EX
Power W			
ON	27.3±11.6		19.1±8.1
OFF	10.9±4.6		
Tlim s	434.1±184.7#	297.2±107.5	315.7±128.7¶
Total work J	9190.3±7295.2#	6133.6±4242.3	6488.1±4537.2¶
V'_{O_2} **mL·kg−1·min−1**	12.55±3.40#	11.92±3.50+	12.65±3.43
V'_{CO_2} **L·min−1**	0.85±0.27#	0.82±0.27+	0.89±0.29
RER	0.93±0.11	0.92±0.11+	0.95±0.14
V'_E **L·min−1**	39.3±11.6#	37.1±11.2+	39.5±12.4
V_T **L**	1.25±0.36	1.21±0.4+	1.28±0.4
BF breaths·min−1	33.0±7.1#	30.8±6.8+	34.2±6.1
V'_E**/MVV**	0.70±0.18#	0.66±0.18+	0.69±0.19
ΔIC L (n=24)	−0.28±0.37	−0.20±0.36+	−0.35±0.29
V_T**/IC (n=24)**	0.69±0.13#	0.63±0.12+	0.70±0.13
S_{pO_2} **%**	93.9±3.1	93.9±3.5	93.9±3.6
P_{tcCO_2} **mmHg**	38.1±5.5#	40.4±5.4	39.6±5.6
HR beats·min−1	114.2±14.3#	110.6±13.9+	116.1±14.8
Borg dyspnoea score	6.46±2.45#	4.35±2.53+	7.38±1.81
Borg effort score	8.19±0.85#	5.00±2.38+	8.00±0.98

Data are expressed as mean±SD. Tlim: time to exhaustion; CONT-EX: upper-limb constant-load exercise; INT-EX: upper-limb interval-load exercise; V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; RER: respiratory exchange ratio; V'_E: minute ventilation; V_T: tidal volume; BF: breathing frequency; MVV: maximum voluntary ventilation; IC: inspiratory capacity; S_{pO_2}: arterial oxygen saturation; P_{tcCO_2}: transcutaneous pressure of CO_2; HR: heart rate. p-value <0.05. #: isotime *versus* Tlim INT-EX; ¶: Tlim CONT-EX *versus* Tlim INT-EX, +: Tlim CONT-EX *versus* isotime.

when patients exercised by INT-EX, the total work performed was greater by ∼30% of that during CONT-EX with equivalent metabolic and ventilatory responses, confirming a greater tolerance to INT-EX.

At isotime, patients exhibited lower metabolic and ventilatory responses, rate of dynamic hyperinflation, heart rate, muscle fatigue and dyspnoea and higher CO_2 blood concentration.

Patients who reached the threshold level for dynamic hyperinflation of a change from baseline >150 mL at isotime were 37.5% in INT-EX and 66.7% in CONT-EX (p<0.001), while at Tlim the percentage was 50% in INT-EX *versus* 75% in CONT-EX, p<0.001 (data available in 24 patients).

Evaluations at isotime

According to the results, and in order to describe the physiological impact of INT-EX and CONT-EX, we have summarised the data of the two groups of patients (*i.e.* n=20 with longer Tlim during INT-EX test and n=6 with longer Tlim during CONT-EX) describing the physiological parameter at isotime (during the two tests; table 3). These patients with longer Tlim during the INT-EX test experienced lower metabolic and ventilatory requirements supported by lower tidal volume and breathing frequency, lower dynamic hyperinflation and, consequently, lower dyspnoea compared to CONT-EX. In addition, muscle discomfort was lower, describing a concomitant beneficial impact on respiratory and muscular systems. Notably, the mechanical efficiency of work was greater during INT-EX. Conversely, in these patients with longer Tlim during CONT-EX, the principal differences were related to oxygen uptake, ventilatory parameters and leg discomfort (table 3).

Figure 3 shows dynamic hyperinflation and mechanical ventilatory constraints with INT-EX as opposed to CONT-EX in the two groups of patients (n=20 with longer Tlim in the INT-EX test (figure 3a, b) and n=6 with longer Tlim in CONT-EX (figure 3c, d)). Only in patients with longer INT-EX, at isotime, the level of dynamic hyperinflation and ventilatory constraints was more evident in CONT-EX (p=0.038), and this aspect was concomitant to the increase of metabolic demand, respiratory rate, tidal volume and dyspnoea (described in supplementary figure 1SM and table 3).

Supplementary figure 1SM shows the time course of oxygen uptake (V'_{O_2}), carbon dioxide uptake (V'_{CO_2}), tidal volume, breathing frequency and symptoms (Borg Fatigue and Dyspnoea) during INT-EX (red line)

TABLE 3 Physiological measures at isotime

	Patients with longer Tlim in INT-EX[#]			Patients with longer Tlim in CONT-EX[¶]		
	INT-EX	CONT-EX	p-value	INT-EX	CONT-EX	p-value
Isotime s	293.70±95.73	293.70±95.73		308.66±150.30	308.66±150.30	
V'_{O_2} mL·min^{-1}·kg^{-1}	12.04±3.42	12.80±3.20	**0.0043**	12.74±3.57	11.51±4.06	**0.0308**
V'_{CO_2} L·min^{-1}	0.84±0.27	0.92±0.28	**0.0002**	0.83±0.27	0.74±0.30	0.1126
RER	0.94±0.12	0.97±0.15	**0.0287**	0.91±0,13	0.86±0.05	0.3807
V'_E L·min^{-1}	39.00±11.37	42.58±11.64	**0.0009**	34.34±9.46	30.73±10.23	**0.0140**
V_T L	1.27±0.33	1.34±0.36	**0.0078**	1.12±0.39	1.03±0.46	**0.0434**
BF breaths·min^{-1}	30.49±6.83	33.75±5.46	**0.0001**	34.32±8.75	31.72±7.18	**0.0194**
ΔIC mL	−0.11±0.29	−0.28±0.30	**0.0380**	−0.41±0.44	−0.49±0.44	0.4524
V_T/IC	63.21±10.64	70.05±10.10	**0.0159**	69.87±11.83	61.50±15.81	0.1612
S_{pO_2} %	94.72±2.31	94.56±2.95	0.7446	92.53±4.79	90.99±5.17	0.3762
P_{tcCO_2} mmHg	39.41±4.98	38.54±4.55	0.2521	38.99±4.33	43.60±6.03	0.1610
HR beats·min^{-1}	111.50±13.26	117.37±14.97	**0.0037**	113.69±12.33	107.38±16.78	0.1479
Borg dyspnoea score	3.70±2.39	7.30±1.92	**0.0001**	7.00±1.67	6.50±1.76	0.4150
Borg arm score	4.55±2.39	7.95±1.05	**0.0001**	8.33±0.52	6.50±1.76	**0.0478**
Gross mechanical efficiency %	6.8±2.66	6.21±2.25	**0.0008**	6.56±1.92	5.97±1.94	0.0528
Net mechanical efficiency %	10.39±6.32	8.88±4.15	**0.0163**	9.36±2.63	8.07±2.44	0.0851

Data are expressed as mean±SD. Bold type denotes statistical significance. Tlim: time to exhaustion; CONT-EX: upper-limb constant-load exercise; INT-EX: upper-limb interval-load exercise; V'_{O_2}: oxygen uptake; V'_{CO_2}: carbon dioxide production; RER: respiratory exchange ratio; V'_E: minute ventilation; V_T: tidal volume; BF: breathing frequency; IC: inspiratory capacity; S_{pO_2}: arterial oxygen saturation; P_{tcCO_2}: transcutaneous pressure of CO_2; HR: heart rate. [#]: n=20; [¶]: n=6.

and CONT-EX (blue line) performance in 20 patients who had longer Tlim during INT-EX. The trends of V'_{O_2} (p=0.007), V'_{CO_2} (p=0.008), breathing frequency (p<0.001) and symptoms (Borg Fatigue p<0.001, Borg Dyspnoea p<0.001) were significantly different between the two conditions describing a major cardiorespiratory involvement during CONT-EX.

Supplementary figure 2SM shows the same evaluations in the six patients with longer Tlim during CONT-EX. The difference between INT-EX and CONT-EX performance is visible only in tidal volume (p=0.042) and Borg Fatigue (p=0.006), which were significantly higher in the INT-EX condition.

Discussion

Main findings

Our physiological study is the first to show greater tolerance to upper-limb interval exercise compared to constant-load exercise in ∼80% of COPD participants with moderate airflow obstruction and resting lung hyperinflation, thus paving the way for broader use of arm exercise in the PR setting. Interval upper-body exercise was associated with lower metabolic and respiratory demands, reduced dynamic hyperinflation and ventilatory constraints, and fewer symptoms of dyspnoea and arm discomfort. Fewer comorbidities and a higher forced vital capacity were apparent in patients with better tolerance to INT-EX.

Locus of exercise limitation

Exercise intolerance involving the upper extremities is related to increased ventilatory and metabolic demands, the development of dynamic hyperinflation and thoracoabdominal asynchrony during these activities [29, 30]. Such physiological requirements are considered responsible for increased sensations of fatigue and breathlessness leading to premature suspension of simple self-care activities of daily living (ADLs) [31]. The most physiologically demanding upper-body activities are those of a continuous or "endurance" nature, while upper-limb muscle strength activities seem to be better preserved in COPD [32]. Furthermore, muscle oxidative capacity is reduced in the upper limbs of patients with COPD [32], and this is most likely associated with early development of lactic acidosis during prolonged activities [33]. Notably, there is also a strong relationship between the power of the upper limbs and the strength of the respiratory muscles being often synergistic in the mobilisation of the upper limbs, rib cage and spine and in breathing mechanisms [34].

A few studies have evaluated the physiological response to upper-limb workouts. A larger shoulder flexion limits exercise endurance capacity during unsupported limb activities secondary to increased metabolic demand, minute ventilation and cardiac response, without worsening dynamic hyperinflation [13].

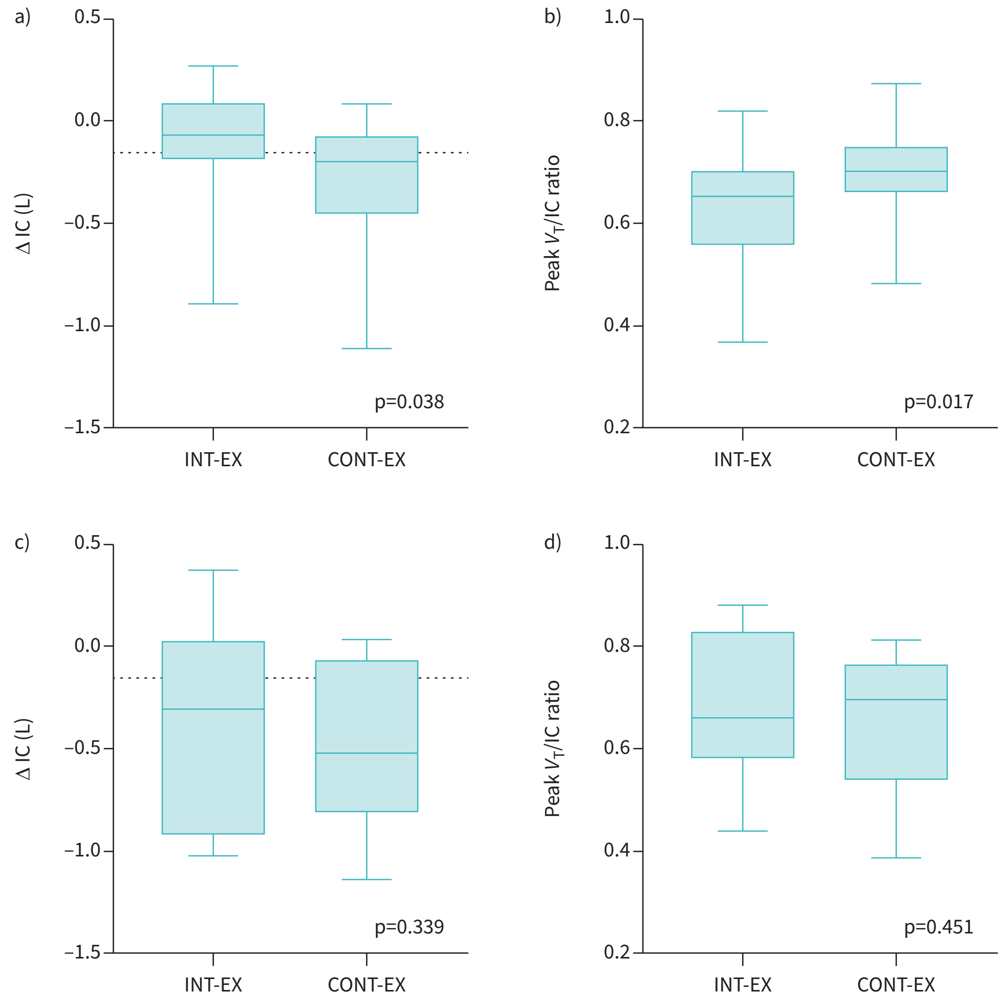

FIGURE 3 Change of inspiratory capacity (IC) from baseline and tidal volume (V_T)/IC ratio at isotime. a, b) n=20 patients with longer Tlim during INT-EX; c, d) n=6 patients with longer Tlim in CONT-EX. Tlim: time to exhaustion; INT-EX: upper-limb interval exercise; CONT-EX: upper-limb continuous exercise. The dotted line refers to the threshold for dynamic insufflation (ΔIC <150 mL) [21].

Conversely, supported upper-limb exercise (arm cranking) seems to allow patients to reach a higher level of oxygen uptake, minute ventilation and afford greater sustainability than unsupported upper-limb exercise [35].

Our data regarding the upper-limb incremental and CONT-EX tests confirm the degree of dynamic hyperinflation and ventilatory and metabolic involvement previously reported for such exercise modalities [36, 37]. The novelty of the present study is the affirmation of the physiological response to upper-limb interval compared to constant-load exercise. Indeed, our study compared the two modalities when sustained at an equivalent work rate to elucidate the mechanisms of exercise intolerance for each modality. The deductions of our findings are made from 1) comparisons at the limit of tolerance (table 2) and 2) comparisons at what we defined as "isotime" – which is the time when work completed was the same between CONT-EX or INT-EX (tables 2 and 3).

Our results emphasise that INT-EX is more efficient than CONT-EX, being associated with greater exercise endurance time, less dynamic hyperinflation and mechanical ventilatory constraints as well as exertional symptoms (tables 2 and 3) in the majority of patients. Table 3 reveals also in patients who had longer Tlim at INT-EX that there is a tendency to have higher mechanical efficiency during INT-EX. However, at the limit of tolerance of INT-EX physiological responses and symptoms were nearly identical to CONT-EX. Indeed, this is the reason why INT-EX was terminated as patients reached their physiological and perception limitations, despite having exercised for longer compared to CONT-EX (table 2).

Possible explanations for the decreased burden caused by INT-EX compared to CONT-EX could be due to a different pattern of upper-limb muscle activation. The alternation between high and low workload may allow for a decrease in the level of fatigue at a given time due to lower metabolite accumulation and metabo-reflex activation [38, 39], and thus delayed metabolic acidosis, that is further supported by significantly lower V'_{CO_2} and respiratory exchange rate. Another possible reason for the delay in the onset of anaerobic metabolism in upper-limb muscles could be related to 1) an increased vascular and microvascular conductance during the low-load phases, which could increase local muscle oxygen availability, and 2) lower recruitment of stabiliser muscles of the upper back [40] working with a sustained isometric contraction when applying a high-intensity exercise with the arms.

This deduction is in line with the study by Romagnoli *et al.* [41] that investigated the chest wall kinematics by optoelectronic plethysmography during constant-load unsupported arm exercise at 80% PWR in patients with COPD, suggesting that the main cause of exercise limitation was arm fatigue and not lower dynamic hyperinflation and breathlessness.

However, our data show that during CONT-EX, the majority of our patients also experienced an impairment of respiratory mechanics manifested by the development of dynamic hyperinflation leading to greater mechanical constraints (figure 3) compared to INT-EX. This could, in turn, have impacted the metabolism of the respiratory muscles by increasing the contribution of anaerobic metabolism due to the disadvantageous working conditions (decrease in respiratory muscle fibre length, poorer blood flow, lower pulmonary compliance with greater resistance to overcome) [42].

Although there are no studies comparing upper-limb INT-EX to CONT-EX, physiological studies performed on the lower limbs document similar findings. Louvaris *et al.* [7] compared continuous exercise at 75% of the PWR and interval exercise designed to produce the same average work rate of 1 min at 100% of PWR alternating with 1 min at 50% in patients with moderate COPD and resting dynamic hyperinflation. They found a longer interval exercise endurance time in all patients and the possibility of reaching a greater total work output when using interval exercise. Similar to our results (figure 3), they found higher dynamic hyperinflation at isotime during continuous exercise and, also, higher symptoms of breathlessness and leg discomfort. These data suggest a similar beneficial impact of interval exercise modality on dynamic hyperinflation for both upper and lower limbs. However, our study reports a few different findings. First, our average Tlim was about half of that described by Louvaris *et al.* [7], probably due to lower sustainably of upper-limb exercise already described in the literature. Second, we identified a small fraction of patients (23%) who do not have a benefit in terms of effort tolerance using interval exercise. This aspect is interesting because patients who achieved a longer interval exercise endurance time were also found to have lower comorbidity and resting lung hyperinflation. Conversely, patients who exhibited longer CONT-EX exhibited greater resting and exercise dynamic hyperinflation, compared to patients with longer INT-EX. They appeared not responsive to the modality of exercise, unlike the patients with longer INT-EX (table 3), who exhibited profoundly lower exercise dynamic hyperinflation during INT-EX compared to CONT-EX and they were therefore more responsive to interval exercise. This aspect was reflected in the intensity of dyspnoea, which was significantly lower at isotime in patients with longer INT-EX compared to CONT-EX. Hence, in COPD patients with profound resting hyperinflation upper arm interval exercise may not convey similar benefits to those seen with lower limb interval exercise [7]. This could suggest the existence of a “window” of benefit during the pathology that could be missed in the most severe pulmonary and clinical conditions, at least regarding upper-limb exercise. Indeed, at present, the physiological studies regarding the use of interval training in patients with COPD have mainly engaged moderate to severe airway obstruction, but none have specifically investigated its application in a very severe population. Indeed, the patients in our study who derived the greatest benefits from interval training exhibited pulmonary function consistent with the findings of Louvaris *et al.* [7] (FEV_1 58%, FVC 82%).

However, recent findings have suggested that the leg cycle ergometer resulted in greater tidal volume, minute ventilation and oxygen consumption than the arm cycle ergometer, while symptomatic responses were similar [13]. Biomechanical aspects of the gesture and modifications in respiratory mechanics when using the upper limbs may preclude a direct comparison with results obtained from studies involving the lower limbs.

Clinical considerations

The benefits of implementing interval training in patients with COPD in the lower limbs are widely recognised, having been shown to improve pulmonary function, exercise capacity and quality of life, which is worthy of clinical promotion for the treatment and care of this population [43]. Interval exercise has been suggested to be superior to continuous training in improving exercise capacity and dyspnoea in patients with chronic respiratory disease; however, the magnitude of the clinical benefit is not considered clinically significant [10] and, currently, the most recent international recommendations suggest interval training as effective as continuous training in a PR setting [3, 4].

Regarding upper-limb training, a recent Cochrane review and other meta-analysis [8–10] compare arm training with no arm training or sham intervention in people with COPD and conclude that this intervention can produce significant improvements in dyspnoea and arm fatigue, function and exercise tolerance suggesting that it should be an essential part of a PR programme for people with COPD. Specifically, when "endurance" arm training was examined in detail, there was a specific capacity to improve the ability to move and lift light weights compared to no training [44].

Despite this fact, the literature still appears limited concerning the comparison between different upper-limb training modalities, and the best exercise modality to propose remains controversial [3, 4]. PR programmes lack specific arm endurance training regimes for COPD, which is unfortunate because COPD patients use their upper arms in daily life and often get very breathless. A recent experts' opinion includes upper-limb training as a "desirable" component of the PR programme, but this treatment was not classified as an "essential" one, due to the lack of strong evidence regarding benefits and the best modality to apply [45]. Nevertheless, people with COPD experience difficulty with arm activities, which is predominantly due to the alterations in the mechanics of breathing, such that the muscles required for arm activities are also required for breathing [10]. Consequently, when performing repeated arm endurance tasks, people with COPD experience breathlessness and early cessation of these tasks, which may affect the quality of life [35]. It is, therefore, conceivable that repeated bouts of arm exercise training could be a useful intervention to improve arm activities in people with COPD; however, there is scant evidence in this area [10, 35].

Indeed, the implementation of interval arm cranking in this context could lead to better physiological adaptations compared to CONT-EX and might be more acceptable by patients because of fewer symptoms.

Novelty

To our knowledge, this is the first study that assessed a supported interval upper-limb exercise and, in this perspective, our work lays the physiological foundation for implementing a new training modality for the upper limbs in a rehabilitation setting, *i.e.* interval "endurance" cycling exercise. With interval arm cranking, patients may find this type of exercise more tolerable (as shown by our results at isotime) and therefore they may engage more during PR. Further clinical studies are necessary to test its efficacy in improving rehabilitation and clinical outcomes in comparison to continuous cycling training and/or strength workouts.

Study limitations

In the present study, we employed specific constant-load and interval protocols without exploring the effectiveness of other intensity or interval modalities presenting various formats of work and recovery phases. Accordingly, the physiological and symptom responses may have been influenced by the choice of these protocols. Our constant-load protocol sustained at 70% PWR is commonly used to assess the efficacy of pharmacological and non-pharmacological interventions and also to compare interval *versus* continuous training in the lower limb on exercise tolerance in patients with COPD [46]. Nevertheless, we cannot exclude the possibility that different protocols may give different results as previously shown in several studies conducted in healthy people and athletes [47]. Different interval exercise protocols such as shorter working phases or longer periods of active rest might yield different results. These alternatives could be explored in patients classified as "non-responders".

In addition, our data lack some important information regarding other factor(s) responsible for the termination of exercise in COPD because we did not test cardiac output, systemic oxygen delivery, local locomotor and respiratory muscle oxygenation, and blood lactate levels. An in-depth evaluation of these aspects, combined with a biomechanical evaluation of movement and respiratory mechanics, would guarantee a broader view of the mechanisms underlying the results obtained. Future studies will need to ensure these assessments.

Finally, our study focused on non-hypoxaemic patients due to technical constraints associated with the use of the portable metabolic cart and the potential confounding factor of oxygen administration. However, this aspect may limit the generalisability of our findings to the population of COPD patients with respiratory failure.

Conclusions

When COPD patients exercise the upper limb by cranking at 70% of peak power output by 1) a constant load at 70% and 2) an interval load alternating between 100% and 40% PWR every 30 s, the time to exhaustion and the total work performed are significantly greater during interval exercise. The present study suggests that upper-limb interval exercise is feasible and more sustainable and efficient than a constant-load exercise in the majority of COPD patients with moderate obstruction, leading to less pulmonary dynamic hyperinflation and symptoms at isotime. Further high-quality studies will evaluate the characteristics of patients who benefit more from this exercise modality and the relationship between ADL and exercise performance in arm cranking exercises in COPD patients, as well as the benefits of its application during PR programmes.

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