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Qualitative dimensions of exertional dyspnea in fibrotic interstitial lung disease

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ABSTRACT

Unsatisfied inspiration is commonly reported during exercise by patients with interstitial lung disease (ILD). However, the physiological basis of perceived dyspnea quality in this population has not been evaluated. We examined the relationship between dyspnea quality and indices of ventilatory-mechanical limitations during exercise in patients with fibrotic ILD.

Sixteen fibrotic ILD patients (12 male) with a median age of 64 years (range 49–81), FVC 71%-predicted (51–100), and DL_{CO} 47%-predicted (27–77) performed incremental and constant work-rate cycle exercise tests to exhaustion. Ventilatory responses were recorded at rest, throughout exercise, and at peak exercise. Dyspnea quality was serially assessed using a 4-item list from which participants selected the phrase that best described their breathing compared to rest.

Increased work/effort was the dominant descriptor of dyspnea throughout exercise, but with increased selection of unsatisfied inspiration following the inflection point of tidal volume relative to ventilation. Delaying or preventing ILD patients from reaching a critically reduced IRV may have implications for symptom management.

1. Introduction

There is increasing evidence that humans can reliably distinguish varying intensities and qualities of dyspnea (Laviolette et al., 2014; Parshall et al., 2012a, b, c). During incremental exercise, healthy individuals report a steady worsening of dyspnea intensity that is typically described as increased work/effort of breathing (Cory et al., 2015). Patients with chronic obstructive pulmonary disease (COPD) also report a progressive increase in dyspnea intensity during incremental exercise, but the predominant descriptor transitions from increased work/effort to unsatisfied inspiration at the tidal volume relative to minute ventilation (V_T/V_E) inflection point (Laveneziana et al., 2011; O'Donnell et al., 2006). At this inflection point, inspiratory reserve volume (IRV) is reduced to the extent where further increases in V_T results in substantial increases in respiratory muscle work (O'Donnell et al., 2006). Breathing at relatively high lung volumes has associated sensory consequences that are observed during incremental and constant-load cycle exercise in patients with COPD (Laveneziana et al., 2011). Patients with interstitial lung disease (ILD) also report unsatisfied inspiration at peak exercise. However, the relationship between the limitation on V_T expansion and dyspnea quality during submaximal exercise has not been evaluated in this population. The purpose of this study was therefore to examine the progression of dyspnea quality during exercise and its relationship to ventilatory limitation in patients with fibrotic ILD.

2. Methods

2.1. Participants

Individuals with mild-to-moderate fibrotic ILD were prospectively recruited from two ILD clinics, including some individuals who concurrently participated in previously published studies that had distinct objectives (Schaeffer et al., 2017, 2018). All participants provided informed written consent prior to enrollment (University of British Columbia Research Ethics Board approval H13-00059). Individuals with

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an arterial oxygen saturation (SpO_2) ≥92% by finger pulse oximetry at rest while breathing room air were eligible. Individuals were excluded for concurrent participation in or recent (< 6 weeks) completion of pulmonary rehabilitation, other diseases that could impair exercise capacity and/or SpO_2, significant emphysema, pulmonary hypertension at rest, and/or the use of prednisone > 10 mg/day for at least two weeks within three months of enrollment. Four participants were excluded from analysis because they did not complete the required study visits (n = 1) or did not have an identifiable V_T/V_E inflection point on both study tests (n = 3).

2.2. Study design

Participation included 3 visits. During Visit 1, participants completed chronic activity-related dyspnea questionnaires (modified Medical Research Council scale and Oxygen Cost Diagram (Mahler and Wells, 1988)), pulmonary function testing, and a symptom-limited incremental cycle exercise test with dyspnea assessment for familiarization. During Visit 2, participants performed another symptom-limited incremental cycle exercise test. During Visit 3, participants performed a symptom-limited constant-load cycle exercise test at 75% of the peak work-rate achieved on Visit 2.

2.3. Pulmonary function

Spirometry, whole-body plethysmography, maximal voluntary ventilation, single-breath diffusing capacity of the lungs for carbon monoxide (DL_{CO}), and maximal inspiratory and expiratory pressures were measured using a commercially available cardiopulmonary testing system (Vmax Encore 229, V62 J Autobox; Carefusion, Yorba Linda, CA, USA) (Gutierrez et al., 2004; Knudson et al., 1983; Morris et al., 1988; Tan et al., 2011).

2.4. Exercise testing protocol

Exercise tests were conducted on an electronically-braked cycle ergometer (Ergoselect 200 P; Ergoline, Bitz, DE) after six min of quiet breathing and one min of unloaded pedaling. Incremental exercise started at 15 W with 15-W stepwise increases in work-rate every two min until volitional exhaustion. Peak work-rate was defined as the highest work-rate sustained for ≥30 s. Constant work-rate exercise tests started with an immediate increase to 75% of peak incremental work-rate until volitional exhaustion. Participants were instructed to self-select a cadence ≥60 rpm for all tests.

2.5. Symptom evaluation

Participants rated the intensity of “breathing discomfort” (dyspnea) and “leg discomfort” at rest, every two min throughout exercise, and at peak exercise using the Borg 0–10 category-ratio scale (Borg, 1982). Participants were also asked to select the phrase that best described their breathing at that moment from a previously-described list of four items: “My breathing requires more work and effort” (work/effort); “I cannot get enough air in” (unsatisfied inspiration); “I cannot get enough air out” (unsatisfied expiration); and “None apply” (Laveneziana et al., 2011). Participants were allowed to select multiple phrases if they were equally applicable.

2.6. Cardiorespiratory responses to exercise

Metabolic and ventilatory responses were measured breath-by-breath and averaged over 30-s epochs (Vmax Encore 229; Carefusion, Yorba Linda, CA, USA). Arterial oxygen saturation was estimated using finger pulse oximetry (Radical-7 Pulse CO Oximeter; Masimo Corporation, Irvine, CA, USA) and heart rate was monitored by 12-lead electrocardiography (Cardiosoft Diagnostics System v6.71; GE Medical Systems, Milwaukee, WI, USA). Operating lung volumes were derived from dynamic inspiratory capacity (IC) maneuvers (Guenette et al., 2013). The V_T/V_E inflection point was determined for each participant by visual examination of individual Hey plots from incremental exercise at Visit 2 by three independent observers (Hey et al., 1966).

2.7. Statistical analyses

A sample size of 16 was chosen based on a similar previously published study in COPD (Laveneziana et al., 2011). Data are presented as mean ± SD or median (interquartile range) unless otherwise specified. Paired t-tests were used to compare outcomes between the incremental and constant work-rate exercise tests at rest, V_T/V_E, and peak exercise. Repeated measures linear regression was used to evaluate between-protocol differences in dyspnea intensity throughout exercise, and to determine the association between dyspnea and each of V_T, V_E, IRV, and SpO_2. Unpaired t-tests were used to assess differences between participants that selected unsatisfied inspiration at any point during exercise on either test protocol and those that never selected unsatisfied inspiration. A p value less than 0.05 was considered statistically significant. Analyses were performed using IBM® SPSS® Statistics for Macintosh, version 25.0 (IBM Corp., Armonk, NY, USA) and STATA® 11.2 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Participants

Participant characteristics are summarized in Table 1. On average, participants had mild reduction in forced vital capacity and moderate reduction in DL_{CO}. None of the participants met regional criteria for home oxygen supplementation (Sandberg and Fleetham, 2013). The eight participants with IPF had similar baseline pulmonary function, peak oxygen consumption, and peak work-rate when expressed as percentages of predicted normal values compared to participants with non-IPF fibrotic ILD.

Table 1
Participant characteristics.

	All participants	“Selectors”	“Non-selectors”
Descriptive characteristics			
Age	65 ± 9	66 ± 7	61 ± 13
Male : Female	12:4	7:4	5:0
BMI, kg/m^2	30 ± 5	28 ± 5	33 ± 5
Diagnosis, number of participants			
IPF	8	6	2
Non-IPF	8	5	3
Time since diagnosis, months	37 (27–46)	40 (27–51)	32 (30–40)
CPI	47 ± 11	48 ± 10	45 ± 14
Modified MRC Dyspnea Scale	1.3 ± 1.1	1.4 ± 1.2	1.0 ± 0.7
Oxygen Cost Diagram, mm	64 ± 15	62 ± 17	68 ± 10
Pulmonary function			
FVC, %predicted	71 (66–86)	81 (66–94)	67 (66–71)
FEV_1, %predicted	77 (71–87)	77 (75–98)	72 (65–74)
FEV_1/FVC, %	80 (78–82)	80 (78–82)	80 (79–81)
TLC, %predicted	67 (59–75)	67 (61–75)	62 (59–73)
DL_{CO}, %predicted	47 (39–57)	46 (42–53)	60 (35–64)
MVV, l/min	114 ± 26	112 ± 26	119 ± 29

Values are mean ± SD or median (interquartile range).
BMI, body mass index; CPI, composite physiologic index; DL_{CO}, diffusing capacity of the lungs for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; MRC, Medical Research Council; MVV, maximal voluntary ventilation; “Non-selectors”, participants that did not select unsatisfied inspiration at any point during exercise; “Selectors”, participants that selected unsatisfied inspiration at any point during exercise; TLC, total lung capacity.

Table 2
Selected sensory and physiological parameters at the V_T/V_E inflection and peak exercise for incremental and constant work-rate exercise tests.

	V_T/V_E Inflection		Peak	
	INCR	CWR	INCR	CWR
Exercise time, min	9.0 ± 3.4	2.5 ± 1.8‡	12.3 ± 4.9	13.1 ± 10.6
Work-rate, W	74 ± 26	73 ± 26	97 ± 35	73 ± 26‡
Dyspnea, 0-10 Borg scale	2.7 ± 2.0	1.7 ± 2.2	5.7 ± 2.2	5.2 ± 2.9
Leg discomfort, 0-10 Borg scale	2.6 ± 1.8	1.6 ± 1.5	5.5 ± 1.9	5.6 ± 2.2
SpO_2, %	92 ± 4	93 ± 3	90 ± 5	90 ± 4
Heart rate, bpm	116 ± 19	112 ± 15	131 ± 20	128 ± 18
Heart rate, %predicted	76 ± 12	74 ± 11	86 ± 11	84 ± 11
VO_2, l/min	1.5 ± 0.4	1.6 ± 0.3	1.8 ± 0.6	1.9 ± 0.5
VO_2, ml/kg/min	17.2 ± 4.8	18.4 ± 5.2	20.9 ± 6.6	22.2 ± 7.0
VO_2, %predicted	58 ± 16	64 ± 20	70 ± 21	76 ± 23
RER	0.99 ± 0.07	1.00 ± 0.11	1.06 ± 0.08	1.03 ± 0.10
V_E, l/min	54 ± 12	55 ± 15	73 ± 18	75 ± 22
V_E/MVV, %	50 ± 19	51 ± 21	66 ± 21	68 ± 23
V_T, l/min	1.53 ± 0.45	1.58 ± 0.47†	1.61 ± 0.51	1.60 ± 0.52
F_B, breaths/min	37 ± 11	37 ± 13	47 ± 10	49 ± 14
EELV, %TLC	56 ± 4	55 ± 5	56 ± 6	55 ± 7
EILV, %TLC	91 ± 6	91 ± 6	92 ± 7	92 ± 8
IRV, l	0.41 ± 0.29	0.39 ± 0.26	0.37 ± 0.26	0.38 ± 0.28

Values are mean ± SD.
CWR, constant work-rate exercise test; EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; F_B, breathing frequency; INCR, incremental exercise test; MVV, maximal voluntary ventilation; RER, respiratory exchange ratio; SpO_2, oxygen saturation by pulse oximetry; TLC, total lung capacity; V_E, minute ventilation; VO_2, oxygen consumption; V_T, tidal volume.
† $p < 0.01$, INCR vs. CWR.
‡ $p < 0.001$, INCR vs. CWR.

3.2. Physiological responses to exercise

Physiological responses to exercise are summarized in Table 2. Participants had reduced peak aerobic capacity compared to predicted values. Breathing pattern and operating lung volumes relative to V_E were similar for incremental and constant work-rate exercise (Fig. 1). The V_T/V_E inflection occurred sooner during constant work-rate exercise compared to incremental exercise (2.5 ± 1.8 vs. 9.0 ± 3.4 min, $p < 0.001$). Beyond the V_T/V_E inflection, further increases in V_E were achieved via increases in breathing frequency (Fig. 1).

3.3. Dyspnea intensity

Baseline dyspnea intensity was greater than zero in three participants prior to incremental exercise and one participant before constant work-rate exercise. There were strong associations between dyspnea intensity and each of V_E, V_T, and IRV in both exercise protocols (all $p < 0.001$). The relationship of dyspnea intensity with V_T as well as IRV was biphasic (Fig. 2), with dyspnea intensity gradually increasing until the V_T/V_E inflection point, after which there was a sharp increase in dyspnea intensity until peak exercise. Median dyspnea intensity at peak exercise was 6 Borg units (range 4–7) for incremental exercise tests and 6 Borg units (3–7) for constant work-rate exercise tests. Dyspnea intensity during incremental exercise was associated with IRV independently of SpO_2 ($p = 0.002$).

3.4. Dyspnea quality

Increased work/effort accounted for 50 and 79% of selections for the description of dyspnea during incremental and constant work-rate exercise, respectively (Fig. 3). Increased work/effort was selected at least once by all participants during incremental exercise and 15 participants (94%) during constant work-rate exercise. Selection frequency of work/effort increased proportionally with increasing dyspnea intensity until the V_T/V_E inflection point, after which the response frequency appeared to plateau (Fig. 4A).

Unsatisfied inspiration was selected at least once by eight participants (50%) during incremental exercise, ten participants (63%) during constant work-rate exercise, and seven participants (44%) on both exercise tests. Selection frequency of unsatisfied inspiration increased after the V_T/V_E inflection during incremental and constant work-rate exercise (Fig. 3). Unsatisfied expiration had the lowest selection frequency of any descriptor throughout exercise, which was never selected during incremental exercise and selected by four participants (25%) accounting for 7% of all selections during constant work-rate exercise (Fig. 3). The selection "None apply" accounted for 38% and 4% of all selections for the description of dyspnea during incremental and constant work-rate exercise, respectively. However, this option was selected early during exercise and no participant selected this descriptor at symptom limitation. Selection frequency of unsatisfied inspiration increased proportionally to increasing dyspnea intensity throughout exercise (Fig. 4B).

3.5. Sub-group analysis

There were no statistically significant differences in resting pulmonary function between participants that selected unsatisfied inspiration ("selectors", n = 11) at any point during exercise compared to participants that never made this selection ("non-selectors", n = 5). Breathing pattern was similar between selectors and non-selectors (Fig. 5A and B). However, our sample size precluded statistical comparison of these sub-groups. The mean IRV at the V_T/V_E inflection tended to be lower in the selectors compared to the non-selectors (0.3 ± 0.2 vs. 0.6 ± 0.4 l, respectively), while selectors had a higher V_T/IC at baseline and throughout exercise (Fig. 5C).

4. Discussion

The main findings of this study are: (i) Ventilatory and perceptual responses to exercise were similar between incremental and constant work-rate protocols in patients with fibrotic ILD, and likely dictated by mechanical limitation on V_T expansion; (ii) perceived work/effort of breathing was the dominant qualitative descriptor of dyspnea throughout incremental and constant work-rate exercise; and (iii) regardless of cycle protocol, selection frequency of unsatisfied inspiration markedly increased at the V_T/V_E inflection point. Collectively, our findings have important implications for exercise rehabilitation programs and symptom management of patients with fibrotic ILD.

4.1. Ventilatory response and limitation

At a given V_E, breathing pattern and operating lung volumes were similar during both exercise protocols. However, ventilatory requirements rose more quickly during constant work-rate compared to incremental exercise, resulting in a limitation on V_T expansion being reached earlier with the constant work-rate protocol. Relationships of dyspnea intensity with V_E, V_T, and IRV during exercise were preserved across protocols, with dyspnea intensity gradually increasing to moderate levels prior to the V_T/V_E inflection, after which dyspnea intensity rose more steeply to severe levels. These data suggest that breathing pattern, dynamic operating lung volumes, and perceived dyspnea intensity in patients with fibrotic ILD are consequences of increased ventilatory requirement in the setting of mechanical limitation on V_T expansion. Furthermore, these changes occurred independently of protocol, oxygenation, and the rate of increase in V_E from rest. Our findings are similar to previously published literature in COPD despite different mechanisms through which a mechanical limitation on V_T expansion occurs in COPD (i.e., dynamic hyperinflation that effectively reduces IRV) (Laveneziana et al., 2011).

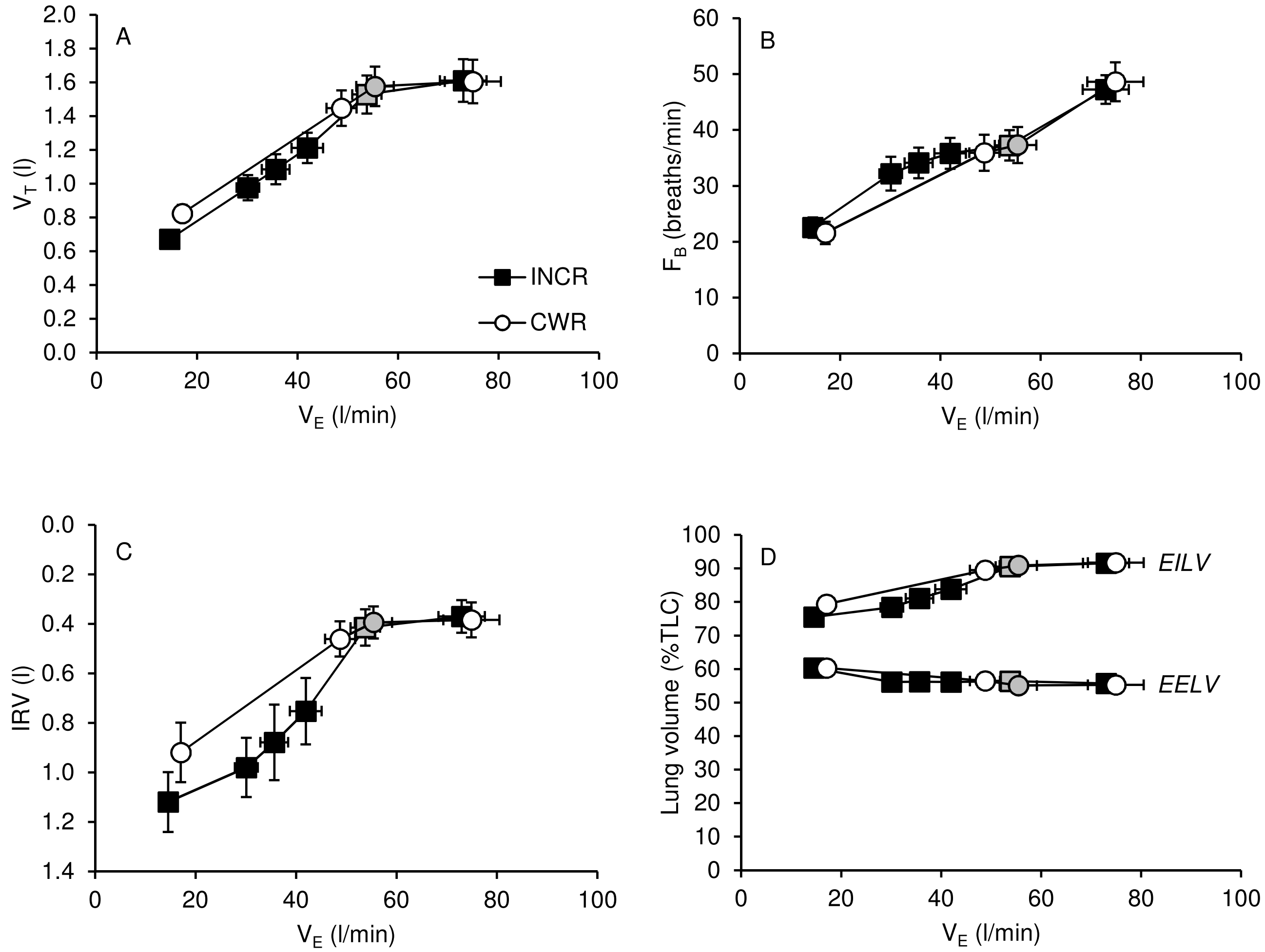

Fig. 1. A) Tidal volume (V_T), B) breathing frequency (F_B), C) inspiratory reserve volume (IRV), and D) operating lung volumes relative to minute ventilation (V_E) during incremental (INCR) and constant work-rate (CWR) exercise. Values are mean ± SEM. Grey markers, V_T/V_E inflection. EELV, end-expiratory lung volume; EILV, end-inspiratory lung volume; TLC, total lung capacity.

4.2. Work/effort and unsatisfied inspiration

Work/effort and unsatisfied inspiration occurred independently of one another during incremental and constant work-rate exercise. Work/effort was the dominant descriptor throughout exercise for both protocols, but selection frequency plateaued despite increasing ventilation and dyspnea intensity after the V_T/V_E inflection point. Conversely, selection frequency of unsatisfied inspiration rose proportionally to increasing dyspnea intensity throughout exercise across protocols. While there was a marked increase in the selection of unsatisfied inspiration after the V_T/V_E inflection point for both protocols, the fraction of participants that identified unsatisfied inspiration as the primary descriptor of dyspnea during exercise never surpassed that of work/effort. This observation differs from previous work in COPD where unsatisfied inspiration is the dominant descriptor of exertional dyspnea after the V_T/V_E inflection point (Laveneziana et al., 2011). These data suggest that the V_T/V_E inflection likely contributes to unsatisfied inspiration in ILD, but that there are likely to be other contributors as well.

It has been suggested that unsatisfied inspiration is a reflection of increased neuromechanical uncoupling (i.e., a disproportionate increase in neural respiratory drive relative to V_T expansion) (O'Donnell et al., 1998). Patients with ILD and COPD have greater neuromechanical uncoupling during exercise compared to age-matched healthy controls, which can largely be attributed to a reduced ventilatory reserve (Faisal et al., 2016). In our study, end-inspiratory lung volume increased up to the V_T/V_E inflection point in patients with ILD. At the V_T/V_E inflection point, these individuals are likely breathing on the upper less-compliant portion of the respiratory system's pressure-volume relationship where greater neural respiratory drive is needed to generate a given inspiratory pressure. The mismatch between neural respiratory drive and the mechanical output of the respiratory system may form the psychophysical basis of unsatisfied inspiration in ILD (O'Donnell et al., 1998).

4.3. Unsatisfied inspiration and inspiratory reserve volume

Previous studies in COPD and asthma have demonstrated that the V_T/V_E inflection point, in the setting of a pathologically reduced IRV, corresponds to an increased perception of unsatisfied inspiration (Laveneziana et al., 2011, 2013). Our results suggest that IRV is similarly important in patients with ILD. Participants in the present study who selected unsatisfied inspiration at any point during incremental or constant work-rate exercise reached a mean minimal IRV of 0.3 l at the V_T/V_E inflection point, whereas those that never made this selection failed to reach this threshold and had a higher mean minimal IRV of 0.6 l. In comparison, the critical, minimal IRV appears to be 0.5 l in both COPD and asthma (Laveneziana et al., 2013; O'Donnell et al., 2006). Our data suggest that sensory consequences of this mechanical event are likely not disease specific, with increased perception of unsatisfied inspiration as a common outcome in patients that reach a V_T/V_E inflection. Additional research is needed to determine if this minimal IRV is similar in more diverse groups of patients.

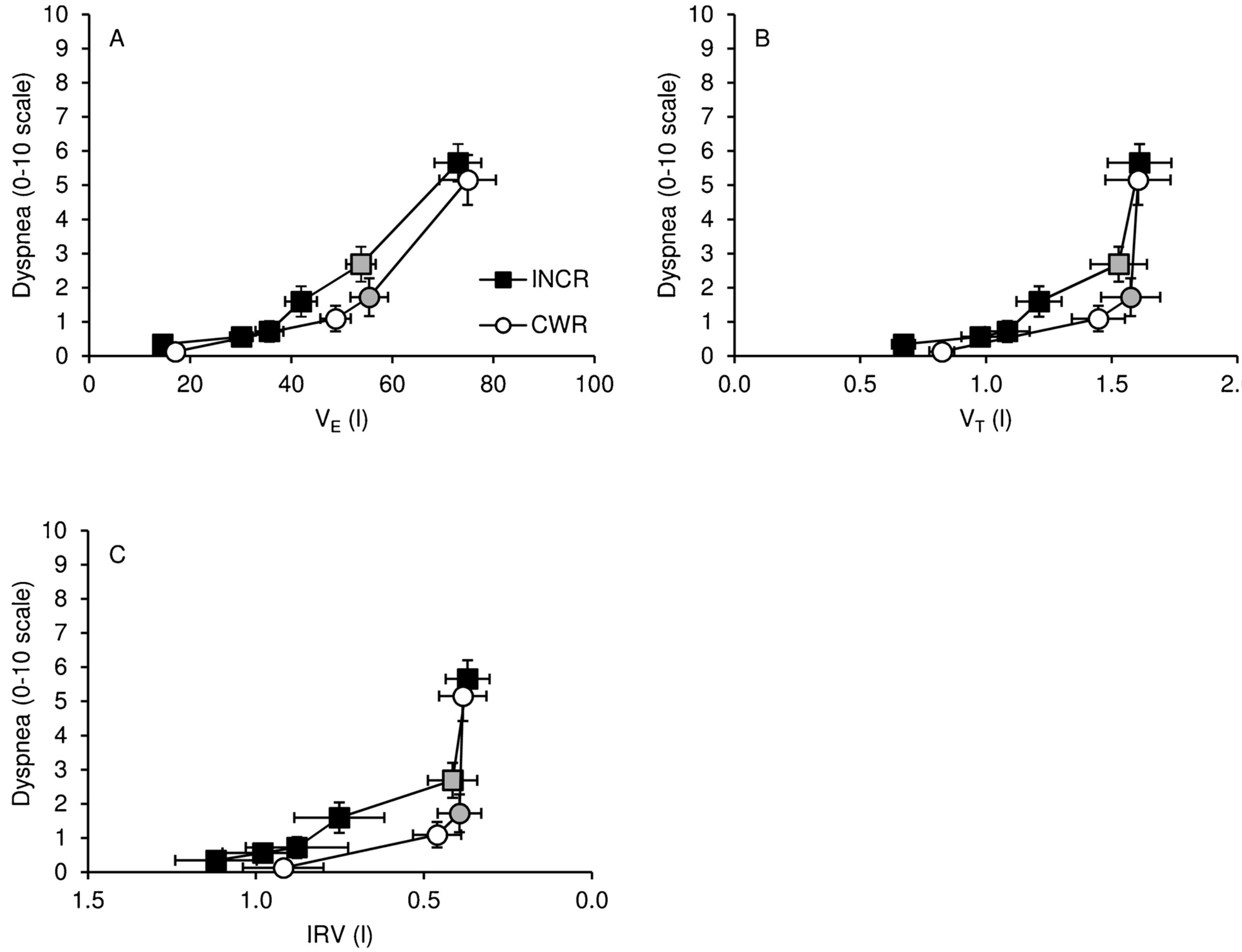

Fig. 2. Dyspnea intensity relative to A) minute ventilation (V_E), B) tidal volume (V_T), and C) inspiratory reserve volume (IRV) during incremental (INCR) and constant work-rate (CWR) exercise. Values are mean ± SEM. Grey markers, V_T/V_E inflection.

We were underpowered to detect significant differences in resting pulmonary function when comparing selectors of unsatisfied inspiration and non-selectors. However, selectors tended to have less pulmonary restriction and worse gas exchange. Interestingly, while resting IC tended to be lower in selectors vs. non-selectors (1.87 vs. 2.47 l, respectively; $p = 0.09$), it was very similar when expressed as a % of the predicted value (60 vs. 62%, respectively; $p = 0.8$). Future studies with larger sample sizes are necessary to determine whether resting pulmonary function can predict perceived dyspnea quality during exercise. Similar to previous work in ILD (O'Donnell et al., 1998), participants that selected unsatisfied inspiration adopted breathing patterns that encroached on their ventilatory capacity to a greater extent than non-selectors, as evidenced by a consistently higher V_T/IC throughout incremental exercise. However, we were limited in our ability to make statistical comparisons between participants that selected unsatisfied inspiration and those that did not, indicating the need for additional studies to test this further.

4.4. Clinical implications

Submaximal dyspnea ratings at a given time point were higher during constant work-rate exercise compared to incremental exercise despite similar durations of exercise and reaching the V_T/V_E inflection earlier during constant work-rate exercise. The incremental exercise tests allowed us to evaluate exercise responses across a spectrum of intensity as well as infer relationships and potential mechanisms of dyspnea quality. The constant work-rate exercise tests allowed us to determine whether those relationships held true under different conditions, and are therefore useful in translating these findings to real world applications. For example, this may be a consideration when designing the exercise components of pulmonary rehabilitation programs (e.g., steady state aerobic exercise, high intensity interval training, etc.). Based upon our findings, interventions that reduce ventilatory requirements and therefore delay the time required to reach the V_T/V_E inflection point in the setting of a minimal IRV are likely to reduce dyspnea intensity and the perception of unsatisfied inspiration in patients with ILD. For example, hyperoxia improves exercise tolerance, and submaximal dyspnea intensity during an acute bout of exercise in patients with fibrotic ILD (Schaeffer et al., 2017). Hyperoxia also results in a more favorable dyspnea quality that may translate into better adherence to a rehabilitation program, with this possibility currently being explored in a large multi-centre clinical trial (Ryerson et al., 2016). These implications are particularly important given the absence of effective symptom-modifying pharmacotherapy for most subtypes of fibrotic ILD (Travis et al., 2013).

4.5. Limitations

There are limitations to this study that must be acknowledged. First, the questionnaire used to assess dyspnea quality during exercise only captured the predominant symptom at each measurement time. For example, while five patients did not select unsatisfied inspiration as the dominant descriptor during exercise, this does not mean that they were not experiencing this sensation. Therefore, we were not able to evaluate

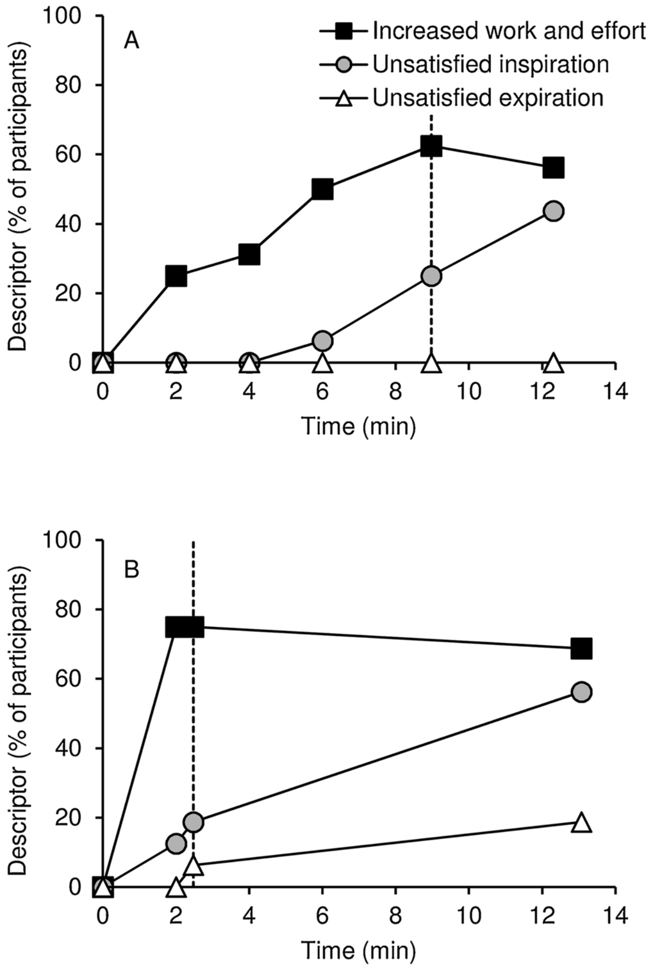

Fig. 3. Selection frequency of dyspnea descriptors during A) incremental and B) constant work-rate exercise. Dashed line, tidal volume relative to minute ventilation (V_T/V_E) inflection.

the intensity of that sensation and/or if any of the other listed sensations were present. Additional studies that assess unsatisfied inspiration using a 0–10 scale would allow for a more mechanistic assessment. Second, we acknowledge that this study has a small sample size and was limited to patients with moderate functional impairment. We recruited from the only two clinics in British Columbia, Canada that specialize in ILD; however, it still took nearly 2 years to reach our sample size. Our sample size is consistent, if not larger, compared to previously published physiological studies in patients with ILD (Bye et al., 1982; Dowman et al., 2017; Faisal et al., 2016; Harris-Eze et al., 1994, 1996; Marciniuk et al., 1994a, b; O'Donnell et al., 1998). This precluded in-depth sub-group analyses between selectors and non-selectors, and furthermore, we are unable to evaluate our findings relative to indices of disease severity. Future studies with larger sample sizes would allow for more translatable findings as well higher-powered sub-group comparisons.

5. Conclusions

The V_T/V_E inflection is an important ventilatory-mechanical event that coincides with a substantial increase in dyspnea intensity during exercise in patients with fibrotic ILD, regardless of exercise protocol. However, this event does not always correspond to a change in the predominant qualitative descriptor of dyspnea from increased work/effort to unsatisfied inspiration. In the present study, the V_T/V_E inflection in the setting of a critically reduced IRV resulted in an increased selection of unsatisfied inspiration as the predominate descriptor of dyspnea. These findings suggest potential strategies that should be tested for their ability to reduce exertional dyspnea in patients with fibrotic ILD.

Author contributions

All authors played a role in the content and writing of the manuscript. MRS, JAG, YMS, AWS, and CJR had input into the study design and conduct of the study; MRS, AHR, SSW, SSD, and CJR collected the data; and MRS, JAG, RAM, SSW, SSD, and CJR performed data analysis.

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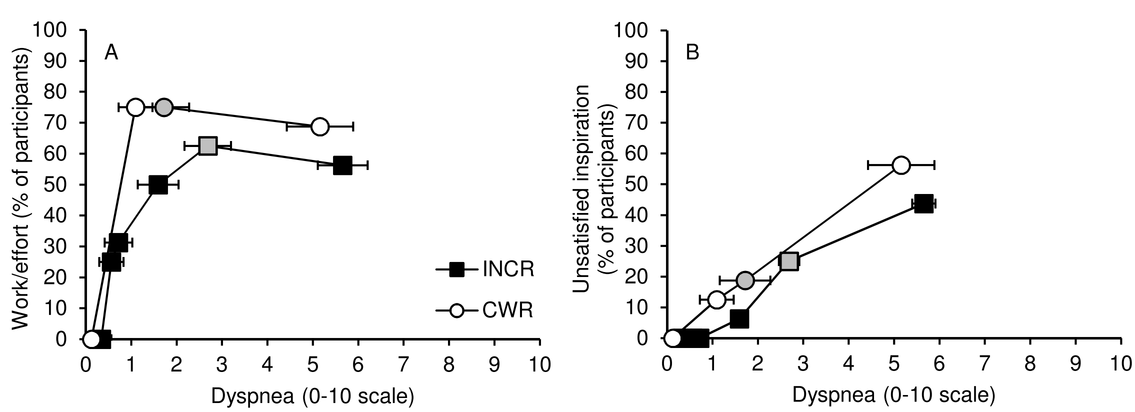

Fig. 4. Selection frequency of A) work/effort and B) unsatisfied inspiration relative to dyspnea intensity during incremental (INCR) and constant work-rate (CWR) exercise. Values are mean ± SEM. Grey markers, tidal volume relative to minute ventilation (V_T/V_E) inflection.

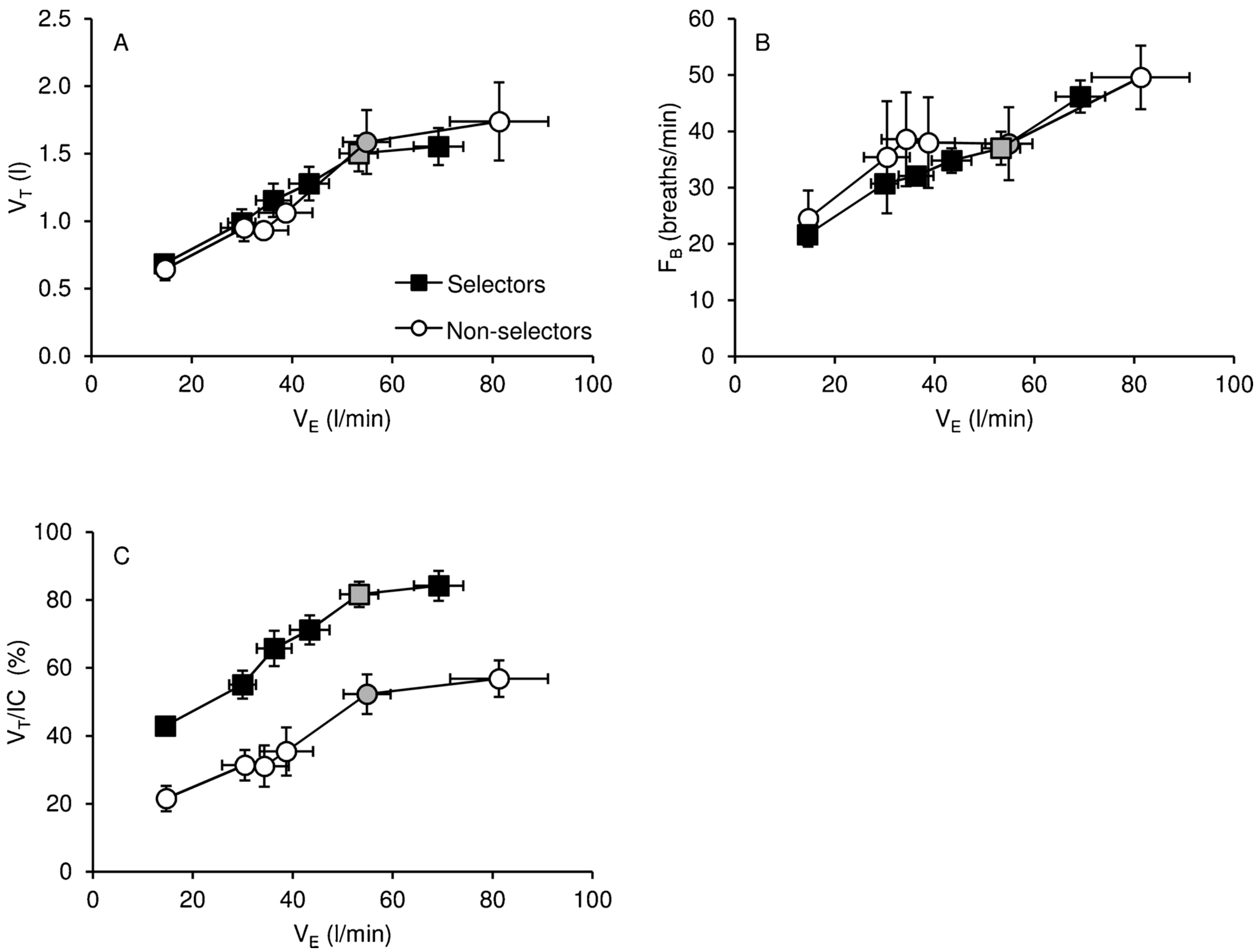

Fig. 5. Ventilatory responses to exercise in participants that selected unsatisfied inspiration (selectors) and participants that did not select unsatisfied inspiration (non-selectors) during incremental exercise. Values are mean ± SEM. Grey markers, tidal volume relative to minute ventilation (V_T/V_E) inflection. F_B, breathing frequency; IC, inspiratory capacity.

Conflict of interests

MRS, AHR, YMS, RAM, SSW, SSD, and AWS have no conflicts of interest that are directly relevant to the content of this article. CRJ reports grants, personal fees and other from Boehringer Ingelheim; grants, personal fees and other from Hoffmann-La Roche; other from ProMetic; other from Syreon Corporation; other from MedImmune; other from Gilead; and other from Actelion; all outside the submitted work. JAG has reports grants from Boehringer Ingelheim outside the submitted work.

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References

Borg, G.A., 1982. Psychophysical bases of perceived exertion. Med. Sci. Sports Exerc. 14, 377–381.
Bye, P.T., Anderson, S.D., Woolcock, A.J., Young, I.H., Alison, J.A., 1982. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. Am. Rev. Respir. Dis. 126, 1005–1012.
Cory, J.M., Schaeffer, M.R., Wilkie, S.S., Ramsook, A.H., Puyat, J.H., Arbour, B., Basran, R., Lam, M., Les, C., MacDonald, B., Jensen, D., Guenette, J.A., 2015. Sex differences in the intensity and qualitative dimensions of exertional dyspnea in physically active young adults. J. Appl. Physiol. 119, 998–1006.
Dowman, L.M., McDonald, C.F., Bozinovski, S., Vlahos, R., Gillies, R., Pouniotis, D., Hill, C.J., Goh, N.S.L., Holland, A.E., 2017. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. Respirology 22, 957–964.
Faisal, A., Alghamdi, B.J., Ciavaglia, C.E., Elbehairy, A.F., Webb, K.A., Ora, J., Neder, J.A., O'Donnell, D.E., 2016. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. Am. J. Respir. Crit. Care Med. 193, 299–309.
Guenette, J.A., Chin, R.C., Cory, J.M., Webb, K.A., O'Donnell, D.E., 2013. Inspiratory capacity during exercise: measurement, analysis, and interpretation. Pulm. Med. 2013, 956081.
Gutierrez, C., Ghezzo, R.H., Abboud, R.T., Cosio, M.G., Dill, J.R., Martin, R.R., McCarthy, D.S., Morse, J.L., Zamel, N., 2004. Reference values of pulmonary function tests for Canadian caucasians. Can. Respir. J. 11, 414–424.
Harris-Eze, A.O., Sridhar, G., Clemens, R.E., Gallagher, C.G., Marciniuk, D.D., 1994. Oxygen improves maximal exercise performance in interstitial lung disease. Am. J. Respir. Crit. Care Med. 150, 1616–1622.
Harris-Eze, A.O., Sridhar, G., Clemens, R.E., Zintel, T.A., Gallagher, C.G., Marciniuk, D.D., 1996. Role of hypoxemia and pulmonary mechanics in exercise limitation in interstitial lung disease. Am. J. Respir. Crit. Care Med. 154, 994–1001.
Hey, E.N., Lloyd, B.B., Cunningham, D.J., Jukes, M.G., Bolton, D.P., 1966. Effects of various respiratory stimuli on the depth and frequency of breathing in man. Respir. Physiol. 1, 193–205.
Knudson, R.J., Lebowitz, M.D., Holberg, C.J., Burrows, B., 1983. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am. Rev. Respir. Dis. 127, 725–734.
Laveneziana, P., Webb, K.A., Ora, J., Wadell, K., O'Donnell, D.E., 2011. Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. Am. J. Respir. Crit. Care Med. 184, 1367–1373.
Laveneziana, P., Bruni, G.I., Presi, I., Stendardi, L., Duranti, R., Scano, G., 2013. Tidal volume inflection and its sensory consequences during exercise in patients with stable asthma. Respir. Physiol. Neurobiol. 185, 374–379.
Laviolette, L., Laveneziana, P., ERS Research Seminar Faculty, 2014. Dyspnoea: a multidimensional and multidisciplinary approach. Eur. Respir. J. 43, 1750–1762.
Mahler, D.A., Wells, C.K., 1988. Evaluation of clinical methods for rating dyspnea. Chest 93, 580–586.
Marciniuk, D.D., Sridhar, G., Clemens, R.E., Zintel, T.A., Gallagher, C.G., 1994a. Lung

volumes and expiratory flow limitation during exercise in interstitial lung disease. J. Appl. Physiol. 77, 963–973.
Marciniuk, D.D., Watts, R.E., Gallagher, C.G., 1994b. Dead space loading and exercise limitation in patients with interstitial lung disease. Chest 105, 183–189.
Morris, J.F., Koski, A., Temple, W.P., Claremont, A., Thomas, D.R., 1988. Fifteen-year interval spirometric evaluation of the Oregon predictive equations. Chest 93, 123–127.
O'Donnell, D.E., Chau, L.K., Webb, K.A., 1998. Qualitative aspects of exertional dyspnea in patients with interstitial lung disease. J. Appl. Physiol. 84, 2000–2009.
O'Donnell, D.E., Hamilton, A.L., Webb, K.A., 2006. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J. Appl. Physiol. 101, 1025–1035.
Parshall, M.B., Carle, A.C., Ice, U., Taylor, R., Powers, J., 2012a. Validation of a three-factor measurement model of dyspnea in hospitalized adults with heart failure. Heart Lung 41, 44–56.
Parshall, M.B., Meek, P.M., Sklar, D., Alcock, J., Bittner, P., 2012b. Test-retest reliability of multidimensional dyspnea profile recall ratings in the emergency department: a prospective, longitudinal study. BMC Emerg. Med. 12.
Parshall, M.B., Schwartzstein, R.M., Adams, L., Banzett, R.B., Manning, H.L., Bourbeau, J., Calverley, P.M., Gift, A.G., Harver, A., Lareau, S.C., Mahler, D.A., Meek, P.M., O'Donnell, D.E., American Thoracic Society Committee on Dyspnea, 2012c. An official ATS statement: update on the mechanisms, assessment, and management of dyspnea. Am. J. Respir. Crit. Care Med. 185, 435–452.
Ryerson, C.J., Camp, P.G., Eves, N.D., Schaeffer, M., Syed, N., Dhillon, S., Jensen, D., Maltais, F., O'Donnell, D.E., Raghavan, N., Roman, M., Stickland, M.K., Assayag, D., Bourbeau, J., Dion, G., Fell, C.D., Hambly, N., Johannson, K.A., Kalluri, M., Khalil, N., Kolb, M., Manganas, H., Moran-Mendoza, O., Provencher, S., Ramesh, W., Rolf, J.D., Wilcox, P.G., Guenette, J.A., 2016. High oxygen delivery to preserve exercise capacity in IPF patients treated with nintedanib: methodology of the HOPE-IPF study. Ann. Am. Thorac. Soc. 13, 1640–1647.
Sandberg, D., Fleetham, J., 2013. Home oxygen therapy in British Columbia. BC Med. J. 55, 149–152.
Schaeffer, M.R., Ryerson, C.J., Ramsook, A.H., Molgat-Seon, Y., Wilkie, S.S., Dhillon, S.S., Mitchell, R.A., Sheel, A.W., Khalil, N., Camp, P.G., Guenette, J.A., 2017. Effects of hyperoxia on dyspnoea and exercise endurance in fibrotic interstitial lung disease. Eur. Respir. J. 49, 1602494.
Schaeffer, M.R., Ryerson, C.J., Ramsook, A.H., Molgat-Seon, Y., Wilkie, S.S., Dhillon, S.S., Mitchell, R.A., Sheel, A.W., Khalil, N., Camp, P.G., Guenette, J.A., 2018. Neurophysiological mechanisms of exertional dyspnea in fibrotic interstitial lung disease. Eur. Respir. J. 51, 1701726.
Tan, W.C., Bourbeau, J., Hernandez, P., Chapman, K., Cowie, R., FitzGerald, M.J., Aaron, S., Marciniuk, D.D., Maltais, F., O'Donnell, D.E., Goldstein, R., Sin, D., LHCE study investigators, 2011. Canadian prediction equations of spirometric lung function for Caucasian adults 20 to 90 years of age: results from the Canadian Obstructive Lung Disease (COLD) study and the Lung Health Canadian Environment (LHCE) study. Can. Respir. J. 18, 321–326.
Travis, W.D., Costabel, U., Hansell, D.M., King Jr., T.E., Lynch, D.A., Nicholson, A.G., Ryerson, C.J., Ryu, J.H., Selman, M., Wells, A.U., Behr, J., Bouros, D., Brown, K.K., Colby, T.V., Collard, H.R., Cordeiro, C.R., Cottin, V., Crestani, B., Drent, M., Dudden, R.F., Egan, J., Flaherty, K., Hogaboam, C., Inoue, Y., Johkoh, T., Kim, D.S., Kitaichi, M., Loyd, J., Martinez, F.J., Myers, J., Protzko, S., Raghu, G., Richeldi, L., Sverzellati, N., Swigris, J., Valeyre, D., ATS/ERS Committee on Idiopathic Interstitial Pneumonias, 2013. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am. J. Respir. Crit. Care Med. 188, 733–748.