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## Resting Hyperinflation Predicts Incremental Shuttle Walk Distance in Chronic Obstructive Pulmonary Disease

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### ABSTRACT

**Rationale:** The incremental shuttle walk test (ISWT) correlates closely with peak oxygen uptake in COPD and relates to important outcomes such as mortality, response to treatment and hospital readmission. Despite this, there is limited data on the physiological determinants of ISWT distance (ISWD) in COPD. **Methods:** In this exploratory, prospective observational study, spirometry, lung volumes, diffusion capacity (DLCO) and oscillometry were performed in patients with confirmed COPD. Patients then completed two ISWT with the results of the best test, measured by distanced walked taken. The determinants of ISWD and dyspnoea measured by BORG score were evaluated. **Results:** 25 COPD patients, mean (SD) age 71 (8.82) years, 48% female with a mean (SD) FEV1 Z-score -2.54 (0.83) were recruited. Median (IQR) ISWD was 350 (210–440) metres (mean (SD) 66.4 (27.9)% predicted distance). Most patients (85%) stopped due to inability to maintain walking speed with submaximal mean heart rate of 77.3 (10.1)% predicted and BORG dyspnoea score of 'severe' (median 5/10 (IQR 4–5.5)). Inspiratory capacity to TLC ratio (IC/TLC) correlated strongly with ISWD, even when corrected for age and height ( $r_s = 0.59$   $p=0.02$ ). Oscillatory reactance ( $X_{rs}$ ) and DLCO were also correlated with ISWD. There were no oscillometric or spirometric predictors of dyspnoea. **Conclusion:** Resting hyperinflation measured by IC/TLC, predicted ISWD despite submaximal dyspnoea, suggesting that hyperinflation may not be the mechanism that limits exercise performance, but rather reflects overall impairment in COPD.

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### KEYWORDS


COPD; shuttle walk test; ISWT; hyperinflation; forced oscillation technique; inspiratory capacity; exercise

## Introduction

Dyspnoea that limits exertion is the cardinal symptom of COPD [1,2]. Walk-tests are simple and practical estimates of exertional capacity and may represent limitations in daily living more accurately than the gold standard of cycle ergometry. The externally paced incremental shuttle walk test (ISWT) relates to mortality and hospital readmission and predicts response to bronchodilators and pulmonary rehabilitation [3–5]. Furthermore, the ISWT distance (ISWD) correlates more closely with peak oxygen uptake than the six-minute walk test (6MWT) distance [6]. There are, however, few data on determinants of ISWD in COPD. Ushiki et al. reported gas trapping (RV/TLC ratio) correlated with ISWD in moderate (as determined by FEV1% predicted) and severe COPD, while DLCO correlated with ISWD in all severities of COPD. FEV1 only correlated with ISWD in severe COPD [7]. Inspiratory capacity (IC) and IC to total lung capacity (IC/TLC) were not specifically assessed.

Hyperinflation is thought to be a strong determinant of exercise limitation in COPD [8] with the premise being that as end-inspiratory volume rises during exercise and comes close to TLC, dyspnoea becomes sufficiently severe that exercise ceases. Expiratory flow limitation (EFL) is the inability to increase expiratory flow rate, despite increases in alveolar driving pressure and is closely linked to

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the development of dynamic hyperinflation. EFL has also been associated with reduced exercise tolerance and greater decline in exercise capacity in COPD [9,10]. Oscillometric reactance (Xrs) reflects the elastic (or dynamic) properties of the respiratory system and is sensitive to lung derecruitment [11] that occurs due to airway narrowing and closure. Xrs at 5 Hz has been shown to correlate closely with measurements of gas trapping and hyperinflation including RV/TLC and single breath alveolar volume (VA)/TLC [11]. Xrs also reflects changes in lung ventilation demonstrated through hyperpolarized helium MRI scans [12]. This is because Xrs closely reflects the volume of lung communicating with the airway opening and is therefore sensitive to gas trapping and dynamic airways collapse.

A greater decrease in Xrs during expiration compared to inspiration accurately predicts EFL. Thus, Xrs as a marker of hyperinflation, gas trapping and EFL may predict ISWD. Our aim was to examine whether Xrs, EFL, measured by the difference between expiratory and inspiratory Xrs ( $\Delta Xrs$ ) and hyperinflation, measured by IC/TLC ratio, correlated with ISWD and dyspnoea induced by ISWT, in COPD.

A subset of the data including oscillometry and lung function was previously published in a study assessing the relationship between supine persistent hyperinflation and oscillatory mechanics [13].

## Materials and methods

### Subjects

This was an exploratory, prospective, observational study. Current or ex-smokers with at least a 10-pack year history, aged >40, with a physician diagnosis of COPD were recruited. Patients with a recent COPD exacerbation (within 8 weeks of enrolment), significant cardiorespiratory, musculoskeletal disease or other major comorbidities, were excluded. Diagnosis was confirmed by post-bronchodilator FEV1/FVC ratio  $\leq$  the lower limit of normal. Ethics approval was obtained prior to patient recruitment (#2021/ETH01142) and all subjects provided written informed consent.

### Lung function

Spirometry, body plethysmography and diffusing capacity (DLCO) were performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria using a Masterscreen Bodybox from Jaeger [14–16]. Pulmonary function was expressed as z-scores, using GLI equations for spirometry, lung volumes and diffusing capacity [17–19]. Resistance (Rrs) and reactance (Xrs) were measured using a TremoFlo oscillometry device (Thorasy, Thoracic Medical Systems) as per European Respiratory Society (ERS) recommendations [20]. A multifrequency signal was used (5, 11, 19 Hz) and quality control was based on laboratory standard protocols in which whole breaths with identified artefacts due to swallows, leaks or coughs were removed. Xrs at 5 Hz was used in the primary analysis as it most closely reflects dynamic compliance and expiratory flow limitation which underpin hyperinflation. IC was measured with the oscillometry device, by three, slow maximal inspiratory breaths from which the mean IC was calculated. Hyperinflation was measured by IC/TLC ratio.

Inspiratory and expiratory reactance (Xrs) were calculated separately and the difference between mean inspiratory and expiratory Xrs ( $\Delta Xrs$ ), was used to assess EFL. A value of  $\Delta Xrs \geq 2.8$  cmH<sub>2</sub>O/(L/s) indicates significant EFL [21]. Predicted values of Oostveen et al. were used for oscillometric parameters [22].

### Walk test

The ISWT was performed as per the ERS/ATS technical standards over a 10-metre interval [3]. Pre-recorded instructions were provided. Patients were instructed to withhold their long-acting bronchodilator medication for 24 h and short acting bronchodilators for 6 h and this was confirmed prior to the walk test. Patients were allowed to use their usual walking aid and those on long term oxygen therapy were allowed to utilise this at their standard flow rate. Walking speed was directed by a standardised, pre-recorded audio signal which increased every minute. The test was terminated if the patient was unable to continue, the operator deemed the patient not fit to continue or the patient

was unable to maintain the required speed. Oxygen saturations, heart rate and modified BORG dyspnoea score were recorded at baseline, at each shuttle and on test completion. Patients were familiarised with the BORG score prior to the test and BORG rating was held up by the investigator on an A3 poster during the test. At the end of each shuttle, patients reported their BORG score to the investigator. If they were unable to report their BORG score, no score was recorded but the end test BORG was taken. Two ISWT were performed, and the results of the best test, based on distance walked (ISWD), were used. Exercise induced breathlessness was measured as the difference between BORG at end exercise and at baseline ( $BORG_{diff}$ ) and through the slope of the BORG score throughout the test ( $BORG_{slope}$ ). The limiting symptom was also recorded. Predicted walk distance was calculated using the reference equation from Probst et al. [23].

### Patient reported outcome measures (PROMs)

Symptom severity was assessed with the St George's Respiratory Questionnaire (SGRQ) and the COPD assessment test (CAT score).

### Statistical analysis

Data was analysed using Jamovi 2.3.28 and SPSS statistics. Graphs were generated using GraphPad Prism version 10.2.2. Values were expressed as mean (SD) for normally distributed data and median (IQR) for non-normal data. To address the hypothesis that hyperinflation, EFL and Xrs correlated with ISWD, univariate relationships were examined using Spearman correlations and multivariate analyses using linear regression, if residuals approximated a normal distribution.

## Results

### Patient demographics

Baseline patient characteristics are summarised in Table 1. Twenty-five patients with a mean age of 70.96 (8.82) years were enrolled. 12 (48%) patients were female and mean body-mass index (BMI)

**Table 1.** Baseline demographic and lung function parameters.  $N=25$ .

Age, years	70.96 (8.82)
Female, N (%)	12 (48)
BMI	27.2 (4.94)
Pack years	34.3 (16.9)
SGRQ	40.7 (13.4)
FEV1 Z-score	-2.54 (0.83)
FEV1 (% predicted)	56.8 (15)
FEV1 (L)	1.44 (0.47)
FVC Z-score	-0.67 (1.08)
FEV1/FVC Z-score	-3.13 (0.82)
TLC Z-score	0.56 (1.06)
TLC (% predicted)	108 (13.4)
TLC (L)	6.09 (1.22)
RV/TLC Z-score	1.59 (0.83)
RV/TLC (% predicted)	132 (17.5)
RV/TLC	49.3 (7.49)
FRC/TLC Z-score	1.11 (1.03)
DLCO Z-score	-3.10 (1.73)
DLCO (% predicted)	57.8 (43-63)
DLCO	10.9 (9.36-15.5)
Rrs <sub>5</sub> Z-score	1.03 (1.7)
Xrs <sub>5</sub> Z-score	-3.65 (3.24)
IC Z-score	-1.25 (0.83)
$\Delta Xrs_5$	2.02 (2.47)

Values are mean (SD) for normally distributed data and median (IQR) for non-normally distributed data. BMI body mass index, RV/TLC residual volume/total lung capacity ratio, FRC/TLC functional residual capacity/total lung capacity ratio, DLCO diffusing capacity for carbon monoxide, IC inspiratory capacity, Rrs<sub>5</sub> respiratory resistance at 5 Hz, Xrs<sub>5</sub> respiratory reactance at 5 Hz,  $\Delta Xrs_5$  difference between inspiratory and expiratory reactance, SGRQ St. George's Respiratory Questionnaire.

was 27.2 (4.94 kg/m<sup>2</sup>). Most patients (76%) were on triple-therapy inhalers and the most common comorbidities were hypertension (48%), musculoskeletal disease (48%) and anxiety (28%). Musculoskeletal disease was mostly reported as mild osteoarthritis with two patients reporting lower back pain that was not currently limiting mobility. One patient utilised a four-wheel walker. This same patient was on long term home oxygen which was also utilised in the walk test. All the other patients walked without aid and without oxygen.

Airflow obstruction was moderate with a mean FEV1 z-score -2.54 (0.83) and FEV1/FVC z-score of -3.12 (0.82) but there was a wide range of FEV1 impairment (-0.78 to -3.8 z-scores). Seated resistance ( $R_{rs_5}$ ) was normal at 1.03 (1.7) z-score and seated reactance  $X_{rs_5}$  was moderately reduced at -3.65 (3.24) z-score. Mean seated  $\Delta X_{rs_5}$  was 2.02 (2.47) cmH<sub>2</sub>O/(L/s), with 32% exceeding the 2.8 cmH<sub>2</sub>O/(L/s) threshold for resting EFL. Mean diffusing capacity (DLCO) was moderately reduced at -3.10 (1.73) z-scores. Mean IC z-score was normal for the group at -0.62 (0.90), and IC/TLC was 0.32 L (0.08) (there are no predicted equations for IC/TLC). RV/TLC was normal at 1.59 (0.83) z-scores.

IC/TLC correlated with age ( $r_s = -0.52$ ,  $p=0.009$ ) and height ( $r_s = 0.48$ ,  $p=0.017$ ). IC/TLC was not related to FEV1 z-score ( $r_s = 0.30$ ,  $p=0.15$ ), FEV1/FVC ratio ( $r_s = 0.25$ ,  $p=0.24$ ) or to diffusing capacity z-score ( $r_s = 0.36$ ,  $p=0.97$ ).

$X_{rs_5}$  correlated with IC/TLC ( $r_s = 0.48$ ,  $p=0.02$ ), RV/TLC ( $r_s = -0.56$ ,  $p=0.005$ ) but not with FRC/TLC ( $r_s = -0.21$ ,  $p=0.32$ ). There was no correlation between IC/TLC and  $X_{rs_5}$  Z score ( $r_s = 0.23$ ,  $p=0.28$ ) or  $\Delta X_{rs_5}$  ( $r_s = -0.27$ ,  $p=0.21$ ).

### Walk test outcomes

Median ISWD was 350 (210–440) metres. The mean percentage of predicted walk distance was 66.4 (27.9)%. Mean end test oxygen saturations were reduced at 89.2 (6.35) % and end test heart rate was elevated at 115 (17.8) beats/minute, which was 77.3 (10.1) % of maximum predicted heart rate. Median modified BORG at baseline was 0 (0.0–1.0) and on test completion was 5 (4.0–5.5), corresponding to a rating of “severe.” The most common reason for test termination was the inability to maintain required speed, in 85% of participants.

### Relationship between lung function and walk test outcomes

Univariate correlations between lung function and walk test outcomes are outlined in Table 2. ISWD correlated with age ( $r_s = -0.43$ ,  $p=0.033$ ), but not with height ( $r_s = 0.306$ ,  $p=0.15$ ) or BMI ( $r_s = 0.07$ ,  $p=0.75$ ). ISWD correlated with IC/TLC ( $r_s = 0.73$ ,  $p<0.001$ ) and there was a borderline correlation with DLCO z-score ( $r_s = 0.42$ ,  $p=0.045$ ). There was a significant relationship between  $X_{rs_5}$  and ISWD (see Figure 1B), but this was not significant when the  $X_{rs_5}$  Z score was used.

When corrected for age and height, IC/TLC was still strongly correlated with ISWD as shown in Figure 1A ( $r_s = 0.59$ ,  $p=0.02$ ). In linear regression, DLCO z-score only contributed an additional 6% of the variance and was not significant ( $p=0.06$ ). FEV1 z-score and FEV1/FVC z-score were not determinants of ISWD ( $r_s = 0.29$ ,  $p=0.16$  and  $r_s = 0.33$ ,  $p=0.11$ , respectively). IC z-score was also not a significant predictor of ISWD ( $r_s = 0.19$ ,  $p=0.38$ ), nor was  $R_{rs}$  or  $\Delta X_{rs}$ .

When looking at predicted walk distance, calculated by reference equation from Probst et al. correlations were found with FEV1 z-score ( $r_s = 0.52$ ,  $p=0.009$ ), RV/TLC z-score ( $r_s = -0.42$ ,  $p=0.045$ ) and IC z-score ( $r_s = 0.42$ ,  $p=0.04$ ).

The difference between BORG at end exercise and at baseline was unrelated to age ( $r_s = -0.130$ ,  $p=0.535$ ), FEV1 z-score ( $r_s = 0.316$ ,  $p=0.124$ ) or FEV1/FVC ( $r_s = 0.371$ ,  $p=0.068$ ), IC or IC/TLC. Similarly, dyspnoea as measured by BORG<sub>slope</sub> was unrelated to any parameter.

### Relationship between symptom scores and walk test outcomes

There were no significant correlations between spirometric or oscillometric parameters and either St George's Respiratory Questionnaire (SGRQ) score or COPD assessment test (CAT) score. There was

**Table 2.** Univariate correlations between lung function and walk test outcomes.

	Distance walked (metres)	Distance walked (% predicted)	BORG <sub>diff</sub>
Age, years	<b>-0.43</b> (0.03)	-0.05 (0.81)	-0.13 (0.54)
Height (cm)	0.27 (0.15)	-0.16 (0.45)	0.06 (0.77)
BMI (kg/m <sup>2</sup> )	0.07 (0.75)	-0.16 (0.44)	0.05 (0.81)
FEV1 Z-score	0.29 (0.16)	<b>0.52</b> <b>0.01</b>	0.32 (0.12)
FVC Z-score	-0.01 (0.97)	0.19 (0.36)	-0.05 (0.82)
FEV1/FVC Z-score	0.33 (0.11)	<b>0.41</b> <b>(0.04)</b>	0.37 (0.07)
TLC Z-score	-0.33 (0.11)	-0.18 (0.41)	-0.41 (0.05)
RV/TLC Z-score	-0.23 (0.29)	<b>-0.42</b> <b>0.045</b>	-0.37 (0.06)
FRC/TLC Z-score	<b>-0.57</b> <b>(0.01)</b>	-0.16 (0.46)	-0.23 (0.30)
DLCO Z-score	<b>0.42</b> <b>(0.045)</b>	0.32 (0.14)	0.23 (0.31)
Rrs <sub>5</sub> Z-score	-0.22 (0.30)	-0.09 (0.66)	-0.11 (0.62)
Rrs <sub>5</sub> cmH <sub>2</sub> O(L/s)	-0.31 (0.13)	-0.13 (0.54)	-0.21 (0.31)
Rrs <sub>5-19</sub> cmH <sub>2</sub> O(L/s)	<b>-0.58</b> <b>(0.004)</b>	-0.39 (0.07)	-0.36 (0.09)
Xrs <sub>5</sub> Z-score	0.24 (0.25)	0.24 (0.26)	0.27 (0.20)
Xrs <sub>5</sub> cmH <sub>2</sub> O(L/s)	<b>0.44</b> <b>(0.03)</b>	0.32 (0.12)	0.38 (0.06)
IC Z-score	0.39 (0.06)	<b>0.42</b> <b>0.04</b>	0.19 (0.38)
IC/TLC	<b>0.73</b> <b>(&lt;0.001)</b>	0.4 (0.06)	0.40 (0.06)
ΔXrs <sub>5</sub> cmH <sub>2</sub> O(L/s)	-0.29 (0.16)	-0.26 (0.21)	-0.37 (0.07)

Values are Spearman correlation coefficients (p-values). **Bold** denotes statistical significance. *N* = 25. BMI body mass index, FRC/TLC functional residual capacity/total lung capacity ratio, RV/TLC residual volume/total lung capacity ratio, DLCO diffusing capacity for carbon monoxide, Rrs<sub>5</sub> respiratory resistance at 5 Hz, Xrs<sub>5</sub> respiratory reactance at 5 Hz, Rrs<sub>5-19</sub> respiratory resistance at 5 Hz- resistance at 19 Hz, IC inspiratory capacity, IC/TLC inspiratory capacity/total lung capacity, ΔXrs<sub>5</sub> difference between inspiratory and expiratory reactance at 5 Hz.

no correlation between overall SGRQ or CAT score and ISWD or dyspnoea, however, a significant relationship was seen between SGRQ symptom sub-score and lower walk distance ( $r_s = -0.41$ ,  $p = 0.04$ ).

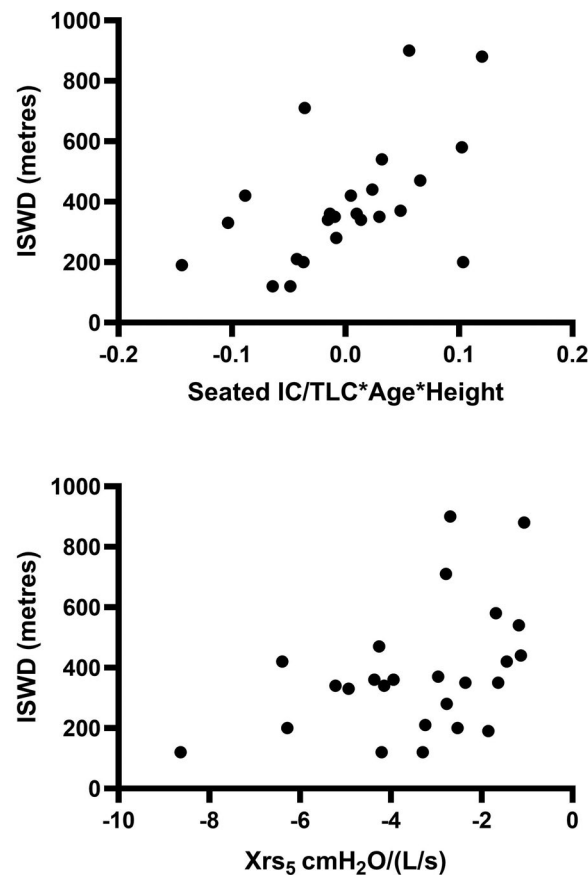
## Discussion

Our novel findings were that resting hyperinflation, as measured by IC/TLC ratio, Xrs<sub>5</sub> and age were predictors of ISWD, but not airflow obstruction measured by spirometry, or EFL (ΔXrs). IC/TLC ratio was the sole predictor of ISWD in multi-variable regression. Despite this strong relationship, dyspnoea was not the limiting factor for exercise termination, with most patients stopping due to inability to maintain walking speed and demonstrating submaximal heart rate responses and dyspnoea severity scores. These findings suggest that hyperinflation is not the mechanism that limits exercise but rather a surrogate measure of functional impairment.

There are few known determinants of ISWD in COPD. Ushiki and colleagues [24] have reported a relationship between the absolute IC and ISWD, the IC not having been corrected for TLC, age or height. In a subsequent larger study, the strongest determinants were diffusing capacity and FEV1% predicted, although the FEV1 correlation was driven by those with severe disease only. The authors did not report any relationships with either IC or IC/TLC<sup>7</sup>.

Although patients in our study did not report breathlessness as the limiting factor, it is possible that they developed dynamic hyperinflation and ventilatory limitation to exercise, and this manifested as an inability to maintain the required walking speed. We did not conduct IC measurements during





**Figure 1.** A) Relationship between seated inspiratory capacity/total lung capacity (IC/TLC) ratio corrected for age and height and total distance walked  $r_s = 0.59$ ,  $p=0.0024$ ; B) Relationship between  $Xrs_5$  cmH<sub>2</sub>O/(L/s) and total distance walked  $r_s = 0.44$ ,  $p=0.027$ .

exercise and therefore cannot comment on dynamic hyperinflation occurring during exercise. The explanation that dynamic hyperinflation occurred and was the cause of exercise termination would be in keeping with previous research postulating strong relationship between dynamic hyperinflation and exercise limitation in COPD<sup>8</sup>. Against this theory in our study is the sub-maximal BORG at end exercise, which is lower than reported in previous studies of COPD patients in symptom limited cycle ergometry [2,25,26]. Similarly, most patients in cycle ergometry studies report dyspnoea as the cause of exercise termination compared with our study where walking speed limited exercise in the majority of patients [8,27]. However, we acknowledge that patient reported symptom measures are inherently subjective and may not be reliable.

The concept that hyperinflation may not be a limiting factor in COPD has been described previously. Guenette and colleagues and Aliverti and colleagues both found no difference in exercise duration and dyspnoea scores between COPD patients deemed to be “hyperinflators” and those who were “non-hyperinflators.” Aliverti and colleagues also found that reducing dynamic hyperinflation in COPD with bronchodilators did not improve mean exercise duration [28–30]. However, an earlier study by O'Donnell and colleagues showed daily administration of tiotropium increased IC with resultant increases in exercise capacity and reduced dyspnoea [26]. An explanation for this discordance may be sample size, with the O'Donnell study including 96 patients compared to 18 patients in the Aliverti study. These differences may also reflect heterogeneity within the COPD cohort, with dynamic hyperinflation being one of several causes of ventilatory limitation.

The relationship between increasing age and reduced walk distance in the present study, is consistent with studies conducted in healthy individuals [23,31] and likely represents age related effects on joints and muscles, and reduced maximal walk speed. There is also the potential for older COPD

patients to have worse hyperinflation,  $Xrs$  and  $\Delta Xrs$ , hence the need to account for age in examining these relationships.

There was a significant relationship between  $Xrs_5$  and ISWD. Other measures of resting hyperinflation including RV/TLC and TLC did not correlate with ISWD. It is possible that IC/TLC and FRC/TLC are better markers of overall mechanical impairment and tidal breathing mechanics in relation to walking. In this study,  $\Delta Xrs_5$  correlated poorly with measures of gas trapping and hyperinflation which is in contrast to our previous study with a larger sample size [13], and this may explain the lack of significant relationship with exercise limitation.

There was a weak relationship between greater patient reported symptoms (SGRQ symptom sub-score) and reduced walk distance, although no relationship was seen with overall SGRQ or CAT score and either ISWD or dyspnoea. This suggests that while the ISWD may reflect lung function and functional reserve, it poorly reflects quality of life in COPD patients who typically self-pace in activities of daily living.

The main weakness of this study is the small sample size, meaning the results are not generalisable to a larger COPD cohort, particularly those with more severe airflow obstruction or more severe resting hyperinflation - noting that the baseline IC and RV/TLC z-scores for our patients were within normal limits. As mentioned above, a major weakness was that IC was not measured at end exercise, meaning that increased dynamic hyperinflation occurring in exercise was not assessed. A larger, pre-planned study with end-exercise IC manoeuvre is currently underway to further investigate this relationship. The use of Oostveen reference equations for oscillometry is a potential weakness as these are derived from different oscillometry devices to that utilised in this study.

In conclusion, resting hyperinflation is a strong determinant of ISWD in COPD, independently of age, while spirometry and EFL are not. The mechanism of exercise limitation appears unrelated to patient reported dyspnoea, suggesting that hyperinflation may be a marker of overall disease severity, rather than the driver of exercise limitation alone, however, further analysis with a larger cohort and measures of hyperinflation during exercise is required for confirmation. Our results support a holistic and multidisciplinary approach to exercise rehabilitation in COPD, where identifying determinants of exercise limitation in addition to hyperinflation, might be useful in customising an exercise program.

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## Ethics approval

Ethics approval was obtained prior to patient recruitment from the Northern Sydney Local Health District (NSLHD) Human Research Ethics Committee 2021/ETH01142. All subjects provided written informed consent.

## Author contributions

M.S. and G.K. conceived and designed the research. M.S. D.T. D.C. and K.B. performed experiments. M.S. and G.K. analysed the data. M.S. and G.K. interpreted results of experiments. M.S. prepared figures and drafted the manuscript. All authors contributed to revising the article, gave final approval for the version to be published and agree to be accountable to all aspects of the work.

## Disclosure statement

Prof King is a non-executive board member of Cyclomedica Ltd, Australia. He has received honoraria for consultancy services from AstraZeneca, Chiesi, GSK, Sanofi. He receives grants from Cyclomedica and philanthropic trusts. A/Prof Tonga has received honoraria for consultancy services from AstraZeneca and Chiesi.



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