Day-to-day variability of forced oscillatory mechanics for early detection of acute exacerbations in COPD

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ABSTRACT

Background: Telemonitoring trials for early detection of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) have provided mixed results. Day-to-day variations in lung function measured by the forced oscillation technique (FOT) may yield greater insight. We evaluated the clinical utility of home telemonitoring of variability in FOT measures in terms of 1) the relationship with symptoms and quality of life (QoL); and 2) the timing of variability of FOT measures and symptom changes prior to AECOPD.

Methods: Daily FOT parameters at 5 Hz (resistance (R) and reactance (X); Resmon Pro Diary, Restech Srl, Milan, Italy), daily symptoms (COPD Assessment Test (CAT)) and 4-weekly QoL data (St George's Respiratory Questionnaire (SGRQ)) were recorded over 8–9 months from chronic obstructive pulmonary disease (COPD) patients. Variability of R and X was calculated as the standard deviation (SD) over 7-day running windows and we also examined the effect of varying window size. The relationship of FOT *versus* CAT and SGRQ was assessed using linear mixed modelling, daily changes in FOT variability and CAT prior to AECOPD using one-way repeated measures ANOVA.

Results: Fifteen participants with a mean±SD age of 69±10 years and a % predicted forced expiratory volume in 1 s (FEV_1) of 39±10% had a median (interquartile range (IQR)) adherence of 95.4% (79.0–98.8%). Variability of the inspiratory component of X (indicated by the standard deviation of inspiratory reactance (SDX_{insp})) related to CAT and weakly to SGRQ (fixed effect estimates 1.57, 95% CI 0.65–2.49 (p=0.001) and 4.41, 95% CI −0.06 to 8.89 (p=0.05), respectively). SDX_{insp} changed significantly on the same day as CAT (1 day before AECOPD, both p=0.02) and earlier when using shorter running windows (3 days before AECOPD, p=0.01; accuracy=0.72 for 5-day windows).

Conclusions: SDX_{insp} from FOT telemonitoring reflects COPD symptoms and may be a sensitive biomarker for early detection of AECOPD.

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Introduction

The bulk of the significant healthcare burden from chronic obstructive pulmonary disease (COPD) is due to acute exacerbations of COPD (AECOPD) [1]. AECOPD is associated with greater worsening of health status [2] and may modify the course of disease *via* permanent loss of lung function [2, 3]. Furthermore, frequent severe AECOPD increase mortality risk [4].

Early treatment of AECOPD can lead to faster recovery, reduced hospitalisation risk and better quality of life (QoL) [5]. Therefore, the ability to detect AECOPD early and reliably may enable timely intervention and ultimately improve COPD outcomes. Observational studies using home telemonitoring with symptom diaries and/or physiological measures have shown promise in detecting AECOPD [6] early [7, 8]; however, interventional trials have provided mixed efficacy results due to heterogeneity in methods and outcome measures [9–13]. A recent large, randomised study (CHROMED) [14] examined the use of home telemonitoring in COPD with the forced oscillation technique (FOT), an objective, effort-independent method to measure airway mechanics. No benefit was demonstrated in time to first hospitalisation or QoL, although there was a 54% reduction in repeat hospitalisations. In that study, the intervention was triggered by detecting linear trends of worsening in FOT parameters.

There may be value in evaluating the day-to-day variability of FOT parameters, as distinct to mean FOT parameters or their linear trends over time. This is because physiological systems exhibit measurable natural variations that alter with disease [15, 16]. Variability of FOT measures is known to be increased in COPD compared with healthy controls [17]. This may reflect the heterogeneous nature of COPD with great variation both between patients and over time (*e.g.* in terms of exacerbation susceptibility [18, 19] or lung function decline [20]). The worsening of airway function during AECOPD [21, 22] potentially further increases this variability. Hence, variability of FOT measures may provide a reliable way of objectively detecting AECOPD onset and may guide management [23]. In asthma, variability of FOT measures has provided the basis for markers with high sensitivity and specificity in detection of lung function-defined exacerbations [24, 25], but this has not been explored in COPD.

To determine its clinical utility, we aimed to examine variability of FOT measures using long-term home telemonitoring in COPD and to relate these measures to symptoms and QoL, as well as their ability to detect AECOPD onset. We also aimed to determine the optimum time frame over which to assess variability of FOT measures. We hypothesised that 1) the variability of FOT measures is related to symptoms and QoL; and 2) the changes in variability of FOT measures occur with symptoms at AECOPD onset.

Methods

Subjects

Adults aged between 40 and 85 years with COPD were eligible, with COPD defined clinically by forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <lower limit of normal (LLN) and FEV_1 <80% predicted (Global Lung Function Initiative (GLI) reference equations [26]) with a ⩾10 pack-year smoking history. Exclusion criteria comprised α_1-antitrypsin deficiency, any systemic disease impairing ventilatory function or significant inflammatory pathology other than COPD, previous lung surgery, any other significant neurological or medical condition (like uncontrolled malignancy, or end-stage cardiac, liver or renal insufficiency), or current enrolment in another research trial. The study was approved by the Sydney Local Health District Human Research Ethics Committee (HREC/13/CRGH/16) and is part of a clinical trial registered on ClinicalTrials.gov (NCT01552031). All subjects provided written informed consent.

Study design

This was a prospective, observational study that recruited participants from three sites across Sydney, Australia (see figure 1 for the study protocol). At enrolment a detailed clinical assessment, including smoking and exacerbation history, medication use and standard lung function measures (pre- and post-bronchodilator spirometry, plethysmographic lung volumes and diffusing capacity of the lung for carbon monoxide (D_{LCO})), was obtained according to American Thoracic Society (ATS)/European

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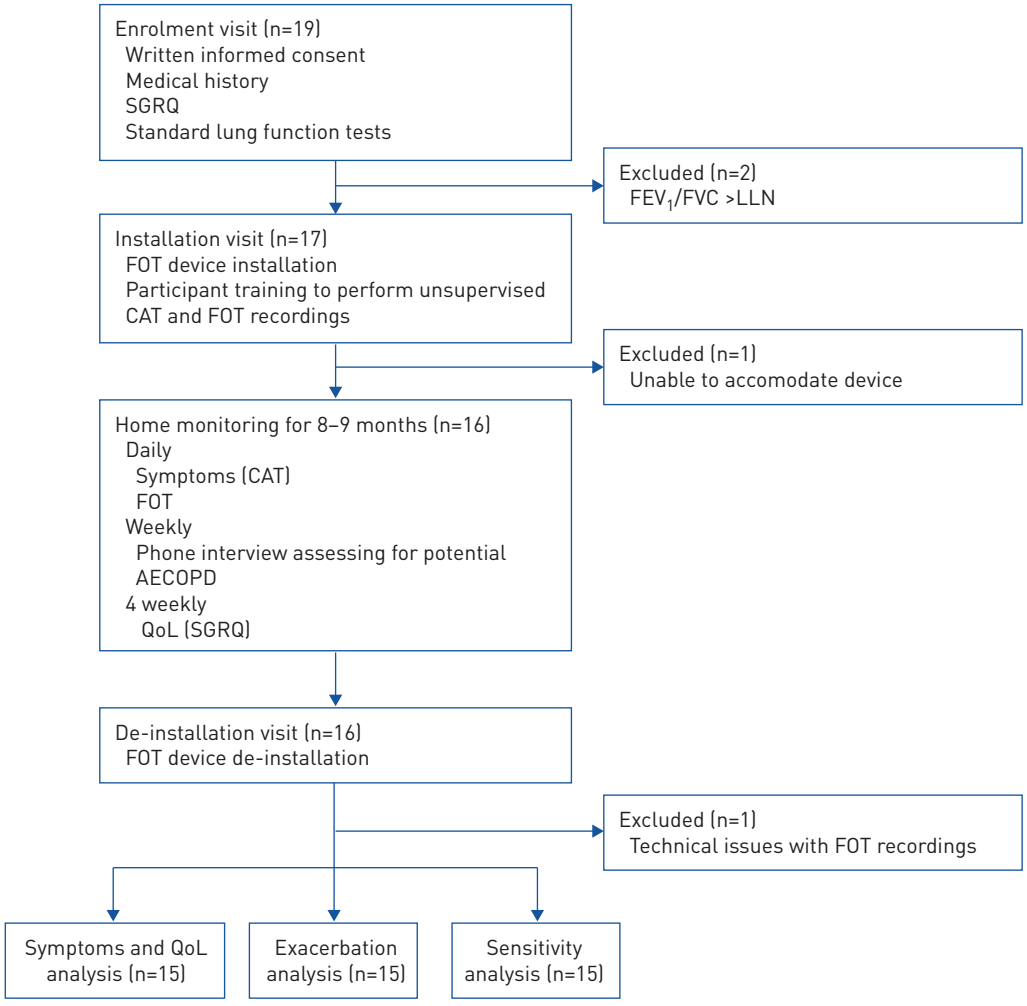

FIGURE 1 Flow diagram for the study protocol. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; SGRQ: St George's Respiratory Questionnaire; FOT: forced oscillation technique; CAT: COPD Assessment Test; AECOPD: acute exacerbation of COPD.

Respiratory Society (ERS) criteria [27] using standard predicted values [26, 28, 29]. Subsequently, study personnel visited the participant's home to install the FOT telemonitoring device (Resmon Pro Diary, Restech Srl, Milan, Italy) and provide training on FOT self-measurement. For 8–9 months, each morning before taking their inhaled COPD medication, participants recorded their symptoms by electronic COPD Assessment Test (CAT) [30] *via* a touch-screen computer built into the FOT device. This was followed by a single, 2-min FOT measurement during tidal breathing. If less than five acceptable breaths were detected, the software automatically prompted the participant to repeat the recording. FOT and symptom data were encrypted and automatically transmitted to the central study server *via* mobile internet (2G/3G). Participants were called weekly to capture any changes in symptoms and/or management, as well as any occurrence of AECOPD. QoL was assessed 4-weekly by telephone using the St George's Respiratory Questionnaire (SGRQ).

Exacerbation definition

An AECOPD, assessed *via* participant recall during the weekly telephone interview, was defined by an increase in respiratory symptoms requiring oral corticosteroids and/or antibiotics, with or without medical review and/or hospitalisation. Consecutive AECOPD episodes were classified as distinct events if separated by a pre-defined interval of $\geqslant$7 days without treatment with corticosteroids and/or antibiotics and/or hospital admission, or else they were combined as a prolonged, non-resolving exacerbation event.

Forced oscillation technique

Measurements of respiratory system impedance were obtained using FOT at 5 Hz to derive mean respiratory resistance (R) and mean respiratory reactance (X). We further examined the inspiratory and

expiratory components of resistance (R_{insp} and R_{exp}, respectively) and reactance (X_{insp} and X_{exp}, respectively), and focus here on reporting R_{insp} and X_{insp}, although detailed results of total and expiratory resistance and reactance can be found in the supplementary material. In addition, we evaluated $R_{5–19}$ (mean R at 5 Hz minus mean R at 19 Hz, a measure of frequency dependence of resistance) and ΔX (mean X_{insp} at 5 Hz minus mean X_{exp} at 5 Hz, a measure of expiratory flow limitation [31]), as well as breathing pattern during the FOT measurements (*i.e.* respiratory rate (RR) and tidal volume (V_T)).

For each parameter, variability was calculated as the standard deviation (SD) over a 7-day time window, running across the entire time series. We also examined variability as assessed by the coefficient of variation (CV) of each window (*i.e.* the SD/mean ratio).

Data processing and statistical analyses

Full details of data processing and statistical analysis can be found in the supplementary material. Data were processed using MATLAB version 9.2 (MathWorks, Natick, MA, USA). All statistical analyses were performed using R version 3.4.1 (The R Project for Statistical Computing, www.r-project.org), with statistical significance defined as $p<0.05$.

Relationship between variability of FOT measures, symptoms and QoL

To assess the relationship between variability of FOT measures and symptoms, we compared the mean and SD of each FOT measure *versus* the corresponding mean CAT score calculated within 7-day windows. Separate linear mixed-effects models were used for each FOT variable or its SD as the fixed effect, with mean weekly CAT score as the outcome and subject as the random effect. This allowed us to adjust for clustering of multiple repeated measurements within the same subject.

To assess the relationship between FOT variability and QoL, separate linear mixed-effects models were again used for each FOT measure or its SD as the fixed effect, with 4-weekly SGRQ score as the outcome and subject as the random effect.

Timing of changes prior to AECOPD

To evaluate the timing of changes in variability of FOT measures and symptoms prior to an AECOPD, we examined the mean and SD of each FOT parameter and the corresponding mean CAT score calculated within each 7-day window in the days leading up to each AECOPD, using one-way repeated measures ANOVA. Each onset of AECOPD was assigned as Day 0 (the date when symptoms started as recalled by the participant during the weekly telephone interview) and Dunnett's *post hoc* test was used to compare each day against a baseline, defined as Day −7 (which represents the mean FOT, SD FOT or mean CAT value calculated for the period ranging from Day −13 to Day −7 before AECOPD onset, respectively). We also used receiver operating characteristic (ROC) curves to assess accuracy in detecting AECOPD (see supplementary material).

Sensitivity analyses

We chose a 7-day running window size for the assessment of variability of FOT measures based on previous similar work in asthma, for both peak expiratory flow (PEF) [32, 33] and FOT [24, 25]. For each analysis in this study, we also evaluated the effect of varying this window size on the results.

Results

Subject demographics

Nineteen participants attended the study enrolment visit. Two of these did not meet the inclusion criteria for airway obstruction and the FOT device could not be accommodated in one home. Following completion of the home-monitoring period, one subject's data had to be excluded from the analyses due to technical concerns over the FOT recordings (recurrently low measurements of R, suggesting the possibility of a significant leak during measurements).

As per intention-to-treat analysis, the data of 15 participants collected over 3525 days were available for analysis. The analysed cohort (11 out of 15 male, mean±SD age 69±10 years, smoking history 51±26 pack-years) had moderate to severe COPD (FEV_1/FVC ratio 34±6, % predicted FEV_1 39±10%) based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging criteria [1] and were severely limited in their health-related quality of life (HRQoL), as assessed by the SGRQ [34] at time of enrolment. Anthropometrics, lung function data and baseline subject characteristics are listed in table 1.

Adherence with the study recordings was high (median 95.4%, interquartile range (IQR) 79.0–98.8%), although this included one premature subject withdrawal after 4 months due to non-adherence with the daily FOT recordings (defined in our study as less than 50%). In terms of acute exacerbations, 13 out of 15 participants experienced a total of 37 AECOPD over the study period (mean±SD 2.47±2.03 (range 1–6)

TABLE 1 Baseline characteristics of study participants

Characteristic	Baseline	Z-score
Subjects	15	
Male sex	11	
Current smoker	2	
Age years	69±10	
BMI kg·m^{-2}	22.4±4.8	
Smoking history pack-years	51±26	
FEV_1 L	1.07±0.29	−3.55±0.68
FEV_1 % predicted	39±10	
FEV_1/FVC %	34±6	−4.37±0.56
D_{LCO}# % predicted	34±11	−5.28±1.93
R total cmH_2O·s·L^{-1}	4.87±1.63	2.56±1.41
X total cmH_2O·s·L^{-1}	−3.90±1.81	−5.79±3.00
MRC dyspnoea score	2.80±0.94	
CAT score	17.6±9.0	
SGRQ total score	49.3±17.9	
Inhaled LAMA, LABA and ICS	15 (100)	
Written COPD action plan#	10 (67)	
⩾1 AECOPD in 12 months pre-enrolment	11 (73)	
⩾2 AECOPD in 12 months pre-enrolment	8 (53)	
1–2 AECOPD hospitalisations in 12 months pre-enrolment	8 (53)	
Cardiovascular comorbidities¶	10 (67)	

Data are presented as n, n (%) and mean±SD, unless otherwise stated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; R: resistance; X: reactance; MRC: Medical Research Council; CAT: COPD Assessment Test; SGRQ: St George's Respiratory Questionnaire; LAMA: long-acting muscarinic antagonist; LABA: long-acting β-agonist; ICS: inhaled corticosteroids; COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD. #: n=14 (one subject was unable to perform the D_{LCO} test). Z-scores represent the number of standard deviations (SD) away from the predicted value (calculated from Quanjer *et al.* [26] for spirometry and Oostveen *et al.* [35] for forced oscillation technique (FOT) measures); ¶: includes hypertension and ischaemic heart disease.

AECOPD per subject), comprising 16 AECOPD requiring oral corticosteroids, 17 AECOPD requiring oral antibiotics and 4 hospitalisations. The duration of an AECOPD in the study cohort was mean±SD 15.0±9.0 days (range 4–43 days) (n=35 for this analysis as the treatment period for two AECOPD was ongoing at the end of the study).

TABLE 2 Relationship between forced oscillation technique (FOT) measures and symptoms (COPD Assessment Test (CAT)) or respiratory quality of life (QoL) (St George's Respiratory Questionnaire (SGRQ))

Parameter	CAT score#		SGRQ total score#	
	Fixed Effect Estimate (95% CI)	p-value	Fixed Effect Estimate (95% CI)	p-value
R_{insp}#	0.002 (−0.37 to 0.37)	0.99	0.27 (−1.73 to 2.27)	0.79
SDR_{insp}	0.43 (−0.38 to 1.24)	0.30	3.39 (−1.11 to 7.89)	0.14
X_{insp}#	**−0.59 (−1.02 to −0.15)**	**0.009**	−1.30 (−3.55 to 0.94)	0.25
SDX_{insp}	**1.57 (0.65–2.49)**	**0.001**	4.41 (−0.06 to 8.89)	0.05
RR#	**0.48 (0.38–0.58)**	**<0.001**	0.01 (−0.48 to 0.50)	0.97
SDRR	**0.41 (0.15–0.67)**	**0.002**	−0.22 (−1.61 to 1.17)	0.75
V_T#	**−12.5 (−15.3 to −9.8)**	**<0.001**	−2.09 (−16.24 to 12.06)	0.77
SDV_T	−0.76 (−6.69 to 8.20)	0.53	−18.00 (−58.57 to 22.57)	0.38

Evaluation of each parameter is over a 7-day running window. The fixed effect estimate represents the change in CAT or SGRQ score per unit change in the corresponding FOT parameter. Values in bold are significant (p<0.05). CI: confidence interval; R_{insp}: inspiratory resistance; SDR_{insp}: standard deviation of inspiratory resistance; X_{insp}: inspiratory reactance; SDX_{insp}: standard deviation of inspiratory reactance; RR: respiratory rate; SDRR: standard deviation of respiratory rate; V_T: tidal volume; SDV_T: standard deviation of tidal volume. #: mean values.

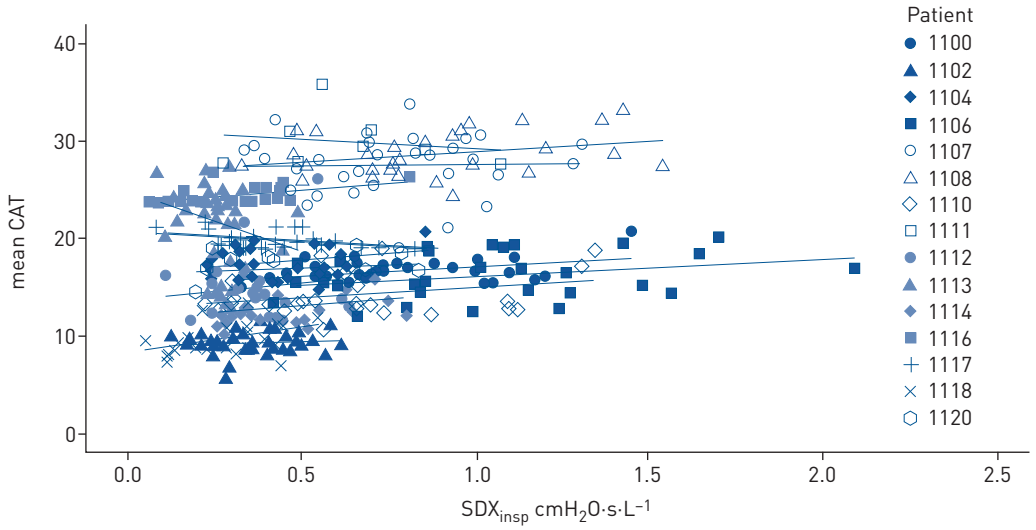

FIGURE 2 Relationship between standard deviation of inspiratory reactance (SDX$_{insp}$) and symptoms (mean COPD Assessment Test (CAT) score), both assessed over 7-day running windows. Symbols and associated regression lines represent individual study subjects (n=15), as indicated by their study IDs (1100–1120).

Relationship with symptoms

Both X$_{insp}$ and standard deviation of inspiratory reactance (SDX$_{insp}$) were related to mean CAT score (fixed effect estimates −0.59 (95% CI −1.02 to −0.15); p=0.009 and 1.57 (95% CI 0.65–2.49); p=0.001, respectively) (table 2 and figure 2). With the exception of three subjects, greater SDX$_{insp}$ was associated with higher mean CAT score, *i.e.* more symptoms (figure 2). Similar results were obtained with the coefficient of variation of inspiratory reactance (CVX$_{insp}$, not shown). No relationships were seen with R$_{insp}$ or standard deviation of inspiratory resistance (SDR$_{insp}$) (supplementary table S1). Measures of breathing pattern (mean RR, variability of RR (standard deviation of respiratory rate (SDRR)), mean V_T and variability of V_T (coefficient of variation of tidal volume (CVV_T))), were also related to mean CAT score (table 2). These relationships were consistently significant when varying window size between 1, 5–7, 10 and 14 days in our sensitivity analyses (within-day variability was used for the 1-day window).

Relationship with quality of life

SDX$_{insp}$ showed a borderline significant relationship with 4-weekly SGRQ score (fixed effect estimate 4.41 (95% CI −0.06 to 8.89); p=0.05) (table 2 and figure 3). This result was not consistently significant when

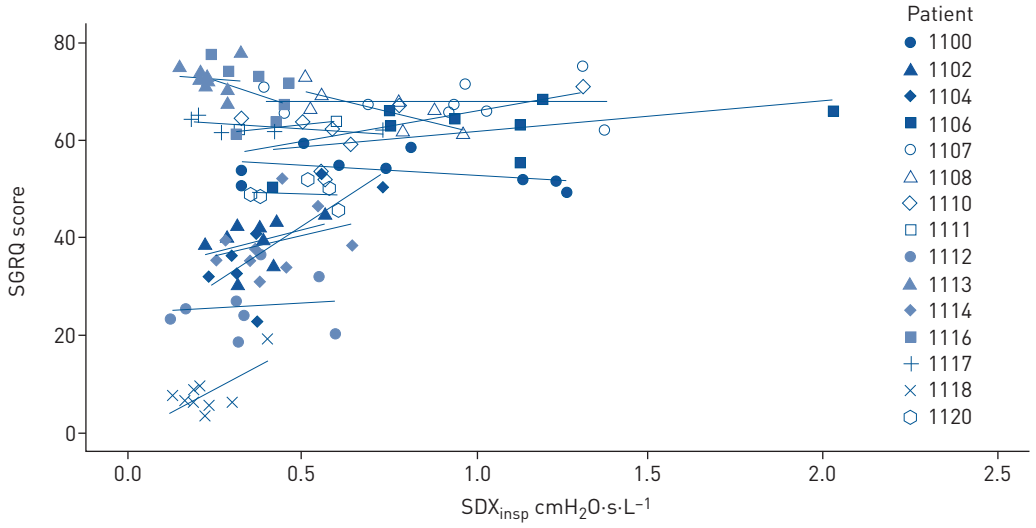

FIGURE 3 Relationship between standard deviation of inspiratory reactance (SDX$_{insp}$) and quality of life (QoL) (St George's Respiratory Questionnaire (SGRQ)), both assessed over 7-day running windows. Symbols and associated regression lines represent individual study subjects (n=15), as indicated by their study IDs (1100–1120).

TABLE 3 Timing of changes in variability of inspiratory forced oscillation technique (FOT) measures (assessed by standard error (SE)) and symptoms in the days before an acute exacerbation of COPD (AECOPD) (demonstrated for 5-day to 7-day analysis windows)

Parameter	Comparison[#]	5-day window		6-day window		7-day window	
		Difference	Adjusted[¶] p-value	Difference	Adjusted[¶] p-value	Difference	Adjusted[¶] p-value
SDR_{insp} $cmH_2O{\cdot}s{\cdot}L^{-1}$	−3	0.046±0.060	0.95	0.007±0.052	1.00	−0.035 ±0.047	0.96
	−2	−0.027 ±0.059	1.00	0.016±0.052	1.00	−0.015 ±0.047	1.00
	−1	−0.017 ±0.060	1.00	−0.035 ±0.052	0.98	0.002±0.046	1.00
	0	0.002±0.060	1.00	−0.012 ±0.053	1.00	−0.023 ±0.047	1.00
SDX_{insp} $cmH_2O{\cdot}s{\cdot}L^{-1}$	**−3**	**0.211±0.064**	**0.005**	**0.159±0.052**	**0.015**	0.085±0.043	0.217
	−2	0.149±0.063	0.093	**0.190±0.052**	**0.002**	0.094±0.043	0.137
	−1	0.107±0.064	0.379	**0.146±0.052**	**0.031**	**0.128±0.043**	**0.017**
	0	0.101±0.064	0.438	0.119±0.053	0.122	0.090±0.043	0.178
CAT score[+]	−3	0.474±0.310	0.479	0.326±0.262	0.686	0.220±0.233	0.154
	−2	0.593±0.307	0.240	0.542±0.261	0.176	0.342±0.233	0.520
	−1	**1.034±0.311**	**0.006**	**0.810±0.261**	**0.011**	**0.682±0.232**	**0.020**
	0	**1.465±0.311**	**0.002**	**1.126±0.263**	**<0.001**	**0.917±0.234**	**<0.001**

Data are presented as n or mean±SE. Values in bold are significant (p<0.05). SDR_{insp}: standard deviation of inspiratory resistance; SDX_{insp}: standard deviation of inspiratory reactance; CAT: COPD Assessment Test. [#]: day before AECOPD; [¶]: adjusted p-value from Dunnett's *post hoc* test; [+]: mean value.

the window size was varied between 1, 5–7, 10, 14 and 28 days. No relationships were observed between R_{insp} measures, X_{insp}, CVX_{insp}, or breathing pattern and SGRQ score, regardless of window size (supplementary table S1).

Timing of changes before AECOPD

SDX_{insp} and mean CAT score changed significantly from baseline at 1 day before AECOPD (p=0.017 and p=0.020, respectively) when using a 7-day analysis window (table 3 and figure 4). Similar results were obtained when using CV in place of SD to assess variability (supplementary table S2). Other FOT variables (including R_{5-19} and ΔX) did not change significantly prior to AECOPD (supplementary table S3).

Notably, when 5-day and 6-day running time windows were used, the change in SDX_{insp} occurred earlier than CAT score, *i.e.* 3 days prior to AECOPD onset *versus* 1 day (p=0.005 *versus* p=0.015 for SDX_{insp} and p=0.014 *versus* p=0.028 for CAT score, respectively) (table 3 and figure 4). Shorter window sizes (3–4 days) did not show any significant changes in (variability of) FOT measures prior to AECOPD, whereas longer window sizes (8–10 days) did not detect changes earlier than Day −3 (data not shown).

Correspondingly, ROC analysis showed that SDX_{insp} calculated over 5-day windows provided the highest accuracy (area under the curve (AUC)=0.72) in detecting AECOPD 3 days prior to onset (as compared to X_{insp}, CVX_{insp} and CAT score), although the ROC curve was not statistically significantly different to that for CAT (figure 5 and supplementary table S4). Furthermore, combining X_{insp} and SDX_{insp} resulted in no significant changes from the AUC for SDX_{insp} alone (Delong method for comparing ROC curves; p=0.94, p=0.92 and p=0.53 for 1, 2 and 3 days prior to onset, respectively).

In terms of breathing pattern, SDRR (but not RR *per se*) was found to change significantly on Day −2 before AECOPD, but only when using smaller window sizes (*i.e.* 3-day windows (p=0.01) and 4-day windows (p=0.02), data not shown). Neither V_T nor standard deviation of tidal volume (SDV_T) showed any significant changes prior to AECOPD onset.

Discussion

In this study, we have shown that the variability of FOT impedance measures, specifically those of X_{insp} (SDX_{insp} and CVX_{insp}), is related to symptoms in COPD and may be used to detect changes prior to an AECOPD as early as 3 days before symptoms manifest. Furthermore, we have identified an optimum time

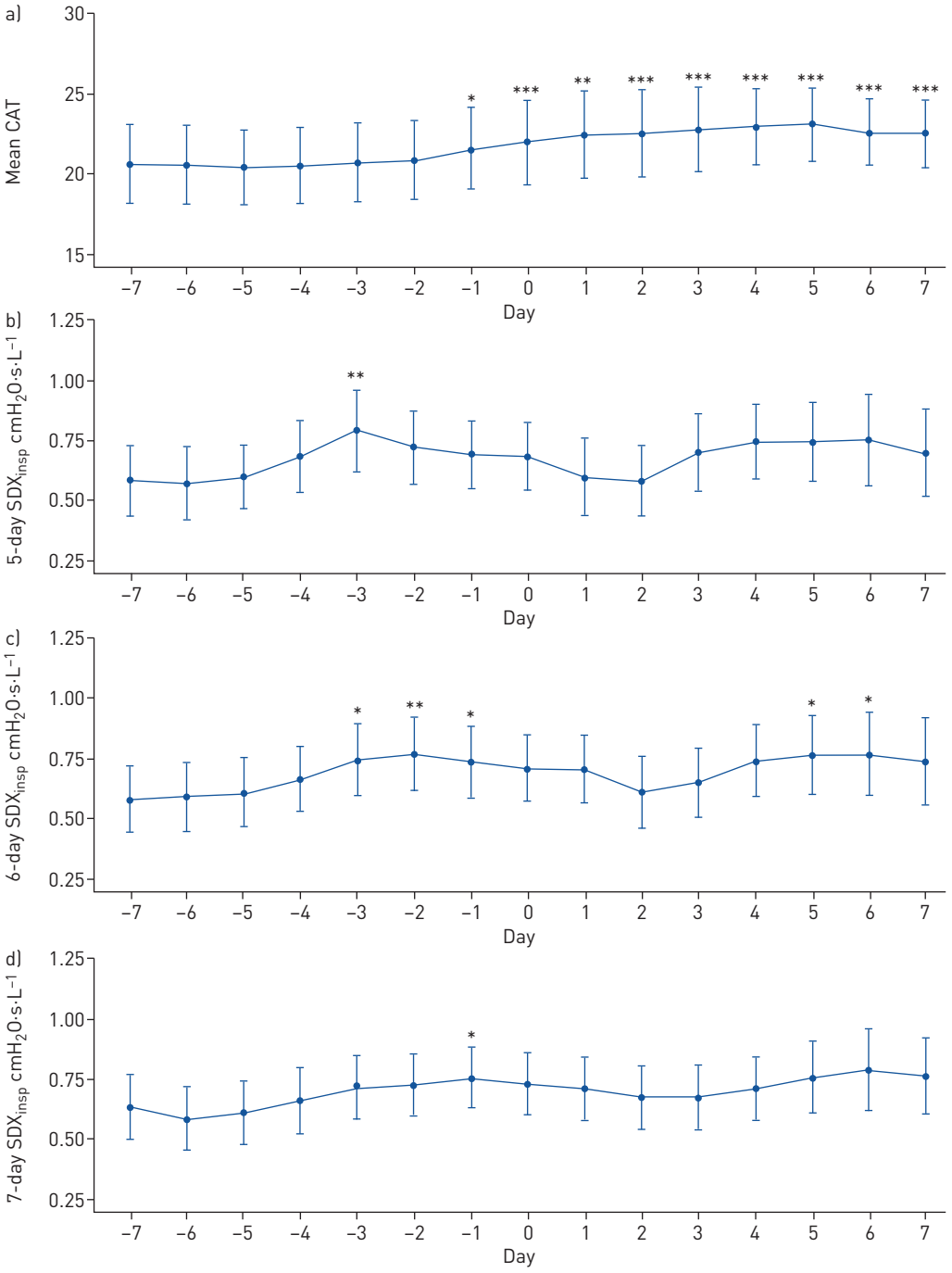

FIGURE 4 Timing of changes in a) mean COPD Assessment Test (CAT) score and (b–d) standard deviation of inspiratory reactance (SDX_{insp}) during the 7 days leading up to and the 7 days following acute exacerbation of COPD (AECOPD). Different running-window lengths were used including b) 5 days, c) 6 days and d) 7 days. Symbols and error bars correspond to the mean and standard error (SE) of the change from baseline for all pooled exacerbations (n=37). *: p<0.05; **: p<0.01; ***: p<0.001.

window for assessing variability of FOT measures in COPD monitoring. Feasibility of COPD home telemonitoring with FOT was high, consistent with previous studies [14, 36], with high adherence (>95%) and low drop-out rates (<7%).

Relationship with patient-centred outcomes

To our knowledge this is the first study to evaluate the relationship between variability of FOT measures and patient-centred outcomes (such as symptoms and QoL), an essential step towards demonstrating

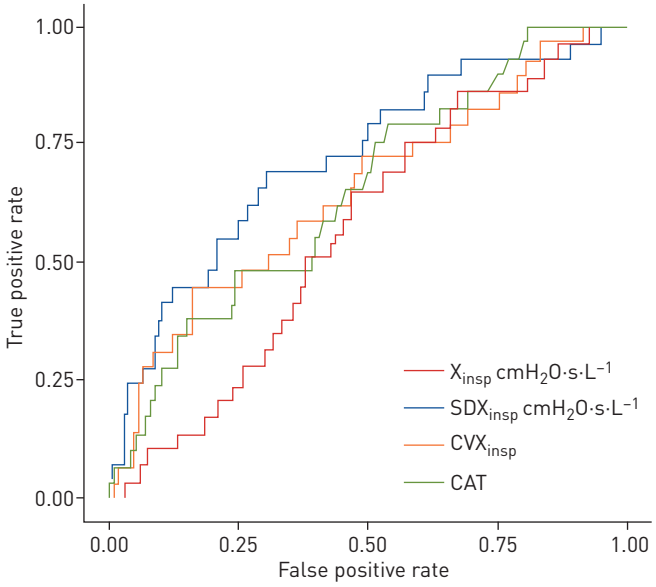

FIGURE 5 Receiver operating characteristic (ROC) curves for detecting acute exacerbation of COPD (AECOPD) (n=37) 3 days prior to onset with 5-day running windows for mean and variability measures of inspiratory reactance (X) and COPD Assessment Test (CAT) score (area under the curve (AUC) scores are: X_{insp}=0.57; SDX_{insp}=0.72; CVX_{insp}=0.65; CAT=0.65). X_{insp}: inspiratory reactance; SDX_{insp}: standard deviation of inspiratory reactance; CVX_{insp}: coefficient of variation of inspiratory reactance.

clinical utility. Previous studies have shown mean measures of X to correlate with symptoms and HRQoL [37, 38], or to predict improvements in symptoms with bronchodilator use [39]; however, they did not examine variability. In our study, both X_{insp} and SDX_{insp} (as well as CVX_{insp}) showed significant relationships with symptoms. The observation that day-to-day variability, regardless of correction by mean X (*i.e.* whether expressed as SD or CV), was related to CAT score suggests that both mean and variability provide distinct information in accounting for symptoms. The consistency of these relationships over a range of 5-day to 10-day time windows adds to the robustness of this finding.

In contrast, the relationship between SDX_{insp} and respiratory QoL was weaker. This may simply be because SGRQ data was collected 4-weekly (it was originally validated as a 3-monthly measure), whereas the CAT was assessed daily and was therefore more likely to reflect day-to-day variations in FOT.

Potential for detection of exacerbation onset

Increased variability can be due to a progressive change in the mean or greater day-to-day swings in lung function. Although both mean and variability indices of X_{insp} were related to symptoms, we found that only variability of X_{insp} (SDX_{insp} and CVX_{insp}) changed significantly prior to AECOPD. This suggests that it is the day-to-day variations that are important for AECOPD detection, rather than a change in the mean value *per se*. More importantly, when using an optimal window size, these changes occur even earlier than the onset of symptom worsening. While symptoms are the primary means of assessing the onset of AECOPD, they can be subject to patient recall bias and perception (there is often disparity between self-perception and actual severity of symptoms [40]); moreover, perception can differ with exacerbation phenotype [41]. Here we show that SDX_{insp} (and CVX_{insp}) may provide a potential objective physiological biomarker for the detection of exacerbation onset that may be more reliable than symptoms. This would facilitate timely intervention, known to shorten AECOPD duration [5].

Significantly, the sensitivity analysis conducted as part of this study suggests an optimum window size for assessing variability of FOT measures, informing future trials aimed at early AECOPD detection and intervention. Time windows between 5 days and 7 days appear to best balance the required sensitivity to detect a significant and sustained increase in variability before AECOPD. Windows <5 days may be too short to adequately capture day-to-day worsening in lung function, especially when there is missing data, whereas time frames >7 days may reduce sensitivity to reflect the timing of these changes.

Physiological significance of inspiratory reactance variability

Parameters for X have been shown to reflect pathophysiological hallmark features of COPD, such as hyperinflation [42], communicating lung volume [43] and expiratory flow limitation (EFL) [31]. Of note, the change to less negative X during inspiration distinguishes COPD subjects from healthy subjects, implying reduced heterogeneity with lung inflation during the breathing cycle [44]. Our results lend support to the idea of X as the more clinically relevant FOT parameter in COPD, in contrast to R. Furthermore, we observed the most consistent relationships in X_{insp} measures, suggesting these relationships are independent of the confounding effects of EFL. In comparison, X_{insp} in particular has been found to track with symptoms during recovery from AECOPD [23].

We found that SDX_{insp} (and CVX_{insp}) increased leading up to an AECOPD. Both increased and decreased variability have been associated with pathology or deviation from health [16]; however, it has been proposed that increased variability may represent instability in a complex disease [15]. We have previously demonstrated that day-to-day SDX_{insp} is increased in stable COPD compared to health [17]. We have also shown X_{insp} to be a reflection of communicating lung volume (*i.e.* distribution of parallel lung units available to the FOT signal, each with their associated time constants [43]). Thus, we speculate that increased SDX_{insp} in COPD *versus* health may reflect both increased magnitude of X_{insp} (*via* greater heterogeneity) and temporal variation in the distribution of time constants (either due to altered resistances and/or compliances within lung units), as well as the resultant effect on the day-to-day dynamics of lung function. Similarly, AECOPD could represent an acute worsening of this heterogeneity *per se*, or the resulting increased instability in day-to-day lung function and our results suggest the latter is more important for detection of AECOPD. Furthermore, the increased instability may perhaps reflect the tug-of-war between the effects of exacerbation and losing ventilated regions or units, and the patient's breathing efforts to reverse these obstructions to recover X.

We did not detect significant changes in the mean or variability of ΔX pre-AECOPD onset in our study cohort. There are a number of possible explanations for this. First, there may be phenotypic differences between patients, as only six out of the 13 subjects who experienced AECOPD during the study period had EFL during their stable periods (based on the threshold of 2.8 $cmH_2O{\cdot}s{\cdot}L^{-1}$ defined by Dellacà *et al.* [31]). Secondly, there may be mechanistic differences between exacerbations, as some were indeed associated with increased ΔX but others were not, consistent with other studies [45]. To illustrate this, of the 26 AECOPD with sufficient data at 7 days both pre- and post-onset, 15 had no flow limitation at baseline (*i.e.* at −7 days). Of these, only four had increased ΔX during the exacerbation to the point of developing EFL. In contrast, 11 did not involve development of EFL and the increased symptoms during these events could have been more predominantly attributed to worsening ventilation heterogeneity (as detected by SDX_{insp}) rather than EFL. In the remaining 11 AECOPD, the patients were already flow-limited at baseline and perhaps had limited capacity to experience further worsening of EFL.

Other studies have identified changes in breathing pattern as potentially important in early detection of AECOPD [7, 8, 46]. In our study cohort, even though RR and V_T were strongly related to symptoms, the assessment of more detailed airway mechanics by FOT appears to demonstrate a superior ability for early detection of AECOPD compared to these parameters.

Implications for further work

Our study shows that even relatively simple measures of variability (SD and CV) have potential value for assessing symptoms and detecting exacerbation onset. These results also form the basis for more advanced variability analyses, such as conditional probability, which have been applied to PEF and FOT to predict lung function deterioration in asthma [24, 25, 33] and which may improve our current accuracy of 72%. Moreover, our reported thresholds maximised both sensitivity and specificity (achieving 70% for both). With further validation, these algorithms may enhance our ability to predict future exacerbation risk in COPD and pave the way for future, better informed interventional studies.

Our results show that, when using a sensitive test providing detailed airway mechanics such as FOT in combination with evaluating the variability of the derived lung function measures, lung function monitoring can be of value in COPD. This novel approach may move us towards an objective, lung-function based definition of exacerbation onset that is also clinically meaningful. When coupled with symptoms, it may furthermore provide additional insight into phenotyping of AECOPD, especially in patients who exhibit discordance between lung function and symptoms.

We examined the false positive rate (FPR) and false negative rate (FNR) across the patients who experienced AECOPD. While the median FPR and FNR were reasonable for prediction on Day −3 for a 7-day window (18.4% and 16.7%, respectively), we found that missed exacerbations tended to occur in the same subjects and, similarly, some participants had none of their exacerbations missed. These results may be of interest in terms of phenotyping as prediction may not work well in a subset of patients, either due to poor perception of symptoms (ultimately how AECOPD is defined) or that these patients may have had an increase in symptoms without an associated significant change in lung function (*e.g.* due to an acute cardiac event or other co-morbidities that might make them more breathless). This is worth exploring in a larger dataset where more events are available.

Study limitations

Its observational character and small subject numbers are limitations of the present study. Nevertheless, its results warrant further validation in larger, interventional studies evaluating the efficacy of AECOPD management based on telemonitoring of FOT measures (similar to Walker *et al.* [14] but using variability

as a target). Furthermore, we had to exclude the data of one participant from our analyses due to technical issues; however, additional quality control could be incorporated into future automated software acquisition algorithms to flag implausibly low R values and prompt a subject to repeat a recording.

Our study was not powered to examine exacerbations of differing severity (*e.g.* those requiring oral corticosteroid and/or antibiotic use only *versus* hospitalisations). Nevertheless, we were able to demonstrate the ability to detect AECOPD irrespective of severity. Also, mild exacerbations (with an increase in symptoms not accompanied by a change in treatment) were not included in our assessment.

Our inferences on AECOPD detection in this study are based on population-based measures. Although significant changes in variability prior to AECOPD onset were determined *via* comparison against each subject's own baseline, there was a wide spread in this baseline between subjects, which may limit the ability to define a universal threshold for detecting significant change. Moreover, we chose to express changes associated with an AECOPD in terms of absolute rather than relative variation from baseline. While it would have been useful to examine relative changes to account for the influence of baseline X_{insp}, expressing the changes in relative terms would cause the optimum threshold to be highly skewed towards those subjects with baseline X_{insp} values that are very close to zero, as the magnitude of their relative changes would be immense. However, advanced techniques such as individual conditional probability [24] will enable us to better characterise the baseline variability specific to a patient, allowing individualised assessment of AECOPD risk.

Conclusion

Home monitoring of FOT is feasible [24, 25, 47], with high adherence amongst COPD patients [14, 36]. We have demonstrated in a small COPD cohort that variability of FOT measures reflects day-to-day symptoms and can detect AECOPD onset even before symptoms manifest, with higher accuracy than FOT *per se*. Thus, variability of FOT parameters may be clinically useful in assessing disease status and in enabling early intervention for AECOPD, potentially reducing the significant healthcare burden associated with it. Our results also inform the development of further advanced variability analyses in COPD, such as those already used in asthma, which may allow us to quantify individualised risk and facilitate personalised disease management. Finally, these results provide further insight into the pathophysiological mechanisms that lead to an AECOPD, which may hopefully evolve into novel physiological biomarkers to better phenotype COPD.

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